



# **10<sup>th</sup> International Meeting of Pediatric Endocrinology:**

## **Individual Abstracts for Free Communication and Poster Sessions**

### **FREE COMMUNICATION SESSIONS:**

#### **Friday, September 15, 2017, 7:30-8:30am**

Growth and GH/IGF Axis #1: FC1 – FC5

Syndromes: FC6 – FC 10

Bone and mineral metabolism #1: FC11 – FC15

#### **Friday, September 15, 2017, 8:45-9:45am**

Sex differentiation/gonads and disorders of sex development: FC16 – FC20

Type 2 diabetes and other carbohydrate metabolism: FC21 – FC25

Global health: FC26 – FC30

#### **Friday, September 15, 2017, 2:30-3:30pm**

Bone and mineral metabolism #2: FC31 – FC35

Type 1 diabetes #1: FC36 – FC40

Gender dysphoria: FC41 – FC45

Obesity, lipids, and co-morbidities #1: FC46 – FC50

#### **Saturday, September 16, 2017, 7:30-8:30am**

Quality improvement: FC51 – FC55

Growth and GH/IGF Axis #2: FC56 – FC60

Obesity, lipids, and co-morbidities #2: FC61 – FC65

#### **Saturday, September 16, 2017, 8:45-9:45am**

Type 2 diabetes and other carbohydrate metabolism #2: FC66 – FC70

Thyroid: FC71 – FC75

Neuroendocrinology including hypothalamic pituitary: FC76 – FC80

#### **Saturday, September 16, 2017, 3:15-4:15pm**

Type 1 diabetes #2: FC81 – FC85

Fetal and neonatal endocrinology and metabolism, including hypoglycemia: FC86 – FC90

Adrenals #1: FC91 – FC95

#### **Sunday, September 17, 2017, 7:30-8:30am**

Adrenals #2: FC96 – FC100

Multisystem endocrine disorders: FC101 – FC105

#### **Sunday, September 17, 2017, 8:45-9:45am**

Puberty: FC106 – FC110

Late Breaking: FC111– FC115

## **POSTER SESSION 1**

**Thursday, September 14, 2017, 5:45-6:45pm**

P1 – Adrenals: P1-100 – P1-135

P1 - Bone and mineral metabolism: P1-200 – P1-234

P1 - Fetal and neonatal endocrinology and metabolism, including hypoglycemia: P1-500 – P1-526

P1 - Growth and GH/IGF Axis: P1-800 – P1-860

P1 - Multisystem endocrine disorders: P1-900 – P1-915

P1 - Neuroendocrinology including hypothalamic pituitary: P1-1000 – P1-1016

P1 - Obesity, lipids, and co-morbidities: P1-1100 – P1-1136

P1 – Other: P1-1200 – P1-1216

P1 – Puberty: P1-1300 – P1-1321

P1 - Quality improvement: P1-1400 – P1-1413

P1 - Sex differentiation/gonads and disorders of sex development: P1-1500 – P1-1522

P1 – Syndromes: P1-1600 – P1-1615

P1 – Thyroid: P1-1700 – P1-1727

P1 - Type 1 diabetes: P1-1800 – P1-1828

P1 - Type 2 diabetes and other carbohydrate metabolism: P1-1900 – P1-1907

## **POSTER SESSION 2**

**Friday, September 15, 2017, 11:30am-12:30pm**

P2 – Adrenals: P2-100 – P2-130

P2 - Bone and mineral metabolism: P2-200 – P2-219

P2 - Ethics in endocrinology: P2-400 – P2-401

P2 - Fetal and neonatal endocrinology and metabolism, including hypoglycemia: P2-500 – P2-530

P2 - Global health: P2-700 – P2-704

P2 - Growth and GH/IGF Axis: P2-800 – P2-857

P2 - Neuroendocrinology including hypothalamic pituitary: P2-1000 – P2-1014

P2 - Obesity, lipids, and co-morbidities: P2-1100 – P2-1146

P2 – Other: P2-1200 – P2-1208

P2 – Puberty: P2-1300 – P2-1326

P2 - Sex differentiation/gonads and disorders of sex development: P2-1500 – P2-1533

P2 – Syndromes: P2-1600 – P2-1620

P2 – Thyroid: P2-1700 – P2-1734

P2 - Type 1 diabetes: P2-1800 – P2-1852

P2 - Type 2 diabetes and other carbohydrate metabolism: P2-1900 – P2-1906

## **POSTER SESSION 3**

**Saturday, September 16, 2017, 12:00-1:00pm**

P3 – Adrenals: P3-100 – P3-132

P3 - Bone and mineral metabolism: P3-200 – P3-238

P3 - Endocrine care transition: P3-300 – P3-304

P3 - Fetal and neonatal endocrinology and metabolism, including hypoglycemia: P3-500 – P3-525

P3 - Gender dysphoria: P3-600 – P3-608

P3 - Growth and GH/IGF Axis: P3-800 – P3-863

P3 - Neuroendocrinology including hypothalamic pituitary: P3-1000 – P3-1012

P3 - Obesity, lipids, and co-morbidities: P3-1100 – P3-1142

P3 – Puberty: P3-1300 – P3-1331

P3 - Sex differentiation/gonads and disorders of sex development: P3-1500 – P3-1539

P3 – Syndromes: P3-1600 – P3-1619

P3 – Thyroid: P3-1700 – P3-1741

P3 - Type 1 diabetes: P3-1800 – P3-1849

P3 - Type 2 diabetes and other carbohydrate metabolism: P3-1900 – P3-1911

Free Communication Session, Friday, September  
15, 2017, 7:30-8:30am  
Growth and GH/IGF Axis #1  
FC1 – FC5

FC1

**PAPPA2 P.ALA1034VAL KNOCK-IN MOUSE MODEL  
RECAPITULATES HOMOZYGOUS HUMAN PAPPA2  
MUTATION ASSOCIATED WITH SHORT STATURE**

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**Objectives:** Pregnancy-associated plasma protein A2 (PAPP-A2), a metalloproteinase, is a key regulator of circulating IGF-1 bioavailability. IGF-I circulates in ternary complex with IGF binding protein IGFBP-3 or IGFBP-5 and acid labile subunit, and the cleavage of IGFBP-5 and IGFBP-3 by PAPP-A2 is hypothesized to free the IGF-I for bioactivities. This critical role of PAPPA2 was recently supported by our report of the first homozygous loss-of-function *PAPPA2* mutations identified in patients with post-natal growth failure and markedly low free IGF-I despite significantly elevated total serum IGF-I levels. Interestingly, one of the two mutations was a missense mutation, p.Ala1033Val, located downstream of the peptidase domain. We demonstrated that this recombinant mutant protein, when compared to wild-type PAPPA2 in over-expressed HEK293 reconstituted systems, was functionally inactive, as it could not proteolyze either recombinant IGFBP-3 or IGFBP-5 proteins. To further validate the biological significance of this missense mutation, we sought to create a mouse model of our patient's homozygous missense mutation.

**Methods:** We successfully generated an *in vivo* knock-in (KI), Pappa2 p.Ala1034Val, mouse model (B6D2F1/J), employing CRISPR/CAS9 methodology. We then phenotyped the mice and measured total and free IGF-1 as well as intact IGFBP-3 in mouse serum via ELISA.

**Results:** Preliminary post-natal growth profiles of the homozygous KI (n=10) at 16 days of age, indicated weights were  $17.7\% \pm 3.0\%$  less than wild-type mice (n=8),  $P < 0.0001$ , and remained lower than wild-type mice at 48 days (weight were  $21.6\% \pm 0.05\%$  lower). Serum samples collected were evaluated for total Igf-I, free Igf-I and intact Igfbp-3. Wild-type mice had total Igf-I of  $30.6 \pm 3.3$  ng/ml, Igf-I of  $1.5 \pm 0.6$  ng/ml and intact Igfbp-3 of  $328.3 \pm 81$  ng/ml, whereas the KI mice had significantly higher total Igf-I of  $52.0 \pm 2$  ng/ml, undetectable free Igf-I and higher intact Igfbp-3,  $710 \pm 48$  ng/ml.

**Conclusions:** In summary, our KI mouse model recapitulates the features of reduced IGF-I bioavailability and impaired post-natal growth profiles observed in our patients. Further investigations are in progress to confirm these results, and to determine if treatment of KI mice with recombinant PAPPA2 can rescue the impaired growth phenotype.

FC2

**GENETIC SCREENING OF PATIENTS WITH CONGENITAL GH  
DEFICIENCY IN THE GENESIS OBSERVATIONAL PROGRAM:  
MUTATION FREQUENCY, PHENOTYPE AND GROWTH  
OUTCOMES**

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**Objectives:** Congenital GH deficiency (GHD) may be caused by mutations in genes involved in pituitary development, GH synthesis or secretion. Defects in *GH1* & *GHRHR* commonly cause isolated GHD (IGHD). Defects in genes for transcription factors (*GLI2*, *HESX1*, *LHX3*, *LHX4*, *SOX3*, *PROP1*, *POU1F1*) that shape the developing pituitary & specify hormone-producing cells, cause multiple pituitary hormone deficiencies (MPHD). Using GeNeSIS DNA Analysis Sub-study data, we investigated mutation frequency, & variability in phenotype & final height (FH) gain in GH-treated patients with & without mutations.

**Methods:** SSCP, dHPLC & direct sequencing analyses were performed based on a candidate gene approach in patients with IGHD or MPHD. DNA variants were classified as pathogenic according to American College of Medical Genetics and Genomics standards. FH was defined by at least 1 of: closed epiphyses, height velocity 14 years-girls/ $>16$  years-boys.

**Results:** The frequency of detected mutations is shown in the table. Baseline features (mean $\pm$ SD &  $p=0.005$  unless specified) significantly different between those with mutation(s) (N=92) & those without (N=825) included age (y)  $5.7 \pm 4.2$  vs  $7.3 \pm 4.7$ ; height standard deviation score (SDS)  $-4.1 \pm 2.2$  vs  $-2.9 \pm 1.5$ ; height minus target height SDS  $-4.0 \pm 2.0$  vs  $-2.4 \pm 1.6$ ; height velocity SDS  $-2.3 \pm 2.0$  vs  $-1.5 \pm 1.9$ ,  $p=0.02$ ; median peak stimulated GH  $1.1$  vs  $3.8$   $\mu$ g/L; IGF-I SDS  $-5.9 \pm 3.5$  vs  $-3.4 \pm 3.3$ . In those who reached FH, features significantly different between those with mutation(s) (N=24) & those without (N=191) were baseline age (y)  $7.4 \pm 4.3$  vs  $9.4 \pm 4.2$ ,  $p=0.03$ ; height SDS  $-4.1 \pm 2.3$  vs  $-2.9 \pm 1.2$ ; height minus target height SDS  $-4.1 \pm 2.1$  vs  $-2.3 \pm 1.5$ ; median peak stimulated GH  $1.0$  vs  $4.7$   $\mu$ g/L; GH therapy duration (y)  $10.7 \pm 4.4$  vs  $7.7 \pm 4.0$ ; & FH SDS gain  $3.4 \pm 1.4$  vs  $2.0 \pm 1.4$ .

**Conclusions:** Children with congenital GHD should be considered for DNA testing in genes involved in pituitary development, GH synthesis & secretion. Patients who had mutations were younger & had more severe GHD than those without. FH gains after GH therapy were greater in those with mutations, possibly because of earlier start of GH treatment. DNA analysis may aid decision making regarding the clinical course of hypopituitarism & outcomes of GH treatment.

Table: Frequency of mutations in genes involved in the regulation of pituitary development, GH synthesis and secretion, split by pituitary secretory status

Gene	IGHD N (%)	MPHD N (%)	All <sup>a</sup> N (%)
All studied	475 (100.0%)	415 (100.0%)	917 (100.0%)
All with mutation <sup>b</sup>	31 (6.5%)	61 (14.7%)	92 (10.0%)
All without mutation <sup>b</sup>	444 (93.5%)	354 (85.3%)	825 (90.0%)
GH1	23 (4.8%)	3 (0.7%)	26 (2.8%)
GHRHR	5 (1.1%)	0 (0.0%)	5 (0.5%)
GLI2	0 (0.0%)	1 (0.2%)	1 (0.1%)
HESX1	0 (0.0%)	1 (0.2%)	1 (0.1%)
LHX3	0 (0.0%)	5 (1.2%)	5 (0.5%)
LHX4	0 (0.0%)	0 (0.0%)	0 (0.0%)
POU1F1	0 (0.0%)	2 (0.5%)	2 (0.2%)
PROP1	1 (0.2%)	48 (11.6%)	49 (5.3%)
PROP1, HESX1	0 (0.0%)	1 (0.2%)	1 (0.1%)
SOX3	2 (0.4%)	0 (0.0%)	2 (0.2%)

Abbreviations: IGH = isolated GH deficiency; MPHD = multiple pituitary hormone deficiencies; N = number  
<sup>a</sup> Includes 27 patients for whom pituitary secretory status could not be assigned.  
<sup>b</sup> DNA variants classified as pathogenic according to Richards S et al 2015. Genet Med; 17:405-424.

FC3

### MECHANISMS OF FIBROBLAST GROWTH FACTOR 21 (FGF21) MEDIATED GROWTH HORMONE RESISTANCE IN HUMAN GROWTH PLATE IN CHRONIC CHILDHOOD CONDITIONS.

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**Objectives:** FGF21 is an essential hormone regulating metabolic processes to the adaptation to fasting; inducing gluconeogenesis, fatty acid oxidation and ketogenesis. Undernutrition and chronic inflammation have been suggested to elevate FGF21 levels, developing Growth Hormone (GH) resistance and subsequent attenuation of longitudinal growth and growth plate chondrogenesis in both mice and humans through unknown mechanisms. We propose that chronic exposure to a high FGF21 environment promotes GH resistance by a direct action on human chondrocytes. The objective of this study is to identify the mechanistic interplay of FGF21 in GH-Receptor (GHR) signalling and GH resistance.

**Methods:** Hek-293 stable lines expressing human GHR were generated and examined for FGF21 and receptor complex (FGFR1/  $\beta$ -KLOTHO) expression. Immunohistochemistry on human growth plate was studied to identify the localisation of FGF21 and co-receptors within growth plate zonation. Stable lines and/or human growth plate explants were evaluated for GHR half-life and the activation of key GHR signalling mediators; STAT5, negative feedback regulator SOCS2 and IGF-1 in the presence or absence of rhGH and rhFGF21. For the validation of clinical significance FGF21 and IGF-1 levels were measured serially in peripubertal Crohn’s patients.

**Results:** Expression of FGF21 receptor complex; FGFR1  $\beta$ /KLOTHO and the molecular integrity of GHR signalling was confirmed in stable lines. In the human growth plate FGF21 and co-receptors were localised within the proliferative and pre-hypertrophic zones. Chronic exposure to FGF21 significantly reduced GHR half-life and GH induced STAT5 phosphorylation, whilst the expression of SOCS2 was increased. *Ex vivo* studies on human growth plate explants verified our *in vitro* findings, whereby elevated FGF21 was seen to increase SOCS2 expression and suppress IGF-1 expression. A negative association ( $p<0.005$ ) of FGF21 with IGF-1 levels was found in peripubertal patients diagnosed with Crohn’s disease.

**Conclusions:** Chronic FGF21 exposure inhibits key GHR signaling mediators, playing a central role in GH resistance secondary to chronic childhood conditions.

FC4

### REGULATION OF GROWTH PLATE CHONDROCYTE DIFFERENTIATION BY SPECIFIC MICRORNAS

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**Objectives:** Growth plate (GP) chondrogenesis is the fundamental process that drives linear growth in children and consequently, defects in chondrogenesis cause short stature. In GP, chondrocytes undergo sequential differentiation to form the resting (RZ), proliferative (PZ), and hypertrophic zones (HZ). The important role of microRNAs in the GP was revealed by cartilage-specific ablation of dicer, an enzyme essential for biogenesis of microRNAs. Here, we sought to identify specific microRNAs that regulate differentiation of PZ chondrocytes to HZ chondrocytes.

**Methods:** Individual GP zones were collected by microdissection from 4-day-old rat proximal tibias. Using Nanostring and RNAseq, we identified microRNAs that were downregulated in HZ vs PZ (>2 fold and FDR<0.05 by Nanostring). To prioritize these microRNAs for subsequent study, we identified microRNAs that were 1) predicted to regulate multiple genes that are differentially expressed in PZ vs HZ, and 2) predicted to target critical regulatory genes in the GP, and 3) highly expressed in GP chondrocytes compared to osteoblasts. For the four highest prioritized microRNAs, inhibitors were transfected into primary rat GP chondrocytes for evaluation of cell proliferation (3H-thymidine labeling) and changes in expression (real-time RT-PCR) of genes that are upregulated in the PZ to HZ transition.

**Results:** Four microRNAs (mir-369-3p, mir-374-5p, mir-379-5p, mir-503-5p) that were downregulated in HZ vs PZ were selected based on the prioritization analysis. When inhibitors for these microRNAs were transfected into chondrocytes, proliferation decreased (38, 26, 46, 49%, respectively,  $P<0.001$ ) vs control (scrambled microRNA). The inhibitors for



three of microRNAs (mir-374-5p, mir-379-5p, mir-503-5p) also increased expression of genes physiologically upregulated in HZ: *Ihh* (7.6, 6.9, 8.0-fold increase respectively,  $P<0.01$ ), *Bmp2* (7.6, 5.4, 5.6-fold,  $P=0.008$ , 0.06, 0.047), *Bmp6* (3.5, 2.9, 3.2-fold,  $P=0.008$ , 0.06, 0.047), and *Col10a1* (5.3, 4.5, 4.4-fold,  $P=0.015$ , 0.051, 0.04).

**Conclusions:** Our findings suggest that mir-374-5p, mir-379-5p, and mir-503-5p are downregulated in the PZ to HZ transition, thereby contributing to the inhibition of proliferation and stimulation of hypertrophic differentiation, which are important steps in endochondral bone formation at the GP.

FC5

**RESPONSE TO RECOMBINANT HUMAN INSULIN-LIKE GROWTH FACTOR-1 AFTER TWO YEARS OF THERAPY IN TWO PATIENTS WITH PAPP-A2 DEFICIENCY**

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**Objectives:** PAPP-A2 is a metalloproteinase that specifically cleaves IGFBP3 and IGFBP5. We have recently described the first mutations in the *PAPP-A2* gene that cause postnatal growth failure in humans and specific skeletal features, due to the resulting decrease in IGF-1 bioavailability. The objectives are: 1. To determine auxological, hormonal and metabolic parameters after administration of rhIGF-1 to two patients with complete lack of PAPP-A2 activity. 2. To assess the safety of this treatment after two years. **Methods:** The study included two prepubertal siblings, a 10.5-year-old female (patient 1) and a 6-year-old boy (patient 2), born to non-consanguineous Spanish parents. Both patients exhibited very high serum levels of IGF-I, IGF-II, ALS, IGFBP3 and IGFBP5, as well as a similar phenotype and short stature due to a homozygous loss-of-function frameshift mutation in the exon 3 of the *PAPP-A2* gene (p.D643fs25\*) and undetectable PAPP-A2 activity. Both siblings were treated with rhIGF-1 (Mecasermin, Increlex®; Ipsen), with progressive doses (40, 80, 100 y 120 µg/kg), twice daily for 2 years. After 6 months of treatment with rhIGF-I, patient 1 entered puberty (Tanner II). In an attempt to improve her final height, she receives Triptorelin (3.75 mg/28 days).

**Results:** Treatment with rhIGF-1 accelerated growth velocity, clearly improving height SDS according to age and sex in both patients at 6 mo, 12 mo and 24 mo of therapy (Table). Acutely, rhIGF-I administration increased bioactive IGF-I 60-120 minutes later. Twelve hours after treatment, serum bioactive IGF-I, total IGF-I and IGFBP-3 levels were similar to their pretreatment levels (Table). At 1 yr of treatment, fasting hyperinsulinemia was normalized (patient 1: 11 µU/mL; patient 2: 8 µU/mL) with normal glycemia and glycosylated hemoglobin before and during treatment. Treatment with rhIGF-1 produced an increase in total body mineral content (DXA) (patient 1: 23% and patient 2: 30%) after 2 years) and increased the percentage of lean body mass in both patients. Neither patient experienced episodes of hypoglycemia or hyperglycemia or any other previously described secondary effect of rhIGF-I.

**Conclusions:** Treatment with rhIGF-I in children with PAPP-A2 deficiency improves growth after two years, with no apparent adverse effects.

TX	CA (yr)	BA (yr)	Height (cm) (SDS)	BMI (kg/m <sup>2</sup> ) (SDS)	HC (cm) (SDS)	GV (cm/yr) (SDS)	IGF-I (µg/L)	Bioactive IGF-I (µg/L)	IGFBP-3 (µg/L)
Patient 1 (female)									
Start	10.54	10.75	132 (-1.25)	14.1 (-1.51)	49 (-2.06)	3.7 (-1.5)	1,054	2.96	658
12 m	11.54	11.25	139.6 (-0.86)	14.8 (-1.44)	49 (-2.08)	7.6 (+1.6)	1,005	2.05	775
24 m	12.54	12.0	145.5 (-0.81)	15.6 (-1.3)	50.5 (-1.78)	5.9 (-1.06)	864	1.62	70
Patient 2 (male)									
Start	6	4.5	111.5 (-0.74)	13.38 (-1.81)	47.5 (-2.76)	5.8 (-1.6)	882	1.35	999
12 m	7	5.5	118.5 (-0.34)	13.64 (-1.69)	48.5 (-2.94)	7 (+1.06)	1,098	0.48	559
24 m	8	6.25	124.5 (-0.31)	14.39 (-1.24)	49.5 (-2.06)	6 (+0.23)	964	1.18	10

**Free Communication Session, Friday, September 15, 2017, 7:30-8:30am**  
**Syndromes**  
**FC6 – FC 10**

FC6

**IDENTIFICATION OF SMCHD1 MUTATIONS IN A SEVERE FORM OF KALLMANN SYNDROME (KS) WITH ABSENCE OF THE NOSE (ARHINIA) ATTESTS TO THE POWER OF EXTREME PHENOTYPES IN HUMAN REPRODUCTIVE GENE DISCOVERY**  
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**Objectives:** The study of patients with extreme clinical phenotypes is an efficient strategy for gene discovery. Harnessing the phenotypic depth and size of our cohort of subjects with hypogonadotropic hypogonadism (HH), we applied this approach to a group of KS subjects with a completely absent external nose (arhinia).

**Methods:** Through an international consortium, we expanded our arhinia cohort to 41 cases, performed whole-exome sequencing (WES) and defined the full reproductive phenotypic spectrum.

**Results:** Rare mutation burden testing in WES data from cases vs ExAC controls identified 1 gene, *SMCHD1*, exceeding genome-wide significance. 86% of cases had a rare, heterozygous missense variant in *SMCHD1*, which encodes an epigenetic repressor that causes a rare form of muscular dystrophy. *SMCHD1* is expressed in the human olfactory

epithelium, a tissue highly relevant to arhinia and GnRH ontogeny. Cases did not harbor rare sequence variants (RSVs) in any genes associated with KS.

Reproductive function was assessed in 22M and 10F; 97% had HH, cryptorchidism, microphallus, or 1o amenorrhea. Three patients had apulsatile LH profiles, consistent with GnRH deficiency, and physiologic GnRH administration induced ovulation in a female while a male (with eutopic testes) had an exaggerated FSH response and modest T rise, suggesting coexistent testicular resistance. Neuroimaging revealed absent olfactory structures. In 3 multiplex families, an *SMCHD1* RSV segregated with arhinia or sub-phenotypes (anosmia) but not with KS, indicating that HH is incompletely penetrant or variably expressed, compatible with oligogenicity.

*Smchd1* suppression in zebrafish produced aberrant facial cartilage and a much shorter GnRH-immunopositive terminal nerve. RNAseq of blood cells from arhinia patients vs unaffected family revealed altered expression of craniofacial but not KS genes.

**Conclusions:** 1) *SMCHD1* alterations cause a broad spectrum of phenotypes that are incompletely penetrant and variably expressed, suggesting pleiotropy, oligogenicity, or environmental modifiers

2) Epigenetic modification by *SMCHD1* appears to play a role in reproductive developmental biology, and

3) KS patients with phenotypic extremes provide critical genetic insights into human reproductive function.

FC7

#### METABOLOMIC PROFILE OF SEVERE VERSUS ATTENUATED MUCOPOLYSACCHARIDOSIS TYPE I

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**Objectives:** Mucopolysaccharidosis type I (MPSI) is a lysosomal storage disease caused by a mutation in the *IDUA* gene that results in progressive multi-system disease. MPSI can be separated into two phenotypes: MPSIH (for MPSI Hurler), which is the most severe phenotype and treated with hematopoietic cell transplantation, and MPSIA (for MPSI attenuated), a "milder" clinical phenotype that is treated with enzyme replacement therapy alone. Both treatments are most effective if initiated prior to the onset of clinical signs of disease. As the era of newborn screening for MPSI begins, so does the promise of early diagnosis and treatment. However, current diagnostics cannot predict which of the two profoundly different MPSI phenotypes will manifest, and thus cannot adequately guide treatments. Thus

we aimed to identify a biochemical signature that distinguishes MPSIH from MPSIA.

**Methods:** Metabolomics analysis was performed on 25 samples from treated patients with MPS I (17 MPSIH; 8 MPSIA). Welch's two-sample *t*-test was used to identify metabolites that differed significantly between groups and an estimate of the false discovery rate (*q*-value) was calculated. Random forest analysis ranked metabolites for their ability to separate groups. Finally a sparse partial least squares discriminant analysis was performed to determine the combination of metabolites that would best predict MPSIH.

**Results:** 125 metabolites were different and generally increased in treated MPSIH versus MPSIA (*p*<0.05); 14 of those metabolites also had a *q*-value<0.05. Random forest analysis identified methionine sulfone, 1-palmitoyl-2-linoleoyl-GPI (16:0/18:2), N-acetylhistidine, 1-methylimidazoleacetate, and cysteine to be the 5 most discriminative metabolites. A single principal component based on two metabolites (1-palmitoyl-2-linoleoyl-GPI and methionine sulfone) achieved 100% discrimination of the two disease types in our sample set.

**Conclusions:** We have identified 14 plasma metabolites that effectively distinguish MPSIH from MPSIA after adjustment for multiple comparisons. Of these, the combination of two biomarkers distinguished MPSIH from MPSIA in our cohort of treated MPSI patients. These findings establish a starting point for evaluating a biomarker-based diagnostic tool to predict phenotype in newborns diagnosed with MPSI.

FC8

#### MIRAGE SYNDROME: ADDITIONAL CASES WITH *SAMD9* MUTATIONS, CLINICAL AND BIOLOGICAL CHARACTERIZATION

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**Objectives:** The new MIRAGE (Myelodysplasia, Infection, Restriction of growth, Adrenal hypoplasia, Genital phenotypes, and Enteropathy) syndrome, described in 2015, is due to *de novo* heterozygotes mutations in *SAMD9* gene. Our objective was to screen the patients of

our cohort with intrauterine growth restriction, adrenal insufficiency and / or disorder of sex differentiation (DSD) and to characterize the adrenal and DSD phenotype.

**Methods:** *SAMD9* Sanger sequencing for 20 patients (20 families)

**Results:** Mutations were found for 8 patients. 3 had the previous described mutations by Narumi *et al*: p.Arg459Gln, p.Glu974Lys. The other mutations were: p.Arg685Gln, p.Thr778Ile, p.Arg982His (2 patients), p.Ser1074Ile. Those mutations have never been reported in databases. They all had MIRAGE syndrome with additional or missing symptoms. All patients had intrauterine growth restriction (IUGR) and born pre-term. They had recurrent invasive infections. All the patients had a 46,XY DSD but with a variable degree of masculinisation. Nevertheless only one was reared as a boy. No müllerian residue has been detected but AMH was always low when available. Gonads were ectopic and testosterone low in most cases. Adrenal insufficiency was revealed rapidly at birth associated with high ACTH and low steroids, except D4 androstenedione and 11-desoxycortisol which could be normal or high, suggesting an impairment of CYP450 type II involved in the steroidogenesis. Additionally, 2 had hypoplastic kidney, 6 had respiratory distress. 1 died in utero, 4 died before 3 months of life, 2 at 1 year old but interestingly one patient is still alive and actually 14 years old. This patient has a particular phenotype without adrenal insufficiency but with thrombocytopenia and necrotizing enterocolitis at birth.

**Conclusions:** As MIRAGE syndrome may be incomplete, sequencing of *SAMD9* gene should be done with the association of IUGR, adrenal insufficiency and/or 46, XY DSD and polymalformative syndrome. Those additional and future cases, with hormonal assays (steroids, AMH, gonadotrophins), are very interesting for a better understanding of the role of this gene on adrenal and gonadal development.

FC9

#### SHOULD 45,X/46,XY BOYS WITHOUT DSD BE EVALUATED? RETROSPECTIVE LONGITUDINAL STUDY OF GROWTH, PUBERTY AND PHENOTYPIC FEATURES OF 34 PATIENTS.

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**Objectives:** Few studies of patients with a 45,X/46,XY mosaicism, have considered those with normal male phenotype, while they represent ~90% of the patients born with this karyotype. The purpose of this study was to evaluate the clinical outcome of 45,X/46,XY boys born with normal or minor abnormalities of external genitalia (unilateral cryptorchidism or glandular hypospadias), in terms of growth, puberty and other phenotypic characteristics.

**Methods:** We present a retrospective longitudinal study of 34 patients followed between 1982 and 2016 in 13 French reference centers for pediatric endocrinology.

**Results:** Twenty patients had a prenatal diagnosis whereas 14 patients had a postnatal diagnosis, mainly for short stature. Most patients had stunted growth, decreasing during puberty with a mean adult height of 156 +/- 6 cm, i.e. -2.3DS with correction for target height. Seventy percent of patients presented with Turner syndrome features including 5 patients with cardiac anomalies (comprising 2 bicuspid aortic valves and 1 aortic dilation) and 3 patients with renal malformations. Nineteen patients had minor abnormalities of external genitalia, and one patient developed a testicular embryonic carcinoma, underlining evidence of some level of gonadal dysgenesis in these patients. Puberty occurred spontaneously in most cases but 56% of patients evaluated at the end of puberty presented signs of declined Sertoli testicular function (increased level of FSH and low level of inhibin B).

**Conclusions:** Despite a clear selection bias, this study emphasizes the need to follow, up to adulthood, 45,X/46,XY patients born with a normal male phenotype, which present similar prognosis to those born with a difference in sex development. Screening for cardiac and renal malformations, and regular testicular examination appear to be indicated in all these patients, as well as monitoring of growth and testicular function during puberty. Currently, most of these patients are diagnosed in adulthood with infertility and azoospermia, which is consistent with our observations of decreased testicular function at the end of the puberty. Early management may lead to fertility preservation strategies in these patients.

FC10

#### CLINICAL AND MOLECULAR ANALYSIS OF PUBERTAL CONTROL IN A COHORT OF SILVER-RUSSELL AND TEMPLE SYNDROMES PATIENTS

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**Objectives:** Epigenetic marks have been related to pubertal timing. Central precocious puberty (CPP) can be caused by *MKRN3* mutations, and the loci *DLK1-GTL2*, *MKRN3-MAGEL2* and *KCNK9* have shown parent-of-origin-specific associations for age at menarche. Silver-Russell syndrome (SRS) and Temple syndrome (TS) are imprinting disorders (ID) with an overlap in clinical features, in which early puberty is frequent. Some patients with ID can present with multilocus methylation defects. The aim of this study is to analyse the pubertal timing in a cohort of SRS and TS, and to look for a correlation with the methylation status of *DLK1-GTL2*, *MKRN3-MAGEL2* and *KCNK9* imprinted loci.

**Methods:** We retrospectively analysed 153 SRS (119 11p15 loss of methylation (LOM) and 34 mUPD7) and 19 TS (14 *DLK1/GTL2* LOM and 5 mUPD14) patients collecting clinical data, sexual steroids levels and baseline IGF-1 levels (prepubertal period without rhGH). We performed Allele-Specific Methylated Multiplex Real-Time Quantitative PCR with leukocyte DNA from all patients, analysing separately the methylation index (MI) of *DLK1-GTL2*, *MKRN3-MAGEL2* and *KCNK9* loci. For comparison, patients were grouped as 11p15 LOM, mUPD7 and chr14 anomalies.

**Results:** The mean ages of CP onset in boys were 10.4y in 11p15 LOM; 9.4y in mUPD7; and 9.6y in chr14 anomalies ( $p=0.01$ ). In girls, they were respectively 9.8y; 8.2y; and 7.6y ( $p=0.0002$ ). The frequencies of CCP were 71% in chr14, 50% in chr7 and 15% in 11p15 anomalies ( $p<0.0001$ ). 11p15 LOM group presented the highest baseline IGF-1 (mean 1.0 SDS;  $p=0.03$ ). We found hypomethylation in *DLK1* locus in three 11p15 LOM patients; one of them had a history of CPP. For all patients, there were no differences between MI from patients with or without CPP for the three loci (*MKRN3*  $p=0.3$ ; *KCNK9*  $p=0.8$ ; *DLK1*  $p=0.7$ ).

**Conclusions:** Central precocious puberty is common among TS patients, as well as among SRS patients, particularly among those with mUPD7. The age of CP onset may be earlier in mUPD7 and TS children than in general population. There were no leukocytes methylation defects in the loci *MKRN3-MAGEL2* and *KCNK9* related to CPP in the cohort of SRS and TS, while one 11p15 LOM patient with CPP also had *DLK1* LOM.

## Free Communication Session, Friday, September 15, 2017, 7:30-8:30am

### Bone and mineral metabolism #1 FC11 – FC15

FC11

#### BONE MINERAL DENSITY AFTER CESSATION OF GH TREATMENT IN YOUNG ADULTS BORN SGA: A 5-YEAR LONGITUDINAL STUDY

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**Objectives:** Short children born small for gestational age (SGA) have a bone mineral density (BMD) below average. Growth hormone (GH) treatment improves height and BMD in short SGA children. Longitudinal data on BMD in adults born SGA, after GH cessation, are lacking. The objective of this study was to determine BMD in young adults born SGA until 5 years after GH cessation.

**Methods:** In 173 GH-treated adults born SGA (SGA-GH), BMD of total body (BMD<sub>TB</sub>) and bone mineral apparent density of lumbar spine (BMAD<sub>LS</sub>) were measured longitudinally at adult height (GH-stop), and 6 months, 2 years and 5 years thereafter. At 5 years after GH-stop (mean age 21 years), data were compared with 45 untreated short SGA adults (SGA-S), 59 SGA adults with spontaneous catch-up (SGA-CU), and 81 adults born appropriate for gestational age (AGA).

**Results:** At GH-stop (mean age 16.4yrs), estimated mean (SE) BMD<sub>TB</sub> SDS was -0.40 (0.1) in males and -0.51 (0.1) in females followed by a trend towards a decrease of BMD<sub>TB</sub> in males to -0.59 (0.1) at 5yrs after GH-stop ( $p=0.06$ ), while it remained stable in females (-0.57 (0.1),  $p=0.33$ ). At GH-stop, BMAD<sub>LS</sub> SDS was -0.01 (0.1) in males and -0.29 (0.1) in females, followed by a decrease in males and females to -0.38 and -0.55 at 5 years after GH-stop, resp. ( $p<0.001$ ). At 5 years after GH-stop, BMD<sub>TB</sub> and BMAD<sub>LS</sub> in SGA-GH were similar compared to SGA-S, SGA-CU and AGA.

**Conclusions:** After cessation of GH treatment, there is a gradual decline of BMAD<sub>LS</sub>, but at the age of 21 years, BMD<sub>TB</sub> and BMAD<sub>LS</sub> are similar as in untreated short SGA adults.

FC12

#### ESTABLISHMENT OF A HUMAN GROWTH PLATE MODEL WITH IPS CELL-DERIVED CARTILAGE

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**Objectives:** Endochondral ossification (EO) in growth plate cartilage (GPC) plays a crucial role in the determination of the

length and shape of long bones. Many skeletal dysplasias cause growth plate dysfunction, resulting in short stature. While biology of GPC in mice is well studied, little is known about the process of EO in humans. We previously reported that human iPS cell-derived cartilage (hiPSC-Cart), when implanted into the subcutaneous spaces of SCID mice for one year, formed skeletal tissue which is composed of epiphyseal cartilage- and diaphyseal bone-like tissues containing GPC-like structure. The aim of the present study is to investigate whether this human iPS cell-derived GPC (hiPSC-GPC) could model the abnormalities of GPC of FGFR3-related diseases.

**Methods:** We used 4 hiPSC lines derived from healthy control and patients with FGFR3-related diseases (thanatophoric dysplasia, achondroplasia and hypochondroplasia). hiPSC-Carts were transplanted into the subcutaneous space of SCID mice of various ages, and their ossification was analyzed with X-ray images over time and EO process was evaluated histologically.

**Results:** Histological analysis showed that control hiPSC-GPC had a zonal arrangement similar to GPC and is associated with bone formation, and each zone expressed marker gene such as indian hedgehog or type X collagen. The EO process in hiPSC-GPC was accelerated when hiPSC-Carts were transplanted in younger mice. When transplanted into 4 weeks-old mice, GPC-like structures were formed 4 weeks later. Cells in cartilage expressed human vimentin, but cells in bone-like structure did not. These results suggest that EO of hiPSC-GPC depends on interaction between the donor cells and host. We observed specific patterns in the hiPSC-GPC generated from patient-specific hiPSC. The patient-specific hiPSC-GPC showed shorter hypertrophic zone and smaller hypertrophic cells than those in control samples. In addition, these changes correlated with the severity of the diseases. By using patient specific hiPSC-GPC as a model, we are searching for candidates that will be useful for the treatment of patients with FGFR3-related diseases.

**Conclusions:** We have established an *in vivo* hiPSC-GPC model. The model should contribute to the investigation of human growth plate biology and pathology.

FC13

#### SYMPTOMATIC VITAMIN D DEFICIENT RICKETS IN MANITOBA - JUST THE TIP OF THE ICEBERG

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**Objectives:** Despite preventative strategies, vitamin D deficient rickets remains a current problem. A recent study in the province of Quebec found a sharp increase, culminating in an annual incidence of 7.9 per 100,000 live births; this was three-times an earlier national survey. Importantly, the true incidence of nutritional rickets is likely underestimated by surveys based on clinical symptoms. The primary objective of this study is to determine the annual incidence of rickets in Manitoba using multiple datasets, including comprehensive laboratory reports of 25-hydroxyvitamin D (25(OH)D) levels.

Secondarily, we are interested in the clinical phenotypes at presentation.

**Methods:** This is a retrospective chart review to determine cases of rickets in our catchment area (Manitoba, NW Ontario and W. Nunavut) from 2003 – 2015. Data sources included endocrine and hospital charts using ICD-9 and -10 codes, hospital radiology reports, and reviews of all laboratory 25(OH)D tests from 2011-2015. For the laboratory assessment, 25(OH)D <30 nmol/L paired with an elevated PTH or alkaline phosphatase prompted a chart review in children <7y of age. We excluded children who were premature or who had other forms of rickets.

**Results:** We identified 123 cases; 13% presented with hypocalcemic seizures, 17% with bony deformities, and 70% were incidental findings. This gave an annual incidence of 35.3 per 100,000 infants and 15.8 per 100,000 children aged 1-7y. No increase in incidence was noted over the study time. Most children were from northern or rural locales; about 50% were of self-declared First Nations' heritage. The majority of children were from families with high material deprivation using area-based socio-economic measures.

**Conclusions:** Our rates of rickets are much higher than previously reported, in part due to our ability to evaluate comprehensive laboratory data. Nutritional vitamin D deficient rickets remains a problem in our catchment area, especially within certain high-risk groups. Strong preventative strategies are essential. Besides providing supplements of a convenient infant vitamin D formulation in drop form at birth for all infants, other methods are clearly needed to improve childhood and maternal vitamin D status.

FC14

#### KRN23 EFFECTS ON PHOSPHATE AND VITAMIN D METABOLISM IN CHILDREN <5 YEARS OLD WITH X-LINKED HYPOPHOSPHATEMIA (XLH)

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**Objectives:** In pediatric XLH, renal phosphate (Pi) wasting due to increased circulating fibroblast growth factor 23 (FGF23) leads to hypophosphatemia, rickets, and skeletal deformities. KRN23, an investigational human monoclonal antibody, binds FGF23 and inhibits its action. Interim results of our Phase 2 study of KRN23 in XLH children (ages 5-12 yrs) showed improvements in serum Pi and rickets. In a new Phase 2 trial we evaluate the efficacy and safety of KRN23 in younger children with XLH.

**Methods:** In an ongoing, open-label, multicenter trial, children 1-4 yrs old with XLH received KRN23 at an initial dose of 0.8 mg/kg subcutaneously every 2 weeks. We evaluated



safety, serum Pi, alkaline phosphatase (ALP), 1,25(OH)<sub>2</sub>D, and KRN23 levels. We report here baseline (BL) data for the first 10 children enrolled, and up to 4 weeks of treatment data for the first 5 children.

**Results:** At BL (N=10), the mean age was 3.0 yrs and 70% were boys. The median standing height percentile was 9.1%. Complications of XLH included gait disturbance (60%), tibial torsion (60%), knee deformity (40%), and misshapen skull (40%). Significant radiographic evidence of rickets was present despite all subjects having received prior conventional therapy for a mean of 19.2 months. All had low serum Pi levels (mean (SE) = 0.83 (0.025) mmol/L) (normal: 1.03 - 1.97) and ALP was elevated in 8 of 10 children. Mean serum Pi level increased during KRN23 treatment by +0.41 (0.030) mmol/L at Week 1, and by +0.36 (0.070) mmol/L at Week 4. Normal serum Pi levels were achieved in 100% and 80% of children at Weeks 1 and 4, respectively. Mean (SE) serum 1,25(OH)<sub>2</sub>D levels increased from 118 (17) pmol/L at BL to 256 (38) pmol/L at Week 1 (normal: 60-220). Serum KRN23 concentrations at Weeks 1 and 4 resembled values observed in the Phase 2 study in older children. All adverse events (AEs) were mild, and except for upper respiratory tract infections (n=2); all other AEs occurred in 1 subject each. No serious AEs were reported.

**Conclusions:** Initial results in 1-4 yr-old children with XLH suggest that pharmacodynamic responses to KRN23 are similar to those of older children. The ongoing study will evaluate changes in rickets severity and growth.

FC15

**INHALED BETA-AGONISTS AND BONE MASS IN CHILDREN AND ADOLESCENTS**

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**Objectives:** Mounting evidence indicates the sympathetic nervous system (SNS) plays a critical role in bone remodeling. Murine studies reveal activation of the SNS leads to bone loss through norepinephrine stimulated beta (β)-adrenergic signaling and epidemiologic data in humans show use of beta-blockers is associated with higher bone mineral density (BMD) and reduced fractures. Stimulant medications, which increase β-adrenergic signaling, are also associated with lower bone mass and reduced turnover in children. While systemic β-agonist modulation of the SNS yields skeletal effects, the role of inhaled β-agonists on bone is unclear. Inhaled β-agonists are widely used to treat acute and chronic symptoms of asthma. Existing literature on inhaled β-agonists reveals conflicting results in adults and the pediatric data is sparse. As childhood is a critical period for bone accrual, it is important to assess effects of inhaled β-agonists on bone mass in this population. This study investigates associations

between inhaled β-agonist use and bone mass in pediatric subjects.

**Methods:** Cross-sectional analysis of data from the 2005–2010 National Health and Nutrition Examination Study (NHANES). 6489 participants ages 8–20 years (mean 13.58±3.58) were analyzed. Outcome measures were total femur, femoral neck and lumbar spine bone mineral content (BMC) and density (BMD) assessed via dual-energy X-ray absorptiometry (DXA).

**Results:** 303 of 6489 subjects used inhaled β-agonists and 81 subjects used combination inhaled β-agonist and corticosteroid (ICS). After multivariable adjustment, there were no significant differences in BMD or BMC in the β-agonist-treated group versus controls at any anatomic site. Combination β-agonist/ICS users had significantly lower total femur BMC than non-users (33.93±0.17 vs 31.79±1.07, p=0.05). No other significant differences were noted.

**Conclusions:** Pediatric subjects using inhaled β-agonists had similar DXA measurements compared to non-users. Use of combination β-agonist/ICS was associated with significantly lower total femur BMC. This suggests that skeletal effects of inhaled β-agonists may be trivial. Additional studies in children using combination β-agonist/ICS are needed to assess skeletal effects compared to ICS use alone.

	Overall (n=6489)	Non Beta Agonist Users (n=6186)	Beta Agonist Users (n=303)	P Value Beta Agonist vs. Nonuser	Non Combo Users (n=6408)	Beta Agonist/ Inhaled corticosteroid combo (n=81)	P Value Combo vs. nonuser
Age, years, mean (SD)	13.58±3.58	13.63±3.58	12.63±3.41	<0.0001	13.59±3.58	13.14±3.12	0.20
Gender, n (%)				0.17			0.01
Male	3372 (52)	3203 (52)	169 (56)		3319 (52)	53 (65)	
Female	3117 (48)	2983 (48)	134 (44)		3089 (48)	28 (35)	
Ethnicity, n (%)				0.04			0.00
Non-Hispanic White	1927 (30)	1829 (30)	98 (32)		1889 (29)	38 (47)	
Hispanic	2451 (38)	2360 (38)	91 (30)		2430 (38)	21 (26)	
Black	1747 (27)	1653 (27)	94 (31)		1728 (27)	19 (23)	
Other	364 (6)	344 (6)	20 (7)		361 (6)	3 (4)	
BMI (Kg/m <sup>2</sup> ), mean (SD)	22.50±5.71	22.50±5.70	22.48±6.00	0.96	22.51±5.72	22.18±5.66	0.61
BMI z-score, mean (SD)	0.68±1.12	0.67±1.12	0.78±1.17	0.10	0.68±1.12	0.69±1.16	0.95
Weight z-score, mean (SD)	0.76±1.16	0.75±1.16	0.93±1.22	0.02	0.76±1.16	0.80±1.21	0.77
Height z-score, mean (SD)	0.36±1.13	0.35±1.13	0.53±1.15	0.001	0.36±1.13	0.47±1.19	0.46
Poverty Income Ratio, mean (SD)	2.11±1.54	2.10±1.54	2.14±1.60	0.68	2.10±1.54	2.35±1.74	0.21
Physical Activity, n (%)				0.05			0.07
No	750 (18)	729 (18)	21 (12)		746 (18)		
Yes	3480 (82)	3328 (82)	152 (88)		3432 (82)		
25OH (ng/mL), mean (SD)	20.74±8.59	20.68±8.62	22.16±7.54	0.07	20.70±8.60	24.07±7.18	0.02
Serum Cortisone Level (ng/mL), mean (SD)	11.66±48.42	11.78±48.83	9.01±38.60	0.26	11.71±48.62	7.22±27.10	0.17

Table 1: Baseline Characteristics of the Adolescents Ages 8-20 Years Enrolled in NHANES 2005-2010

**Free Communication Session, Friday, September 15, 2017, 8:45-9:45am**  
**Sex differentiation/gonads and disorders of sex development**  
**FC16 – FC20**

FC16

**MAPPING THE STEROID METABOLOME IN INBORN STEROIDOGENIC DISORDERS: PERFORMANCE OF A NOVEL COMPUTATIONAL APPROACH IN COMPARISON TO CONVENTIONAL GC-MS ANALYSIS.**  
Elizabeth S Baranowski, MBChB, University of Birmingham, Birmingham, N/A, United Kingdom; Kerstin Bunte, PhD, University of Groningen, Groningen, Netherlands; Cedric HL

Shackleton, Professor; Angela E Taylor, PhD; Beverley A Hughes, BS/BA, University of Birmingham, Birmingham, United Kingdom; Michael Biehl, Professor, University of Groningen, Groningen, Netherlands; Peter Tino, Professor, University of Birmingham, Birmingham, United Kingdom; Tulay Guran, MD, Marmara University, Istanbul, Turkey; Wiebke Arlt, Professor, University of Birmingham, Birmingham, United Kingdom

**Objectives:** We developed and applied a novel computational tool to analyse gas chromatography-mass spectrometry (GC-MS) steroid metabolite profiling data that functions irrespective of age and sample type variation and assessed its performance in comparison to established GC-MS analysis utilising steroid substrate/product ratios.

**Methods:** We collected urine (nappy, spot and 24hr) from 829 healthy controls (<1m: n=85; 1-3m: n=89; 3m-1y: n=131; 1-4yr: n=96; 4-10y: n=44; 10-16y: n=24; 16-30y: n=90; 30-50y: n=146; >50y: n=90) and 118 patients with genetically confirmed inborn steroidogenic disorders including CAH due to mutations in 21-hydroxylase, 11 $\beta$ -hydroxylase, 17-hydroxylase deficiency, P450 oxidoreductase and 3 $\beta$ -HSD2, and 46XY DSD due to mutations in 5 $\alpha$ -reductase type 2, 17 $\beta$ -HSD3, and cytochrome b5. We undertook GC-MS analysis for identification and quantitation of 34 individual steroid metabolites, calculated age-specific medians, 5<sup>th</sup>/95<sup>th</sup> centiles and 22 defined steroid ratios conventionally used for diagnosis of these disorders. We then analysed the steroid profiling results employing our newly developed machine learning approach, Angle Learning Vector Quantization (ALVQ). Using vectors created from ratios of metabolites, the model develops prototypes as typical representative fingerprints of a category and an adaptive dissimilarity measure based on angles between vectors. Healthy control projections were visualised to assess for age correlation.

**Results:** Our data showed a high degree of variation in both individual steroid metabolites and the conventionally defined diagnostic steroid ratios over life when looking at centile data, with substantial overlap between distinct disease groups. By contrast, ALVQ correctly categorised healthy control and patient data by distance to projected prototype with 100% sensitivity and 97% specificity, and compensated for missing values and heterogeneity regards age/sex/units/method of collection.

**Conclusions:** The newly developed machine learning-based method provides higher sensitivity and profoundly better specificity in diagnosing inborn steroidogenic disorders than currently applied conventional biochemical analysis, with highly promising potential for implementation in routine clinical practice.

FC17

## MOLECULAR STUDY OF RAS/MAPK PATHWAY GENES IN PATIENTS WITH CRYPTORCHIDISM

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**Objectives:** Cryptorchidism is a frequent finding in patients with RASopathies, which are caused by derangements in Ras/MAPK genes. Our aim was to determine whether patients with only one feature of this condition, such as cryptorchidism, exhibit alterations (mutations or copy number variations) in some genes of the Ras/MAPK pathway.

**Methods:** Two hundred and forty three patients with cryptorchidism were recruited and classified into three study groups, according to their height and presence of a phenotype suggestive of RASopathy. Genomic DNA was extracted for molecular analysis of *PTPN11*, *SOS1*, *KRAS*, *NRAS*, *HRAS*, *RAF1*, *BRAF*, *MAP2K1* and *MAP2K2* genes. Molecular analysis involves: i) screening of mutations through High Resolution Melting (HRM) followed by sequencing and ii) determination of gene copy number variation by comparative genomic hybridization and SNPs array.

**Results:** A total of 193 patients had isolated cryptorchidism (G1), 19 had cryptorchidism, short stature and no other RASopathy feature (G2), and 31 had cryptorchidism, short stature and a phenotype suggestive of RASopathy (G3). Molecular analysis of G1 showed one synonymous substitution (*BRAF\_p.Q456Q*) in two patients; five missense substitutions (*SOS1\_p.R497Q*, *BRAF\_p.W619C*, *BRAF\_p.F595L*, *NRAS\_p.T50I* and *MAP2K2\_p.Y134C*) in six patients, and a ~175 Kb microduplication including *RAF1* in two patients. Group 2 analyses did not show any molecular alteration. Finally, G3 analysis showed five missense substitutions (*PTPN11\_p.E139D*, *PTPN11\_p.F285L*, *PTPN11\_p.T468M*, *SOS1\_p.R552G* and *HRAS\_p.G12S*), which have been previously reported in RASopathy patients. Analysis of the synonymous substitution *BRAF\_p.Q456Q* with software ESEfinder2.0 predicts that it might alter mRNA editing. On the other hand, the missense substitutions found in G1 patients have been associated with Noonan and Cranio-facio-cutaneous syndromes. Finally, a *RAF1* microduplication similar to that found in our patients was described in a patient with testicular aplasia.

**Conclusions:** We report the first molecular study of RASopathies in a cohort of patients with isolated cryptorchidism. Our results suggest that some patients with isolated cryptorchidism may harbour Ras/MAPK pathway gene alterations. (Fondocyt1140450)



## ANDROGEN INSENSITIVITY DUE TO INCREASED METHYLATION IN THE ANDROGEN RECEPTOR PROMOTER

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**Objectives:** Androgen insensitivity syndrome (AIS) is a common cause of 46,XY differences in sex development. Although classically defined as the inability of the androgen receptor (AR) to respond to androgens only 40% of clinically diagnosed AIS cases reveal a partial or complete loss of function mutation in the AR-gene. This leaves a considerable amount of AIS patients without a clear diagnosis and underlines the need of factors outside the AR for proper androgen action.

**Objective:** To investigate, if changes in AR-transcription can explain AIS in the absence of an AR-gene mutation.

**Methods:** Analysis of AR function (APOD-assay) and AR mRNA levels in AR-gene mutation negative cultured genital skin fibroblasts (GF) from individuals with the clinical diagnosis AIS as well as bisulfite-sequencing of the AR-promoter in these GF. In order to define AIS on a functional basis we previously established an assay measuring the transcriptional activity of the AR to induce its target gene Apolipoprotein D (APOD) in GF. The APOD-assay clearly distinguishes AR-activity in GF of male controls from GF of individuals with a mutation in the AR gene ( $p < 0.0001$ ).

**Results:** Applying this assay to GF from clinically diagnosed AIS individuals but no mutation in the AR gene we saw a reduced AR function in about one-third of the cases ( $n=23$ ). This subgroup can be defined as functional AIS in the absence of an AR-gene mutation (AIS type II). Analyzing AR mRNA levels in these 23 GF revealed a reduced AR mRNA expression in 8 cases compared to age and tissue matched controls. Methylation analysis of the AR-promoter in these cases showed a significantly increased methylation at specific, so far not described sites in 5 cases.

**Conclusions:** Using the APOD-assay we were previously able to validate the clinical diagnosis AIS on functional grounds (AIS type II). In search for co-regulators of androgen action in AIS type II we identified a region in the AR promoter necessary for proper AR expression. We postulate that high methylation of this promoter region leads to a reduced AR-transcription and thereby androgen insensitivity in the absence of a mutation in the AR gene.

## 12 MONTH SURGICAL OUTCOMES FOLLOWING GENITOPLASTY IN CHILDREN WITH MODERATE-TO-SEVERE GENITAL ATYPIA

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**Objectives:** There are few prospective studies on short and long-term outcomes following genitoplasty among children with atypical genitalia. Historically, studies report suboptimal outcomes. We report complication rates and cosmetic outcomes as rated by surgeons and parents within one year of a child born with atypical genitalia receiving genitoplasty.

**Methods:** This 10-site, prospective, observational study included children: 2 years of age or younger, with Prader 3-5

or Quigley 3-6 external genitalia, no prior genitoplasty and no other malformations other than urogenital at the time of enrollment. Genital appearance was rated on a 4-point Likert scale. Paired t-tests were used to evaluate differences in mean cosmesis ratings. We examined 12-month outcomes for planned 1-stage repairs on girls, planned 1-stage repairs on boys, and planned 2-stage repairs on boys.

**Results:** Fifty-four percent (15) of children had congenital adrenal hyperplasia, 32% (9) had an unknown diagnosis, 10% (3) had gonadal dysgenesis and 1 patient had partial androgen insensitivity syndrome. Among children who had feminizing genitoplasty (16), vaginoplasty was performed in all, clitoroplasty in 56% (9), external genitoplasty in 75% (12), urethroplasty in 25% (4), perineoplasty in 25% (4) and total urogenital sinus mobilization in 1. Two girls (13%) developed complications: vaginal stenosis and a vaginal mucosal polyp. Twelve children had masculinizing genitoplasty; complications occurred in 25% (1/4) of boys with a planned 1-stage genitoplasty and 50% (4/8) of boys with a planned 2-stage genitoplasty: glans dehiscence, urethral dehiscence, distal fistula, other fistula and urinary tract infection. Cosmesis scores significantly improved from pre-op to 6-month post-op and were similar between 6- and 12-month visits for all raters (Table). There were no significant differences between 6- and 12-month ratings, with all scores "good" or "satisfied."

**Conclusions:** Parents and surgeons were equally satisfied with the cosmetic outcomes 12 months after genitoplasty. Boys who received planned 2-stage genitoplasty procedures had the highest complication rates.

FC20

#### **ANTENATALLY DETERMINED SESQUIZYGOSITY IN GENDER DISCORDANT MONOCHORIONIC DIAMNIOTIC TWINS (46,XX/46,XY):- POSTNATAL CLINICAL AND GONADAL PHENOTYPE.**

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**Objectives:** Sesquizygosity is an exceptional intermediate between mono- and dizygotic twinning.

A spontaneously conceived twin pregnancy had monochorionic, diamniotic placentation from the 6 week ultrasound (US) (confirmed postnatally). From 14 weeks gestation, US showed phenotypic gender discordance in

otherwise structurally normal twins with male (twin A) and female (twin B) phenotypes.

FISH / SNP karyotyping on mid-trimester amniotic fluid showed twin A 50:50 XX/XY and twin B 90:10 XX/XY. Similar ratios were later confirmed in cord tissue.

Genotyping indicated (i) maternally identical, sharing half their paternal genome, hence three-quarter identical or sesquizygotic twins (ii) parthenogenetic activation of the haploid oocyte as the initial step in the aetiology.

**Objective:-**Describe the postnatal clinical and gonadal phenotype.

**Methods:** Postnatal clinical and US assessments; FSH, AMH, Inhibin B levels; gonad biopsies with histopathology, immunohistochemistry and cytogenetics.

**Results:** Postnatal assessments confirmed twin A to be phenotypically male and twin B female with accordant gender of rearing.

The female had granulosa cell compromise suggested by FSH, AMH, Inhibin B at age 4.5 and 16 months. Bilateral intra-abdominal gonad biopsies at age 16 months showed dysgenesis with ovarian type stroma, abnormal primordial follicles and no seminiferous tubules. There were islands of cells, some cystic, with partly cribriform architecture, the largest consistent with gonadoblastoma. On immunohistochemistry, these islands of cells were positive for OCT-4, c-KIT, PLAP and Inhibin B. Ki-67 (proliferation marker) was positive in 2-10% of these cells. Cytogenetics (FISH) identified XY in 2.8-8.5% of cells, but confined to those islands of cells. The gonads were removed (no invasive germ cell tumour).

The male had robust Sertoli cell markers at age 4.5mths. Bilateral intra-scrotal gonad biopsies at 25 months showed normal testes for age (OCT-4, c-KIT negative). Cytogenetics (FISH): 50% and 40% of cells XY in the gonads.

**Conclusions:** This adds to the one prior report<sup>1</sup> in which postnatal genotyping suggested sesquizygotic twins, 46,XX/46,XY but with phenotypic differences and no immunohistochemistry reported.

<sup>1</sup>Souter VL *et al.* Hum Genet (2007) 121:179-185

#### **Free Communication Session, Friday, September 15, 2017, 8:45-9:45am**

##### **Type 2 diabetes and other carbohydrate metabolism**

##### **FC21 – FC25**

FC21

#### **NOVEL METABOLIC PHENOTYPE FROM ACAD 10 DEFICIENCY IN MICE**

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**Objectives:** Acyl-CoA Dehydrogenase Family Member 10 (ACAD10) has conserved acyl-CoA dehydrogenases domain, which catalyzes  $\alpha$ ,  $\beta$ -dehydrogenation reactions, including the first step in mitochondrial fatty acid oxidation (FAO), and intermediary reactions in amino acids catabolism. ACAD10 gene polymorphisms associated with obesity and type 2 diabetes in Pima Indians that could be linked to impaired fatty acid oxidation.

We investigated the function of ACAD10 in glucose homeostasis using *Acad10*<sup>-/-</sup> (KO) mouse model.

**Methods:** Glucose homeostasis and insulin sensitivity were analyzed by glucose and insulin tolerance tests (GTT, ITT) in *Acad10*<sup>-/-</sup> mice and compared to wild type littermate (WT) controls. Gluconeogenesis was evaluated by pyruvate tolerance test (PTT). Unbiased RNA-Seq and Ingenuity Pathway Analysis (IPA) approaches were performed to identify differentially expressed genes in the liver of KO and WT female mice (n=4 each) using Illumina NextSeq 500.

**Results:** *Acad10*<sup>-/-</sup> mice demonstrate profound fasting hypoglycemia (50–89 mg/d L,  $p < 0.03$ ) compared to WT.

However, unlike FAO defects, fasting hypoglycemia is associated with increased ketogenesis. Gluconeogenesis was robust on PTT ( $P < 0.03$ ) in *Acad10*<sup>-/-</sup> mice compared to WT. RNA-Seq data and Ingenuity pathway analysis showed i) higher PEPCK expression (key gluconeogenic enzyme); ii) upregulation of PPAR- $\alpha$  signaling; iii) increased FGF21 expression and iv) higher expression of genes involved in bile acid synthesis and signaling such as *cyp4a11*, *cyp7a1* and *FXR*. All gene changes were validated by RT-PCR. In particular, RT-PCR showed a 10 fold higher expression of *Fgf21* in ACAD 10<sup>-/-</sup> mice.

**Conclusions:** ACAD10 deficiency induces fasting hypoglycemia along with increased gluconeogenesis and ketogenesis. Significant changes in FGF21 and bile acid pathway contribute to the phenotype and indicate a novel metabolic pathway.

FC22

#### IMPACT OF METRELEPTIN ON HEPATOMEGALY IN PEDIATRIC PATIENTS WITH GENERALIZED LIPODYSTROPHY

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**Objectives:** Generalized lipodystrophy (GL) is a rare disease, inherited or acquired, progressive and often life-threatening. The underlying pathogenesis is the irreversible, widespread loss of adipose tissue, leading to low leptin levels and storage of excess calories as triglycerides (TG) in ectopic locations such as the liver. The goal of this study was to examine the effect of leptin replacement (metreleptin, ML) on liver

volume (LV) and key metabolic parameters in pediatric patients with GL.

**Methods:** This is a post hoc analysis of an open-label, prospective study of ML in GL conducted at NIH. LV by MRI, was assessed for all available pediatric patients enrolled from 2000–2008. Normal LV was estimated as 2.5 MN, respectively. Triglycerides, hemoglobin A1c (A1c), AST, and ALT were measured at baseline and after ML treatment.

**Results:** Baseline and follow-up liver volumetric measurements were obtained in 13 patients (age < 18 years, mean  $14 \pm 3$ ) with GL. The majority were female (69%), 69% had congenital GL, 85% had diabetes, and 77% had hypertriglyceridemia. At baseline, all had enlarged liver with a mean  $\pm$  SD LV of  $3459 \pm 1178$  mL, ranging from 1.2–6 times normal. For patients assessed within a year after initiating ML (n=13, mean treatment duration of  $9.4 \pm 3.2$  months), LV decreased by  $25.2 \pm 15.4\%$ . Patients (n=9) with longer exposure ( $46.2 \pm 26.9$  months) appeared to have a larger decrease in LV relative to baseline of  $34.3 \pm 18.1\%$ . Treatment with ML for 1 year resulted in significant reductions in A1c [n=11,  $-2.2 \pm 1.4\%$ ], AST [n=11,  $-56.3 \pm 75.3$  U/L], ALT [n=11,  $-90.5 \pm 128.6$  U/L], and TG [n=9,  $-43.1 \pm 30.8$  mg/dL]. ML was generally well tolerated; gastrointestinal disorders including abdominal pain and pancreatitis were the most commonly reported adverse events. The 2 patients with pancreatitis also reported it in their past medical history.

**Conclusions:** Moderate to severe hepatomegaly, usually due to hepatic TG accumulation, is a common feature in pediatric patients with GL. In addition to its metabolic effects, this post hoc analysis provides additional evidence that ML may have a significant and sustained effect in reducing LV in pediatric patients with GL.

FC23

#### PREVALENCE OF “PREDIABETES” RANGE HEMOGLOBIN A1C IN NORMAL WEIGHT YOUTH FROM THE HEALTHY STUDY

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**Objectives:** Hemoglobin A1c (HbA1c) cutpoints set in adults to diagnose prediabetes and diabetes have been extrapolated to youth. However, little is known about normal variation of HbA1c in youth, particularly during the time of physiologic pubertal insulin resistance. This study is a secondary analysis from the HEALTHY Study to evaluate HbA1c variation in normal weight 6<sup>th</sup> and 8<sup>th</sup> graders.

**Methods:** Study population – Normal weight girls (n=2849) and boys (n=2367) aged 11–15 years from HEALTHY, a randomized trial to assess school-based intervention on

diabetes risk factors in 6<sup>th</sup>-8<sup>th</sup> graders. Descriptive statistics were performed to assess the normal distribution of HbA1c in the whole cohort and by race/ethnicity. Puberty staging was performed by self-assessment.

**Results:** In 6<sup>th</sup> and 8<sup>th</sup> graders, respectively, mean (SD) age (years) was 11.3±0.6 and 13.7±0.6; BMI %ile 50.8±23.9 and 54.2±23.3, and HbA1c (%) 5.11±0.29 and 5.11±0.31. The majority were pubertal (88% and 99.8% of 6<sup>th</sup> and 8<sup>th</sup> graders, respectively). There was significant racial/ethnic variability in the cohort (51.3% Hispanic, 18.9% Black, 20.1% White and 9.6% other). Just under 2% of this normal weight cohort had an HbA1c 5.7%-6.0%. In both boys and girls, HbA1c was significantly higher in Blacks than in Hispanics ( $p<0.0001$ ) and Whites ( $p<0.0001$ ).

**Conclusions:** A small, but clinically meaningful, proportion of normal weight youth have an HbA1c in the prediabetes range, based on adult criteria; thus, caution needs to be taken in interpreting HbA1c when used as a screening tool for diabetes in otherwise healthy youth, particularly in Black youth. Further research is needed to better understand the potential impact of pubertal insulin resistance on glycemic variability in healthy youth.

FC24

#### PREDICTIVE UTILITY OF 10-SNPS GENETIC RISK SCORE FOR PEDIATRIC-ONSET TYPE 2 DIABETES.

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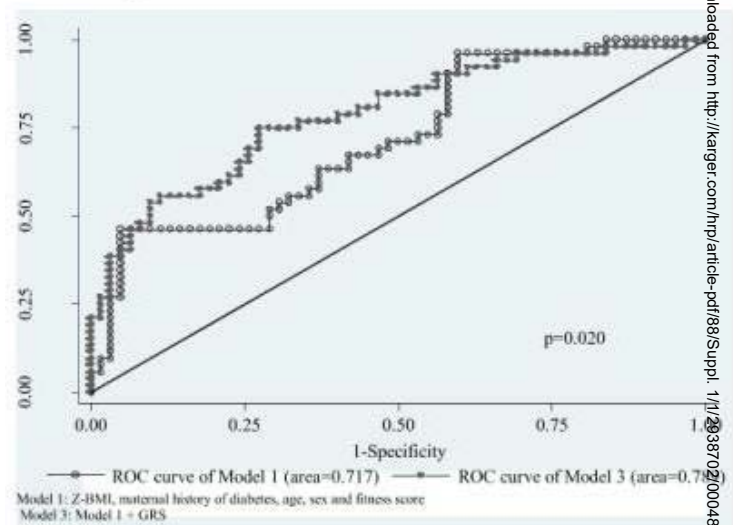
**Objectives:** To evaluate whether a genetic risk score (GRS) could improve pediatric-onset T2D risk prediction in Mexicans.

**Methods:** We performed a case-control study. A total of 97 individuals with pediatric-onset T2D and 84 controls less than 19 years without T2D (population controls) were included. We obtained information about family history of T2D, demographic, anthropometric, biochemical, lifestyle information and fitness score. We also genotyped 10 single nucleotide polymorphisms (SNPs) previously associated with T2D in Mexican children and adolescents (*ADORA1/rs903361*, *CADM2/rs13078807*, *GNPDA2/rs10938397*, *POC5/rs2112347*, *VEGFA/rs6905288*, *RPS10/rs206936*, *GLIS3/rs7034200*, *LINGO/rs10968576*, *FTO/rs9939609* and *SLC16A11/rs13342232*). Allele frequencies and genotype distributions were analyzed. The genetic risk score (GRS) was constructed by summing the 10 risk alleles. A logistic regression analysis, adjusted for age, sex and maternal history of diabetes and Z score of body mass index (Z-BMI) was performed to evaluate the probability of presenting T2D in a first model. A second model was evaluated by adding the GRS. The areas under the curve (AUC) were calculated to assess the discriminatory ability of each model.

**Results:** The Z-BMI was found to be an independent environmental factor associated with pediatric-onset T2D (OR=1.7;  $p=0.004$ ), as well as maternal history of T2D (OR=6.4;  $p<0.001$ ). We didn't observe association with another environment factors. The patients with T2D have higher risk alleles in relation to controls. The GRS showed also a significant association (OR=1.2;  $p=0.008$ ). The AUC of the full model, which combined, age, sex, Z-BMI, maternal history of diabetes and GRS was significantly bigger than the model without this last variable (0.71 vs 0.78 respectively,  $p=0.020$ ) (Figure 1).

**Conclusions:** A GRS based on these 10-SNPs is associated with pediatric-onset T2D in Mexicans. The GRS in conjunction with non-genetic risk factors significantly improves the prediction of pediatric-onset T2D.

Figure 1. Area under curve for the genetic risk score and common risk factors for Type 2 Diabetes Risk prediction.



FC25

#### TRENDS IN GLYCEMIC MEDICATIONS AND CONTROL IN YOUTHS WITH TYPE 2 DIABETES (T2D): THE SEARCH FOR DIABETES IN YOUTH STUDY

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**Objectives:** To assess temporal changes in pharmacologic treatment of T2D youths.

**Methods:** Using data from the US SEARCH for Diabetes in Youth Study, we conducted 1) a cross-sectional comparison of medication use for 646 incident T2D cases (age 15.4 [±2.7] years, 62% female, 18.9% Non-Hispanic white) who completed a SEARCH baseline visit in two periods (2002-2005

vs. 2008 and 2012), and 2) a longitudinal analysis for a subset of 322 participants who also had a follow up visit on average after 7.1±2.1 years. For the cross-sectional analyses, data are presented as 2002-2005 vs. 2008 and 2012.

**Results:** The majority of incident cases in each period received metformin (64.9% vs. 70.4% and/or insulin (38.1% vs. 38.4%), while fewer were treated with sulfonylurea (5.6% to 3.6%), with non-significant changes over time. There was a significant reduction in thiazolidinedione (TZD) use (5.0% vs. 2.0%,  $p<0.05$ ).

At baseline, participants on metformin monotherapy had a lower unadjusted A1C ( $6.4\pm1.4\%$ ) compared to those on insulin monotherapy ( $8.4\pm2.2\%$ ,  $p<0.0001$ ) or insulin plus an oral diabetes medication (ODM) ( $7.7\pm2.2\%$ ,  $p<0.0001$ ).

Among participants on metformin monotherapy at baseline ( $n=138$ ), only 29.7% reported metformin monotherapy at follow up, with the remainder either adding (19.6%) or switching (8.0% to insulin, another ODM (15.9%), or not on any medication (26.8%). Of those receiving insulin ( $\pm$ ODM) at baseline ( $n=129$ ), 76% were continuing on insulin ( $\pm$ ODM) at follow up.

Overall, 35% of the 322 patients in the longitudinal follow up analyses were at an A1C goals of  $<7.0\%$  at the follow up visit: 44.1% of patients on metformin monotherapy at baseline, 20.6% of those on insulin ( $\pm$ ODM) at baseline, and 64.5% of those with no reported medication use at baseline had an A1C  $<7.0\%$  at the follow up visit.

**Conclusions:** Despite the growing number of medications available for T2D adults, youths with T2D are still largely being treated with metformin and/or insulin, which are the only medications approved for pediatric use in the US, with a recent decline in TZD use as seen in adults. A majority of the youths with T2D receiving treatment for an average of 7 years were not at the A1A-recommended A1C goal.

## Free Communication Session, Friday, September 15, 2017, 8:45-9:45am

### Global health

#### FC26 – FC30

FC26

#### EVALUATION OF THE EFFECTIVENESS OF A PEDIATRIC ENDOCRINOLOGY EDUCATION PROGRAM FOR HAITI (PEEP-H): A PRELIMINARY REPORT

Renault Louis, MD, Hôpital Universitaire de Mirebalais, Mirebalais, Haiti; Daphné Cloutier, MD; Marie-Ève Robinson, MD, McGill University Health Centre, Montréal, QC, Canada; Dearthlie Benardeau, MD; Clorène Cadet, MD, Hôpital Universitaire de Mirebalais, Mirebalais, Haiti; Renée Alcée, MD; Steeven Joseph, MD, NPH Haiti Saint Damien Pediatric Hospital, Port-au-Prince, Haiti; Guy Van Vliet, MD, Centre Hospitalier Universitaire Sainte-Justine, Montréal, QC, Canada; Julia Von Oettingen, MD, McGill University Health Centre, Montréal, QC, Haiti

**Objectives:** To evaluate the effectiveness of a pediatric endocrinology education program in a low-resource setting on its participants' knowledge and skills in general pediatric endocrinology.

**Methods:** The Pediatric Endocrinology Education Program for Haiti (PEEP-H), supported by the Pediatric Endocrine Society (PES) and the European Society for Pediatric Endocrinology (ESPE), was developed with the objective to establish pediatric endocrinology training in Haiti. A two-year curriculum is taught during bi-monthly onsite training visits by a rotating body of francophone pediatric endocrinologists. Monthly teleconferences, e-learning and a remote consultation platform supplement the training. Using a prospective cohort study design, we collected participants' demographic information, and evaluated the impact of PEEP-H by means of pre/post training examinations, and quantitative and qualitative evaluation.

**Results:** Six onsite visits were held for 52 trainees between March 2016 and February 2017. Residents were in their first, second and third year of training or were pediatricians in 17, 48, 29 and 7%, respectively. Ninety percent had completed medical school in Haiti and only 7% had previously participated in a pediatric endocrinology rotation. More than 60% evaluated their knowledge in 8 different areas of pediatric endocrinology as insufficient or fair: On a scale of 1 (insufficient) to 5 (excellent), the mean rating was  $1.8\pm0.8$ . Mean examination scores ranged between 37-45% before and 62-65% after onsite training, with mean percentage increments ranging from 17 to 28%. Forty Haitian trainees and 14 pediatric endocrinologists from three different countries registered on the consultation platform. Thirteen cases were discussed, and 157 messages were exchanged. Trainees positively evaluated training and consultation interactions.

**Conclusions:** Pediatric residents in Haiti subjectively and objectively have insufficient pediatric endocrine knowledge. Knowledge level improves following PEEP-H training, and trainees see benefit in the training modules offered. While interim results are encouraging, long-term evaluation is needed to assess the program's value and potential as a subspecialty training model for additional specialties and other resource-limited settings.

FC27

#### EARLY LIFE STRESS INDUCES TYPE 2 DIABETES AT ADULTHOOD IN MALE MICE

Hanna Ilchmann, MS/MA; Maiwenn Olier, PhD; Corinne Lencina, research technician; Sandrine Ellero-Simatos, PhD; Michèle Nankap, MS/MA; Ambre Riba, PhD; Caroline Sommer, research technician; Hervé Guillou, PhD; Laurence Guzylack-Piriou, PhD; Vassilia Théodorou, PhD; Sandrine Ménard, PhD, INRA, Toulouse, France

**Objectives:** The incidence of metabolic disorders is increasing worldwide. Besides diet and life style habits, epidemiological studies highlighted an association between post-traumatic stress and metabolic disorders. Based on the concept of Developmental Origins of Health and Diseases our study

aimed to investigate whether early life stress can trigger metabolic disorders and associated key features i.e. low-grade inflammation and microbiota dysbiosis.

**Methods:** Maternal separation (MS) is an established model of early life stress in rodent. C3H/HeN mice pups were separated from their dam and the rest of the litter 3 hours per day during 10 days starting at post-natal day 2 (PND2). All experiments were carried out in male offspring aged of PND350 on standard diet. Metabolic state was evaluated by oral glucose tolerance test (OGTT) and intraperitoneal insulin tolerance test (ITT). Cellular immune response was analyzed by primary cell culture of spleen, *lamina propria* and mesenteric lymph nodes. Plasmatic and fecal Ig concentrations were measured by ELISA. Fecal microbiota composition was analyzed by GUT Low-Density Array (GULDA).

**Results:** MS had no effect on body weight in male mice but increased fasted blood glycemia. Furthermore, MS induced glucose intolerance, measurable during OGTT. Blood glucose was higher at 15 min and 30 min in MS mice after oral administration of glucose. During ITT, blood glucose in MS mice diminished slower resulting in an increase of the area under the curve (blood glucose mg/dL/30min). MS did not affect cellular immune response. However, MS decreased IgG concentrations in plasma and feces without modification of IgA concentrations. Finally, MS induced fecal dysbiosis favoring pathobionts (*Bacteroides vulgatus*, *Enterobacteriaceae*, *Escherichia coli*, *Enterococcus spp*).

**Conclusions:** We demonstrated for the first time that early life stress induces glucose intolerance associated with a loss of insulin sensitivity in mice non-genetically predisposed to metabolic disorders and fed with standard diet. Interestingly, glucose intolerance is not associated with local or systemic low-grade inflammation but is associated with a decrease of humoral (IgG) response. Furthermore, MS induces a fecal dysbiosis favoring pathobionts.

FC28

## SEXUAL DIMORPHISM OF SIZE: ONTOGENY AND LIFE HISTORY

Alina German, MD, Bnei Zion medical Center, Haifa, Israel; Ze'Ev Hochberg, MD, PhD, Technion-Israel Institute of Technology, Haifa, Israel

**Objectives:** Sexual dimorphism in size (stature and weight) is the outcome of boys and girls responding differently to environmental cues, but may also have fitness advantage. It results from the sex-specific interaction between size-related survival and size-related obstetric complications and fertility. Our Hypotheses were: 1. Living standard and health affect size dimorphism; 2. Variations in size dimorphism are due to differential responding by boys and girls to environmental cues; 3. Size dimorphism will be greatest where population average height and weight are greatest.

**Methods:** 1. We characterized size dimorphism in the CDC2000 database from age 0-20. 2. We correlated 161 countries' a-gross domestic product (GDP per capita), b-life

expectancy (LE), c-population average size with adult M/F ratio in height and weight per country. 3. We correlated M/F ratio in 44 present-day preindustrial societies with average size, LE, total population and density.

**Results:** 1. Size dimorphism appears and disappears at minipuberty and then is gradually established when the boys enter puberty. (Figure) 2. Stature and weight M/F ratio correlate with the LE ( $r=.572^{**}$ ,  $r=.262^{*}$ , resp.) and average M ( $r=.519^{**}$ ,  $r=.523^{**}$ ) and F height ( $r=.183^{*}$ ,  $p=0.019$ ,  $r=.299^{**}$ ), but not with the GDP. 3. In 44 preindustrial societies, size dimorphism correlates positively with average M ( $r=.410^{*}$ ) but not F height, and weight dimorphism correlates with the total population ( $r=-.534^{*}$ ). Density and LE at birth and age 15 did not correlate with size dimorphism.  $*p<.001^{**}p<.0001$ .

**Conclusions:** 1. Minipuberty is associated with adult-type size dimorphism. 2. Size dimorphism is established during puberty. 3. In industrial, but not in preindustrial societies, health, but not living standards, positively correlates with size dimorphism. 4. Female's growth is more resilient to negative health effects. 5. Size dimorphism is greatest where human size is largest (hyperallometry).

FC29

## A STUDY OF THE INCIDENCE OF PERMANENT CONGENITAL HYPOTHYROIDISM BASED ON REEVALUATIONS IN THE NIIGATA PREFECTURE JAPAN

Keisuke Nagasaki, MD, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; Hiromi Nyuuzuki, MD; Sunao Sasaki, MD; Yohei Ogawa, MD, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

**Objectives:** More than 30 years have passed since screening for congenital hypothyroidism (CH) was started in Japan, but the true incidence rate of CH in Japan is not yet apparent. Periodic reevaluation at appropriate times is necessary for patients with positive neonatal mass screening in order to determine the true frequency of CH since transient CH or transient hyperthyroxinemia are included among positive results. We investigated the incidence of permanent CH based on reevaluation and definitive diagnoses for CH mass screening-positive patients in Niigata Prefecture, Japan.

**Methods:** Between April 2002 and March 2006, 106,114 newborns were screened for CH in Niigata Prefecture. A blood TSH cutoff level of 8 mU/L was established. 116 newborns were considered positive for CH and 104 (90%) of those patients were referred to our institution and evaluated. To determine the true incidence of CH, we conducted a retrospective study based on the use of levothyroxine Na (LT4) therapy, the situation at first visit, reevaluation at two to three years of age and definitive diagnosis at five years old or later.

**Results:** Among the 104 patients, 72 (69%) were started on oral levothyroxine therapy for CH at their first visit. Of the remaining 32 patients, nine were started on LT4 therapy by the age of one due to the continuation of slightly high levels



of serum TSH. Therefore, 81 patients (78%) had received LT4 treatment by the age of two. Of these, 51 patients were reevaluated at two to three years of age to assess whether they continued to need levothyroxine. Fourteen patients were able to discontinue LT4 therapy at reevaluation. Five patients have moved away during this period. At the age of five, 62 patients (60%) were receiving LT4 treatment, and of these 56 patients had received definitive diagnoses. Eighteen patients were able to discontinue LT4 therapy, and 44 patients were to continued LT4 therapy.

**Conclusions:** The incidence of permanent CH in Niigata, Japan was from 1:2,000 to 1:2,500. About half of the patients who received LT4 therapy had transient CH or transient hyperthyroxinemia.

FC30

## SECULAR CHANGES OF ADULT HEIGHTS IN THE NORDIC COUNTRIES

Anton Holmgren, MD, University of Gothenburg/Halland Hospital Halmstad, Gothenburg/Halmstad, Sweden; A. Stefan Aronson, MD, PhD, Halland Hospital Halmstad, Halmstad, Sweden; Aimon Niklasson, MD, PhD; Kerstin Albertsson-Wikland, MD, PhD, Sahlgrenska Academy; University of Gothenburg, Gothenburg, Sweden

**Objectives:** To investigate if the secular trend with taller adult heights is still ongoing by comparing data regarding mean adult heights for both sexes from a new Swedish growth cohort with previous data from Sweden and the other Nordic countries.

**Methods:** The results of mean adult heights for females and males from the new Swedish longitudinal growth birth cohort *GrowUpGothenburg1990* (n 1901) was analysed and compared with data from the *GrowUpGothenburg1974* birth cohort (present national growth reference) and the former Swedish national growth reference of individuals born 1956. The results were also compared with information of mean adult heights from previous and present growth references in the other Nordic countries. No corrections have been done for different definitions of adult height or different selections of individuals in the studies.

**Results:** Adult height was greater in the *GrowUp1990* cohort (mean 168.3/181.7 cm, females/males), than in the previous Swedish cohort, born 16 years earlier, with increased adult heights of 4/10 mm for females/males ( $p=0.023/p<0.001$ ). All three Swedish neighbour countries; Denmark, Finland and Norway have presented new growth references based on cross-sectional datasets within the last 6 years, also showing continuous secular trends regarding adult heights for both females and males (Figure; left females, right males). The Swedish females and males were the tallest, with the exception of Danish females (18 mm taller than the Swedish females); females were 11 mm taller in Sweden compared to Norway and Finland (Figure, left). The Swedish males were 13, 7 and 10 mm taller than the males in Denmark, Norway and Finland, respectively (Figure, right).

**Conclusions:** The Nordic countries, having among the tallest populations of the world, are still showing continuous

positive secular trends regarding adult heights for both females and males, demonstrating the need of regularly updated national growth references.

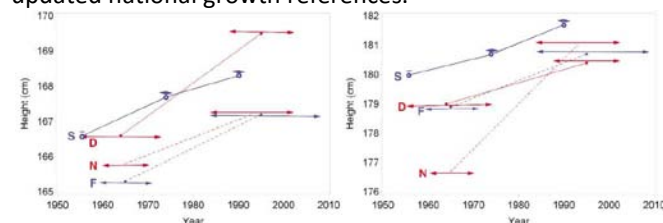


Figure. Adult heights females (left) and males (right) in the Nordic countries. Arrows indicating year of birth. S = Sweden, D = Denmark, N = Norway, F = Finland.

## Free Communication Session, Friday, September 15, 2017, 2:30-3:30pm

### Bone and mineral metabolism #2

#### FC31 – FC35

FC31

## DIFFERENTIAL EFFECTS OF LOW-WEIGHT, AMENORRHEA AND EXERCISE ON BONE MICROARCHITECTURE AND STRENGTH ESTIMATES AT WEIGHT BEARING AND NON-WEIGHT BEARING SITES IN ADOLESCENT GIRLS AND YOUNG ADULTS

Nurgun Kandemir, MD, Hacettepe University, Ankara, Turkey; Karen J Campoverde Reyes, MD; Vibha Singhal, MD; Meghan Slattery, NP; Kathryn Ackerman, MD; Shreya Tulsiani, BS/BA; Hang Lee, PhD; Karen K Miller, MD; Kamryn T Eddy, PhD; Anne Klibanski, MD; Madhusmita Misra, MD, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

**Objectives:** Bone microarchitecture is impaired in low weight amenorrheic girls with anorexia nervosa (AN) compared to controls, and normal-weight oligo-amenorrheic athletes (AA) compared with eumenorrheic athletes (EA) and non-athletes (NA). However, data directly comparing the differential effects of low-weight, amenorrhea, and athletic activity on bone structure are lacking. Our objective was to evaluate effects of low-weight, oligo-amenorrhea, and weight bearing exercise on cortical and trabecular microarchitecture and strength estimates in females with AN, AA, EA and NA at the non-weight bearing radius and weight bearing tibia.

**Methods:** 267 females 14-25 yo were included: 61 AN, 106 AA, 43 EA and 57 NA. All participants underwent HRpQCT of the distal radius and tibia.

**Results:** Groups did not differ for age and height. AN had lower BMI than other groups. **Distal radius:** On extended cortical analysis (ECA), AN had lower total volumetric BMD (vBMD), cortical area (CA) and thickness (CT), and cortical total and bone volume (CTV and CBV) than NA. On individual trabecula segmentation (ITS), AN had lower total trabecular (trab.) bone volume fraction (BV/TV), plate (P), axial and rod (R) BV/TV and R-P junction density than EA. AN and AA had comparably lower trab. plate number density, and P-P junction density than EA. On finite element analysis (FEA), AN had lower stiffness and failure load than EA and NA. **Distal tibia:** On ECA, AN had lower total vBMD, lower CA, CT, CTV

and CBV than EA and NA. Cortical porosity was higher in AN than EA and NA. Both AN and AA had lower cortical vBMD than NA. EA had higher cortical and endocortical perimeter than AN and NA. On ITS, AN had lower trab. vBMD, trab. number and plate BV/TV, and higher trab. separation than AA and EA. EA had higher trab. vBMD than NA. On FEA, AN had lower stiffness and failure load than AA, EA and NA.

**Conclusions:** Athletic activity has a favorable effect on cortical structure of weight bearing bone. Amenorrhea is detrimental to the trabecular compartment of non-weight bearing bone, and cortical density of weight bearing bone (despite weight bearing activity). Low weight and amenorrhea have a strong negative effect on cortical and trabecular morphology and strength at weight bearing and non-weight bearing sites

FC32

#### APPLICATION OF <sup>18</sup>F-NAF PET/CT IMAGING IN FIBROUS DYSPLASIA

*Georgios Z Papadakis, MD, Institute of Computer Science, Crete, Greece; Georgios C Manikis, MS/MA, Institute of Computer Science, Crete, Greece; Apostolos H Karantanas, MD, University of Crete School of Medicine, Crete, Greece; Kostas Marias, PhD, Institute of Computer Science, Crete, Greece; Michael T Collins, MD; Alison M Boyce, MD, National Institutes of Health, Bethesda, MD, United States*

**Objectives:** Fibrous dysplasia (FD) is a mosaic disease in which bone is replaced with fibro-osseous tissue, leading to fractures, disability, & pain. Clinical evaluation is challenging, because there are no surrogate markers to assess disease burden, & no methods to quantify FD lesion activity. <sup>18</sup>F-NaF is a radiopharmaceutical which can target skeletal processes in FD. This study investigates application of <sup>18</sup>F-NaF PET/CT in evaluating FD disease burden & activity.

**Methods:** 16 subjects had <sup>18</sup>F-NaF PET/CT scans (mean 26y, 6-57). PET scans were obtained on dedicated scanners, 58-70 min after injecting <sup>18</sup>F-NaF 2.7-3.3 mCi. Low dose, non-diagnostic CTs were performed for co-registration & to correct attenuation. <sup>18</sup>F-NaF activity was quantified with MIM Vista (v6.5.9). A volume of interest encompassing the skeleton was drawn, & SUVmax (max standardized uptake value) threshold was customized. Areas of unrelated <sup>18</sup>F-NaF activity were manually excluded. The following parameters were obtained: SUVmax, SUVmean, & entire skeleton indices of total volume (TV) of <sup>18</sup>F-NaF avid FD lesions, & total activity (TA) determined as the summation of activity of each FD lesion, calculated as the product of lesion volume and its SUVmean. Spearman's rank & Mann Whitney tests determined associations between <sup>18</sup>F-NaF parameters & clinical endpoints, including fractures, orthopedic & craniofacial procedures, ambulation, & pain.

**Results:** Lifetime & mean fractures per year were strongly correlated with TA & TV of FD involving the total body less head ( $r_s=0.8729$ ,  $ps=0.8296$ ,  $p<0.01$ )( $r_s=0.8721$ ,  $ps=0.8108$ ,  $p<0.01$ ). Strong associations were similarly found with lifetime & mean orthopedic surgeries/year ( $r_s=0.8803$ ,

$ps=0.9055$ ,  $p<0.01$ )( $r_s=0.8774$ ,  $ps=0.8948$ ,  $p<0.01$ ). TA & TV of total body less head FD distinguished subjects with impaired ambulation & pain ( $p<0.05$ ). Skull FD TA & TV were strongly associated with lifetime & mean craniofacial surgeries/year ( $r_s=0.8314$ ,  $ps=0.8548$ ,  $p<0.01$ )( $r_s=0.8348$ ,  $ps=0.86$ ,  $p<0.01$ ).

**Conclusions:** <sup>18</sup>F-NaF PET/CT imaging is of prognostic value in assessing FD. This hybrid (functional/anatomical) technique holds great potential for clinical evaluation & as a surrogate endpoint for trials.

FC33

#### POOR CORRELATION BETWEEN DISCREPANCY OF BONE MINERAL DENSITY Z-SCORES BY DUAL-ENERGY X-RAY ABSORPTIOMETRY AND VERTEBRAL FRACTURES IN CHILDREN

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**Objectives:** Dual-energy X-ray absorptiometry (DXA) remains the most common mode of bone mineral density (BMD) evaluation in adults and children. In adults, the presence of a disproportionately BMD Z-score (>1 SD difference) between adjacent lumbar vertebrae could be an indicator of a vertebral fracture and, therefore, warrant further evaluation of the lateral vertebral morphology. However, in children, the skeleton is still growing and reshaping, introducing developmental aspects as a confounding variable. The study's objective was to correlate the results of a lumbar spine DXA with lateral lumbar spine morphology to elucidate the clinical significance of discrepancies between individual vertebral BMD Z-scores.

**Methods:** A retrospective chart review identified 360 DXA scans performed between 9/01/2014 and 5/01/2016 in patients <18 years of age. DXA scans were cross-referenced against all lumbar spine x-ray and vertebral fracture analysis (VFA) database within the 6 months preceding or following the date of a DXA scan.

**Results:** Out of 360 DXA scans, 52 (14.4%) had both a DXA scan, and either lumbar spine x-ray or DX VFA. Thirty of 52 patients (58%) had a vertebral BMD L1-L4 Z-score >1 SD difference between adjacent vertebrae. None of the patients who had vertebral BMD L1-L4 Z-score >1 SD difference between adjacent vertebrae had lumbar fracture. The most common vertebra with the highest BMD Z-score was L1 (63%), followed by L3 (33%), L2 (3%) and L4 (7%).

**Conclusions:** We concluded that the correlation between the finding of discrepancy >1 SD difference between adjacent vertebral BMD Z-scores by DXA scan and vertebral fracture



was low and likely represented developmental variants in children. Therefore, it does not appear justified to recommend further imaging based solely on the results of a DXA scan without clinically meaningful indications. Due to these variations, it may be more appropriate to use L2-L4 average rather than L1-L4 average for reporting BMD Z-scores in children. VFA may be useful in some cases in children, although the quality of the image is inferior compared to the radiograph, particularly in younger patients.

FC34

## THE RELATIONSHIP BETWEEN ADIPOSITY AND BONE DENSITY IN U.S. CHILDREN AND ADOLESCENTS

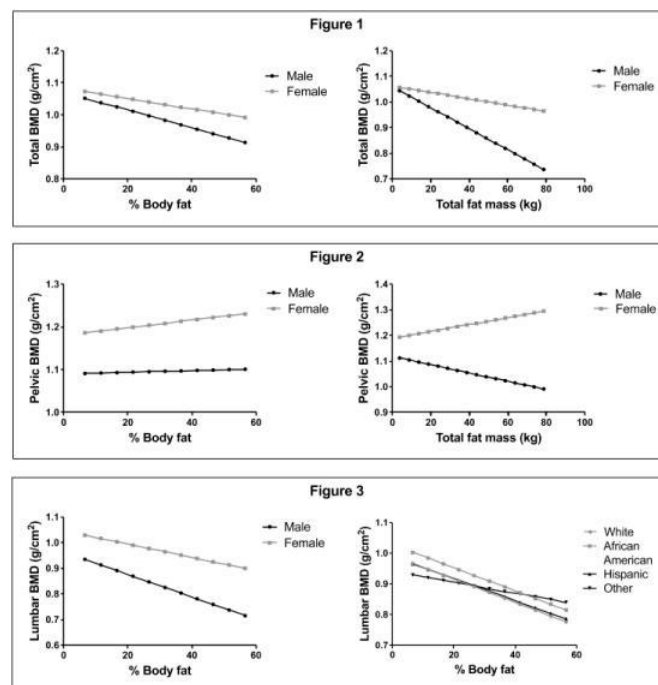
Cecilia Gállego Suárez, MD; Joyce M Lee, MD; Achameyeh Gebremariam, MS/MA; Kanakadurga Singer, MD, University of Michigan, Ann Arbor, MI, United States

**Objectives:** The effects of excess adiposity on bone health are not completely understood. Since childhood and adolescence are critical stages for skeletal mineralization, it is important to understand how body composition during this period may influence bone mineralization and may affect bone health. The objective of this study was to examine associations between percent body fat and total fat mass (in kg) on total, pelvic and lumbar bone mineral density (BMD) in a nationally representative sample of U.S. children and adolescents, and to examine gender and race/ethnicity interactions in these associations. We hypothesized that higher percent body fat would be associated with lower BMD across all regions.

**Methods:** We used data from National Health and Nutrition Examination Survey (NHANES) 1999-2006. A total of 8,348 participants 8-18 years of age had whole body DXA scans performed. We conducted linear regressions to examine the relationship between percent body fat and total fat mass (in kg) with outcome variables of total, pelvic and lumbar BMD, controlling for lean body mass and assessing for gender and race/ethnicity interactions.

**Results:** The average age was 13 years, and 17% and 18.8% of subjects had overweight and obesity, respectively. A higher proportion of African American and Hispanic children were overweight or obese compared with White children. Total BMD decreased with increasing percent body fat and total fat mass (kg) in both genders and all races (figure 1). Pelvic BMD showed a positive trend with increasing percent body fat in both males and females, and with increasing total fat mass (kg) only in females. For pelvic BMD, relationships were mixed for the different races (figure 2). Lumbar BMD decreased with increasing percent body fat in both genders and all races (figure 3).

**Conclusions:** We found significant interactions by gender and race/ethnicity in the relationship of adiposity with total, pelvic and lumbar BMD; finding decreases in total and lumbar BMD with increasing percent body fat and total fat mass (kg), but less consistent patterns for pelvic BMD. Our findings emphasize the need for further investigations to understand the impact of adiposity on bone health outcomes since childhood.



FC35

## CLINICAL AND STRUCTURAL IMPACT OF MUTATIONS AFFECTING THE PLS3 GENE IN PATIENTS WITH BMND18

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**Objectives:** Bone Mineral Density Quantitative Trait Locus 18 (BMND18) is a recently described X-linked disease with early-onset osteoporosis and osteoporotic fractures. This rare hereditary disorder is caused by loss-of-function mutation in the gene encoding the plastin 3 (PLS3), which is a protein involved in actin bundle formation in the cytoskeleton. The aim of this study is to report a case of BMND18 with a novel mutation in PLS3. Moreover, we construct the structure of PLS3 and find the impact of all the reported mutations on the conformation and function of PLS3.

**Methods:** We clarified the patient's genetic sequence through focused-exome sequencing analysis and verified the results via Sanger sequencing. We constructed the structure of PLS3 through homology modeling.

**Results:** We identified a novel nonsense mutation in the PLS3 gene (c.745 G>T) causing truncation of a highly conserved amino acid residue (p.E249X) of plastin 3 in a boy with early-

onset osteoporosis and osteoporotic fractures (**Fig 1.**). This unique mutation affects the integrity of the Actin-binding Domain 1(ABD1) and Actin-binding Domain 2(ABD2) fragments of PLS3, and thereby hinders PLS3 from cross-linking actin filaments into higher-order assemblies like bundles.

This led us to study the molecular impact of all the mutations previously detected in patients on the structure and function of PLS3 protein. By homology modeling, we constructed models of wild type and mutants of PLS3 (**Fig 2.**). Structural analysis of these models showed that the structural integrity is essential for the function of PLS3. More importantly, residues p.239-267, which connect CH1 and CH2 domains of ABD1 fragment, are highly conserved among species (**Fig 3.**) and sensitive to the conformation (**Fig 2.**). Mutations in this critical region will impair the integral conformation of PLS3, and thus affect its function.

**Conclusions:** In summary, we analyzed the impact of mutations affecting the PLS3 gene using a bioinformatics approach, which provides a mechanistic view of their pathogenic effect.

## Free Communication Session, Friday, September 15, 2017, 2:30-3:30pm

### Type 1 diabetes #1

#### FC36 – FC40

FC36

#### CARNOSINE AS AN ADJUVANT THERAPY IN PEDIATRIC PATIENTS WITH DIABETIC NEPHROPATHY: A RANDOMIZED PLACEBO-CONTROLLED TRIAL

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**Objectives:** Oxidative stress is a significant contributor to the pathogenesis of diabetic nephropathy. Carnosine is a natural radical oxygen species scavenger. The aim of this study is to investigate the effect of carnosine as an adjuvant therapy on urinary albumin excretion (UAE), the tubular damage marker alpha 1-microglobulin (A1M), and oxidative stress in pediatric patients with type 1 diabetes and nephropathy.

**Methods:** This randomized placebo-controlled clinical trial included 90 patients with diabetic nephropathy, despite oral angiotensin-converting enzyme inhibitors (ACE-Is), who were randomly assigned to receive either 12 weeks of carnosine 1g/day (n = 45), or matching placebo (n = 45). Both groups were followed-up with assessment of hemoglobin A1c (HbA1c), UAE, A1M, total antioxidant capacity (TAC) and malondialdehyde (MDA).

**Results:** Baseline clinical and laboratory parameters were consistent between carnosine and placebo groups (p>0.05). After 12 weeks, carnosine treatment resulted in significant decrease of HbA1c, UAE, A1M, MDA levels while TAC levels

were increased compared with baseline levels or placebo group (p<0.001). No adverse reactions due to carnosine supplementation were reported. Baseline TAC was inversely correlated to HbA1c and A1M among the carnosine group (p<0.05).

**Conclusions:** Oral supplementation with L-Carnosine for 12 weeks resulted in a significant improvement of oxidative stress, glycemic control and renal function. Thus, carnosine can be a safe and effective strategy for treatment of pediatric patients with diabetic nephropathy.

FC37

#### CONTINUOUS SUBCUTANEOUS INSULIN INFUSION COMPARED TO MULTIPLE DAILY INJECTION REGIMENS IN CHILDREN AND YOUNG PEOPLE AT DIAGNOSIS OF TYPE I DIABETES: A PRAGMATIC RANDOMISED CONTROLLED TRIAL AND ECONOMIC EVALUATION (SCIPI TRIAL)

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**Objectives:** To compare glycaemic control (primary outcome), quality of life (QoL), safety and cost effectiveness of treatment with continuous subcutaneous insulin infusions (CSII) with multiple daily injections (MDI) in pediatric patients newly diagnosed with type I diabetes.

**Methods:** Patients age 7months-15years were randomised to CSII or MDI on a 1:1 ratio, stratified by age and treatment center. All patients had structured education. Randomised treatment started within 14 days of diagnosis. Resource use and clinical data (HbA1c, height, weight, insulin dose, adverse events) were collected at randomisation, 3, 6, 9 and 12 months. QoL was assessed by the Pediatric QoL Inventory, diabetes module, at 6 and 12 months. The Health Utilities Index was completed at all study visits.

Partial remission was defined as Insulin Dose Adjusted A1c <9.

**Results:** 293 patients age 9.8yrs (0.7 - 16) from 15 British diabetes clinics were randomised (CSII:149, MDI:144). Baseline characteristics did not differ between treatment arms (Table 1). Completeness of primary outcome data was 97%

At 12 months, there was no difference in HbA1c: CSII mean (95th CI): 60.9(58.5,63.3), MDI: 58.5 (56.1,60.9), % of patients with HbA1c in target (<48mmol/mol): CSII 15.4, MDI 20.4 relative risk (RR) 0.75 (0.46,1.25), partial remission rates (%):

CSII: 24.4, MDI: 32.8, RR 0.74 (0.45,1.24). Reported insulin dose was higher in the CSII arm: CSII - MDI 0.1unit/kg/day (0.0,0.2) p=0.01. Parents, but not patients, reported superior QoL during CSII treatment: PedsQL score CSII-MDI 4.1 (0.6,7.6) p=0.02. The incidence of severe hypoglycaemia (CSII:6/144, MDI: 2/149) and diabetic ketoacidosis (CSII: 2/144, MDI 0/149) were low. 68 adverse events (14 serious) were reported in the CSII arm, and 24 (8 serious) in the MDI arm. CSII was more expensive: £1,863 (1,620, 2,137), with no additional Quality Adjusted Life Year gains [-0.006 (-0.031,0.0180)].

**Conclusions:** No clinical benefit of CSII over MDI was identified. CSII is not cost effective in patients representative of the study population. The generalisability of our data beyond 12 months is uncertain.

Table 1: Patient characteristics at randomisation

	CSII	MDI	Total
Age at randomisation (yrs)Median (IQR)	9.9 (5.7, 12.2)	9.4 (5.8, 12.5)	9.8 (5.7, 12.3)
Female: N (%)	71 (49.3)	69 (46.3)	140 (47.8)
Asian or Asian British: N (%)	4 (4.2)	7 (6.1)	10 (5.6)
Black or British Black: N (%)	0 (0)	3 (2.1)	3 (1)
British White: N (%)	124 (86.7)	118 (80.8)	242 (83.7)
Mixed: N (%)	4 (2.8)	6 (4.1)	10 (3.5)
Other White: N (%)	9 (6.3)	10 (6.9)	19 (6.0)
Deprivation score*: Median (IQR)	19.4 (8.9, 37.9)	14.7 (7.8, 31.8)	17 (8.4, 35.8)
BMI SDS : Median (IQR)	0.2 (-0.7, 0.9)	0.1 (-0.8, 1)	0.2 (-0.8, 1)
Height SDS: Median (IQR)	0.1 (-0.4, 1.1)	0.4 (-0.3, 1.1)	0.3 (-0.4, 1.1)
HbA1c (mmol/mol): Median (IQR)	105 (87.5, 127.0)	103 (81, 127)	105 (84, 127)
Blood glucose (mmol/L): Median (IQR)	26.2 (20.2, 32.5)	25.6 (19.5, 32.6)	25.7 (19.7, 32)
Blood pH: Median (IQR)	7.4 (7.3, 7.4)	7.4 (7.2, 7.4)	7.4 (7.3, 7.4)

\* Deprivation Score 0 to 100 with 0 indicating greatest deprivation

FC38

ANTI CD4 AND ANTI CD8 ANTIBODY CO-THERAPY INDUCES REMISSION OF DIABETES IN NEW ONSET NOD MICE VIA LOCALIZED INDUCTION OF T CELL EGRESS FROM THE PANCREAS

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**Objectives:** Previous studies have shown that anti-CD4/anti-CD8 antibody treatment produced indefinite diabetes remission in new onset non-obese diabetic mice. Histologic studies of the mice reveal reduced T cell pancreatic islet infiltration. How the antibodies induce pancreatic T cell egress is unknown. A recently completed study showed that IFN-γ injections caused diabetes recurrence in mice with anti-CD4/anti-CD8 induced remission. It is hypothesized that anti-CD4/anti-CD8 antibody treatment decreases T cell secretion of IFN-γ and IL-2, blunting the local inflammatory response, ultimately facilitating T cell egress.

**Methods:** Female NOD mice with confirmed new onset diabetes (BG > 250 x2 days) were injected intraperitoneally with rat anti-mouse CD4 and CD8 or rat anti-mouse 2A3

control antibody once daily for two days. Treatment doses were serially diluted from 160 to 0.625μg/mL. Seventy two hours after antibody injection, mice were sacrificed for analyses of sera and organ T cell content. Single-cell suspensions were prepared from tissues. Leukocytes were removed from islets via an enzyme-free dissociation buffer with cytokine levels measured via ELISA and T cell counts calculated via flow cytometry.

**Results:** Diabetes was reversed in 79% (n= 24) of anti-CD4/anti-CD8 treated NOD mice but persisted in the control group. Both IFN-γ and IL-2 levels and total pancreatic T cell counts decreased exponentially with increasing concentrations of anti-CD4/anti-CD8 antibody while no change was seen in the control group. There was no decrease in splenic T cell counts of the treatment or control groups.

**Conclusions:** The results are consistent with previous studies showing anti-CD4/anti-CD8 antibody treatment reversing diabetes in new onset NOD mice. Furthermore, anti-CD4/anti-CD8 treatment causes a dose dependent decrease in concentrations of IFN-γ and IL-2 with an exponential decrease of T cell counts in the pancreas. Normal splenic T cell counts indicate the effects are localized and not due to systemic immunosuppression. Studies examining the FOXO1 pathway, via RT-PCR, are underway. It is theorized that FOXO1 moves into the nucleus of unstimulated T cells, causing downregulation of CD69, an early T cell activation cofactor, and upregulation of S1P, a membrane protein thought to promote T cell egress from tissue.

FC39

THE RISK OF PROGRESSION TO TYPE 1 DIABETES (T1D) IN INDIVIDUALS OF DIVERSE AGES WITH MULTIPLE AUTOANTIBODIES

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**Objectives:** Young children with multiple autoantibodies (≥2 Abs) are at high risk for the development of type 1 diabetes (T1D) with reported 5 and 10-year risks of 0.44 and 0.70. However, the risk in individuals of diverse ages with multiple Abs has not been studied in depth.

**Methods:** We examined the impact of age, the Diabetes Prevention Trial Risk Score (DPTSR), and types of Abs upon the risk of T1D in TrialNet Pathway to Prevention (PTP) participants with ≥2 Abs (IAA, GADA, IA-2A, ICA, ZnT8), a

cohort with a wide age range [n=1896; mean±SD age: 13.5±10.7 years (range 1-45 years); ZnT8A measured in 1119]. Findings are shown for the full cohort, since they were similar with or without ZnT8A.

**Results:** Based on the hazard ratio (HR) from a Cox regression analysis, there was 4.5% (95% CI: 3.3%, 5.6%) less risk for T1D per year increase in age (p<0.001). In the analysis of the DPTRS (based upon age, BMI, log fasting C-peptide, glucose and C-peptide sums from 30 to 120 minutes during 2-hr OGTTs), among PTP participants with normal glucose levels, the cumulative incidence for T1D was higher for values ≥6.5 than values <6.5 (p<0.001), both among individuals with 2 Abs [5-year risks: 49% (n=184) vs. 12% (n=429)] and >2 Abs [(5-year risks: 57% (n=397) vs. 21% (n=368)]. In the Ab analysis, adjusting for Ab number, those with GADA as one of the ≥2 Abs had less risk than the others [HR: 0.337 (0.281, 0.505); p<0.001]. In contrast, those with IA-2A as one of the ≥2 Abs were at higher risk [HR: 1.78 (1.33, 2.38); p<0.001]. 10-year risks for 2 Abs with DPTRS values <6.5 (n=429), or ≥2 Abs with GADA in the absence of IA-2A (n=556), were approximately 20% and 40% respectively.

**Conclusions:** In summary, the risk for T1D in a diversely aged population with ≥2 Abs becomes quite low as individuals age. A lower risk is also evident among those with normal glucose levels and DPTRS values <6.5, and among those with GADA as one of the ≥2 Abs in the absence of IA-2A. In conclusion, the findings suggest that a considerable proportion of diversely aged individuals with ≥2 Abs appear unlikely to progress to T1D.

FC40

#### **DOMINANT TNFA AND IMPAIRED IL-2 CYTOKINE EXPRESSION PROFILES OF CD4+ MEMORY T CELLS FROM CHILDREN WITH TYPE 1 DIABETES ARE PROMOTED BY IL-7**

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**Objectives:** Aberrantly activated CD4+ T memory cells play a central role in the development of type-1-diabetes. Interleukin-7 (IL-7) promotes generation of autoimmune memory T cells and increased IL-7 availability is associated with type-1-diabetes susceptibility. T-cell mediated immune pathology at onset of disease is well defined, but characteristics of long-term symptomatic disease stages remain largely elusive. In the present study memory CD4<sup>+</sup> T-cell activation and cytokine expression as well as sensitivity to IL-7 *in vitro* were compared between patients with type-1-diabetes at clinical onset (n=25), long-term symptomatic

disease (median duration 4.5 years, n=19), and matched healthy controls (n=21).

**Methods:** Sample collection was performed in the framework of the pediatric diabetes biomaterial bank in German Center for Diabetes Research. The effect of IL-7 co-stimulation on T-cell activation dependent cytokine expression and differences between the study groups were assessed by intracellular cytokine staining and flow cytometric analysis of donors PBMC.

**Results:** T-cell responses of type-1-diabetes patients were characterized by higher frequencies of cytokine and activation marker expressing CD4+ memory T cells as compared to healthy controls. Notably, qualitative differences of cytokine profiles characterized by significantly increased TNFα and decreased IL-2 expressing T-cell proportions were solely detected in long-term type-1-diabetes patients. IL-7 mediated T-cell co-stimulation induced quantitative and qualitative cytokine expression differences highly similar to type-1-diabetes specific profiles. In addition, CD4+ memory T cells from children with long-term type-1-diabetes were more sensitive to *in vitro* IL-7 co-stimulation. Global transcriptome analysis revealed IL-7 induced expression differences of CD4+ T cells including increased IL-2R expression and effects on subsequent T-cell receptor activation.

**Conclusions:** Our results indicate that long-term symptomatic type-1-diabetes patients differ in memory T-cell cytokine profiles and IL-7 co-stimulation. Regulation of IL-2 expression and sensitivity are affected with possible consequences for the course of disease and severity at long-term type-1-diabetes stages.

#### **Free Communication Session, Friday, September 15, 2017, 2:30-3:30pm**

##### **Gender dysphoria FC41 – FC45**

FC41

#### **TESTOSTERONE MAKES YOUNG TRANSGENDER POST-PUBERTAL MEN GROW**

*Tiffani K Rees, BA MBBS MBA; Sara Kleczewski, BSc RN; Professor Gary E Butler, MD FRCPCH; Elaine Perkins, PA; Caroline E Brain, MBBS MRCP FRCPCH MD; Kirpal Adu-Gyamfi, Physician's Assistant; Claire Goedhart, RN, University College London Hospital, National Gender Identity Development Service, London, United Kingdom*

**Objectives:** Young transgender men, birth assigned females, starting on cross sex hormone (testosterone) are often keen to increase their height. No objective data exist to inform the growth potential of transgender young men who are undergoing puberty in a cross-sex hormonal environment, so our objective is to provide the first national study of this kind.

**Methods:** This retrospective notes study analysed data of 41 transgender men aged 15-19 who began GnRH analogue therapy post menarche and had been on the GnRH analogue

for at least one year prior to starting testosterone. We reviewed their height at six-monthly intervals from initiation of therapy, induction of cross-sex hormonal treatment and at subsequent dose increases of testosterone.

**Results:** A total of 5 six-monthly longitudinal height measurements were performed by trained auxologists in the early afternoon. We included growth data for 39 patients after 6 months on testosterone, and for 25 patients after one year on testosterone. The difference in height from the time of commencing the hypothalamic blocker to when they had been on testosterone for 6 months was on average a 0.9 cm increase, with all but 5 men achieving height increases of whom three subsequently grew on increasing the testosterone dose. The height increase from time of starting blocker to 1 year on testosterone was on average a 1.4 cm increase, with all but one man becoming taller. The average age of participants at 1 year on testosterone was 18.4 years. At this point, many are lost to follow-up as they transition to adult services. Our cohort does include 5 men after 1.5 years on testosterone and 2 men after 2 years on testosterone. All of these men grew taller, an average of 1.9cm after 1.5 years, and of 2.4 cm after 2 years.

**Conclusions:** The difference in height from the time of commencing the hypothalamic blocker to when they had been on testosterone for 1 year on testosterone was on average a 1.4 cm increase. The expected height increase for post-pubertal natal females is 0 cm according to the national standards. This first-of-its-kind study shows that pubertal induction with testosterone after menarche can give many young transgender men hope of a potential increase in height.

FC42

#### WHAT ARE THE PERSPECTIVES AMONG TRANSGENDER YOUTH AND THEIR PARENTS REGARDING FUTURE FERTILITY? INSIGHTS FROM THE FERTILITY AND REPRODUCTIVE HEALTH SURVEY OF TRANSGENDER YOUTH (FROST) STUDY

Lyne N. Chiniara, MD; Christine Viner, MD; Herbert J. Bonifacio, MD, MSc, MPH, MA; Mark R. Palmert, MD, PhD, Hospital for Sick Children/University of Toronto, Toronto, ON, Canada

**Objectives:** Fertility is an important topic for patients, families, and care providers when considering medical and/or surgical treatment for gender dysphoria (GD). The aim of this study was to investigate the perspectives of youth with GD and their parents concerning fertility and future parenthood.

**Methods:** A prospective, questionnaire-based study among transgender youth and their parents designed to collect baseline demographic information, knowledge of potential effects of treatments on fertility, current and perceived future life priorities, and preferences regarding future fertility/parenting options.

**Results:** A total of 61 youth (82% female bodied youth (FBY), 18% male bodied youth (MBY), 70% between ages 16-18 years, 26% between 13-15 years) and 56 parents participated.

47 youth identified as male, 10 as female, and 4 as non-binary. The top three current life priorities for youth were: (1) *Being in good health*, (2) *Have lots of friends* and (3) *Do well in school/work*. The least important priority was *Having children*. This was ranked last by 58% of FBY and 64% of MBY. Perceived life priorities in 10 years were ranked similarly. Parents' rankings paralleled the youth responses in terms of their top three current priorities for their child. Similarly, parents ranked having children as the lowest current life priority but ranked it a much higher priority for the FBY but not MBY youth in 10 years.

The majority of youth (68% FBY, 73% MBY) want to be a parent in the future. However, most do not envision having a biological child. A large majority (72% FBY, 82% MBY) were open to adoption with smaller numbers open to surrogacy and fewer still considering sperm or egg donation.

All youth knew treatment with cross-sex hormones could alter future fertility but only 6% of FBY and no MBY would delay start of hormone blockers or cross-sex hormones to pursue potential treatments to preserve fertility.

**Conclusions:** Fertility is a low current and future life priority for transgender youth. Fertility is also a low current priority for parents, although parents of FBY view it as a higher future life priority. The majority of youth wish to become parents but are open to alternative strategies for building a family. Further studies are needed to assess if youths' life priorities change over time.

FC43

#### BODY COMPOSITION OF YOUNG ADULT TRANSWOMEN WHO STARTED GENDER REASSIGNMENT IN ADOLESCENCE

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**Objectives:** Sex steroids influence body composition. During gender reassignment (GR) natal adolescent boys with gender dysphoria (GD) (transwomen) are treated with gonadotropin-releasing hormone analogs (GnRHa) and estrogens. Currently, effects of this treatment regime on body composition in adulthood are not known. Our objective is to study body composition and body mass index (BMI) during GR and at the age of 22 in young adult transwomen who commenced treatment in adolescence

**Methods:** In a longitudinal observational study at a tertiary referral center, young adults diagnosed with GD (DSM IV-TR) who started GR in puberty and had undergone gonadectomy between June 1998 and April 2016 were included. After a median duration of GnRHa monotherapy of 1.4 years 17-B-estradiol was added for median duration of 5.9 years. GnRHa was discontinued after gonadectomy. In 26 subjects BMI, waist circumference (W), hip circumference (H) and body fat percentage (BFP), as determined by dual-energy X-ray absorptiometry, was measured at start GnRHa, start estrogens and at age 22.

**Results:** During GnRHa monotherapy BMI increased from 19.5 to 21.0 kg/m<sup>2</sup> ( $p < 0.01$ ), whereas BMI standard deviation

score (SDS) calculated for both natal and desired sex remained stable ( $n=26$ ). Total BFP ( $n=24$ ) increased with +6% (CI95%0;12) ( $p=0.01$ ), percentage gynoid fat increased with +8% (CI95%2;13) ( $p=0.01$ ) whereas the percentage android fat increased with +4% (CI95%0;11) ( $p=0.01$ ). W-SDS and WHR-SDS did not change.

When estrogens were added till the age of 22, BMI increased to  $21.5 \text{ kg/m}^2$  ( $p<0.01$ ) but SDS did not change. Total BFP increased with +3% (CI95%-2;12) ( $p=0.03$ ), and percentage gynoid and android fat with +3% (CI95%-2;9) ( $p=0.01$ ) and +1% (CI95%-5;17) ( $p=0.20$ ), respectively. W-SDS and WHR-SDS did not change.

**Conclusions:** GR in adolescence was not associated with unfavorable weight increase in young adulthood. During GR total BFP, gynoid fat and android fat increased in transwomen. This increase was most pronounced during GnRHa monotherapy coinciding with a higher increase in gynoid fat than in android fat. These changes may reflect a more feminized phenotype of body fat distribution.

FC44

#### MENTAL HEALTH CONCERNS AND INSURANCE DENIALS AMONG TRANSGENDER ADOLESCENTS

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**Objectives:** Transgender youth are at high risk for mental health concerns. Based on treatment guidelines, puberty blockers and gender-affirming hormone therapy should be considered to alleviate distress due to discordance between an individual's assigned sex and gender identity. The goal of this study was to examine the: 1) prevalence of mental health diagnoses, self-injurious behaviors, and school victimization, and 2) rates of insurance coverage for hormone therapy, among a cohort of transgender adolescents at a large pediatric gender program, to understand access to recommended therapy.

**Methods:** An IRB-approved retrospective medical record review (2014-2016) was conducted of patients with ICD 9/10 codes for gender dysphoria referred to pediatric endocrinology within a large multidisciplinary gender program. Researchers extracted: demographics, age, assigned sex, identified gender, insurance provider/coverage, mental health diagnoses, self-injurious behavior, and school victimization.

**Results:** Seventy-nine records (51 transgender males, 28 transgender females) met inclusion criteria (median age: 15 years, range: 9-18). Seventy-three subjects (92.4%) were diagnosed with one or more of the following conditions: depression, anxiety, post-traumatic stress disorder, eating

disorders, autism spectrum disorder, and bipolar disorder. Fifty-nine (74.7%) reported suicidal ideation, 49 (55.7%) exhibited self-injurious behavior, and 24 (30.4%) had one or more suicide attempts. Forty-six (58.2%) subjects reported school victimization. Of the 27 patients prescribed gonadotropin-releasing hormone analogues, only 8 (29.6%) received insurance coverage.

**Conclusions:** Transgender youth face significant barriers in accessing appropriate hormone therapy. Given the high rates of mental health concerns, self-injurious behavior, and school victimization among this vulnerable population, healthcare professionals must work alongside policy makers towards insurance coverage reform.

FC45

#### EVALUATING ACCESS TO PRESCRIBED MEDICATIONS AND ASSOCIATED PSYCHIATRIC COMORBIDITIES IN TRANSGENDER YOUTH

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**Objectives:** To determine if transgender and gender nonconforming youth attending a multidisciplinary clinic are able to access prescribed medications, including pubertal blockers.

Transgender youth have unique healthcare needs. It is recommended by multiple professional societies (WPATH, Endocrine Society, PES) that transgender children be offered treatment with pubertal blockers once they reach Tanner stage 2 of puberty. However, these medications may be prohibitively expensive if not covered by insurance. The risks of not obtaining and starting these medications in a timely fashion include continued pubertal progression and development of secondary sexual characteristics opposite those of the child's affirmed gender. This may lead to a future need for increased surgical intervention as well as increased psychological distress for the patient.

**Methods:** In this retrospective chart review study, 19 patient charts were analyzed over the treatment period from January 1 – August 15, 2016 for prescriptions for pubertal blockers (GnRH analog (GnRHa) therapy) and whether or not these medications were approved by insurance and initiated during this time period.

**Results:** GnRHa were prescribed in over half of the patient charts reviewed. Of note, patients 12 and younger were not prescribed these medications, likely due to being assessed as prepubertal during their visits with our clinic and therefore not qualifying for this therapy. In patients aged 13-17, 60% of those prescribed GnRHa therapy were able to obtain and start the medication, while in patients aged 18 and over only 40% of those prescribed the medication were able to start therapy. In assessing psychiatric comorbidities, 60% of those patients treated with GnRHa displayed psychiatric comorbidities, while 71% of those not treated with GnRHa were diagnosed with psychiatric disorders.

**Conclusions:** Patients in our transgender clinic have difficulty obtaining prescribed therapy with GnRHa. Additionally, there are high rates of psychiatric comorbidities in our patient population, as has been previously described in transgender youth. The rate of psychiatric disorders was slightly higher in patients not treated with GnRHa, though this would need to be repeated in a larger population to determine if this difference is statistically significant.

**Table 1:** Rates of GnRH analog prescription and therapy initiation

Age range	Total patients in age range	GnRHa prescribed	GnRHa started
18+	9	5	2
13-17	7	5	3
12 or younger	3	0	0

**Table 2:** Rates of psychiatric comorbidities classified by current therapy

	GnRHa	No GnRHa
Psychiatric disorder	3	10
No psychiatric disorder	2	4

Psychiatric disorders may include any psychiatric diagnosis (excluding gender dysphoria)

**Free Communication Session, Friday, September 15, 2017, 2:30-3:30pm**  
**Obesity, lipids, and co-morbidities #1**  
**FC46 – FC50**

FC46

**ANG1-7 EXERTS ANTI-OBESITY EFFECT THROUGH PROLIFERATION OF BAT**

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**Background, Aims and Objectives:** Angiotensin II (Ang II) is converted to Angiotensin1-7 (Ang1-7) by ACE2. Ang1-7 binds to Mas receptor, a specific receptor of Ang1-7, and exerts a counteracting effect of Ang II, such as improvement in either fatty acid or glucose metabolism. On the other hand, in recent years, brown adipose tissue (BAT), which is essential for energy consumption, has attracted attention from the viewpoint of treating obesity. Here, we studied the role of BAT on anti-obesity effect of Ang1-7.

**Methods:** Four-week-old C57BL/6J male mice were fed normal chow or High-Fat-diet (HFD) for 8 weeks. Ang1-7 (0.5 mg/kg per day) was administered subcutaneously via implanted micro-osmotic pump during last 4 weeks.

**Results:** In HFD-fed mice, Ang1-7 treatment decreased body weight with no alteration of food intake and increased O2 consumption. Glucose tolerance test and insulin tolerance test showed Ang1-7 treatment ameliorated insulin resistance in HFD-fed mice. Either subcutaneous or visceral white adipose tissue (WAT) in HFD-fed mice was decreased with

administration of Ang1-7, concomitant with the smaller size of adipocyte in WAT. On the other hand, the volume of BAT was increased and lipid droplets in BAT became smaller by Ang1-7 treatment, accompanied with amelioration of insulin signaling and increase UCP1 expression. Furthermore, protein levels of PRDM16 and phosphorylation of AMPKα were upregulated in BAT with administration of Ang1-7.

**Conclusions:** We identified that Ang1-7 promotes differentiation and proliferation of brown adipocytes leading to the increase of energy expenditure. Furthermore, we demonstrated that Ang1-7 ameliorate insulin signaling in BAT. These findings suggest that Ang 1-7 can be a new therapeutic tool for obesity.

FC47

**USE OF ELEVATED HOMA-IR AND BLOOD PRESSURE VALUES IN DECIDING IN WHICH OBESE CHILDREN SHOULD OGTT BE PERFORMED**

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**Objectives:** The prevalence of impaired glucose tolerance (IGT) in obese children is rising with the pandemic of obesity. Having in mind the high numbers of the obese children, it is important to identify those at risk for IGT/T2DM, in which OGTT should be performed. Current ADA recommendations are that OGTT should be performed in obese children with any of the following: family history of T2DM, ethnic predisposition, acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary syndrome. However this approach results in high number of false positives and sensitivity in detecting obese children with IGT has not been thoroughly evaluated. Objective was to evaluate the sensitivity and number needed to screen (NNS) using findings of basal insulin resistance or elevated blood pressure in identification of obese children with IGT, and to compare the results with sensitivity and NNS of current ADA criteria.

**Methods:** Data regarding basal values of glucose, insulin, blood pressure and OGTT results were collected from the medical records of 290 obese (BMI≥95<sup>th</sup> percentile) children and adolescents with normal fasting glucose. The screen was considered positive if subjects had either HOMA-IR>3 or blood pressure ≥130/85 mmHg. Second screening was performed for comparison purposes using the ADA criteria.

**Results:** Of the total of 290 obese children with normal fasting glucose levels, 22 (7.6%) had IGT and one (0.3%) had T2DM according to the OGTT 120 min. glucose levels. ADA criteria identified 240 children as at risk for IGT, amongst which 21 had abnormal 120 min. glucose values. There were 2 missed children with IGT (8.7%) and NNS was 11.4. Identifying children in whom OGTT should be performed on the basis of either insulin resistance or hypertension resulted in identification of 223 subjects, of whom 23 had abnormal



120 min. glucose values. None of the subjects with IGT were missed using this approach, and NNS was 9.7.

**Conclusions:** Performing OGTT in children who have either HOMA-IR>3 or blood pressure  $\geq 130/85$  mmHg has higher sensitivity and lower NNS than when using current ADA guidelines. We suggest considering OGTT in children with either basal insulin resistance or high blood pressure.

FC48

#### THE RS626283 VARIANT IN THE MBOAT7 GENE CONFERS AN INCREASED RISK OF NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) AND INSULIN RESISTANCE TO CAUCASIAN YOUTHS

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**Objectives:** Non Alcoholic Fatty Liver Disease (NAFLD) is a leading cause of liver damage in U.S. The disease occurrence is influenced by genetic and environmental factors. Recently, the rs626283 polymorphism in the *MBOAT7* gene has been found to be associated with Alcoholic Liver Disease and NAFLD in adults. In this study we sought to evaluate the association between the rs626283 variant and NAFLD in a pediatric multiethnic cohort.

**Methods:** 467 obese youths (190 Caucasians, 126 African Americans, and 151 Hispanics) were enrolled (mean age  $13.6 \pm 3.6$  years; mean BMI  $31.18 \pm 6.7$  Kg/m<sup>2</sup>). All of them underwent a MRI to measure intra-hepatic fat content (HFF%), an oral glucose tolerance test (OGTT) to assess glucose metabolism and insulin sensitivity and the genotyping of the rs626283 polymorphism in the *MBOAT7* gene by Sequenom Massarray.

**Results:** The genotype frequencies were in Hardy-Weinberg equilibrium in all the ethnic groups. The three ethnic groups did not differ for age, gender and BMI. Caucasian youths homozygous for the minor allele (CC) showed significantly higher HFF% ( $p=0.034$ ) compared to heterozygous (CG) and major allele carriers (GG). Moreover, Caucasian youths homozygous for the C allele presented the features of insulin resistance: higher fasting glucose ( $p=0.045$ ), higher fasting insulin ( $p=0.023$ ), higher HbA1c ( $p=0.016$ ), lower degree of whole body insulin sensitivity ( $p=0.007$ ), and a trend towards an impairment of insulin secretion determined by calculating the disposition index (DI) ( $p=0.056$ ). In contrast, there was no difference in HFF% among the genotypes in African Americans and Hispanics ( $p>0.05$ ).

**Conclusions:** The rs626283 variant in the *MBOAT7* gene is associated with NAFLD and alterations of glucose metabolism in obese Caucasian youths. Further studies are needed to confirm this finding and to clarify the mechanisms by which

this gene variant might predispose to pediatric NAFLD and insulin resistance.

FC49

#### STRUCTURAL AND FUNCTIONAL ABNORMALITIES IN THE HYPOTHALAMUS OF OBESE CHILDREN

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**Objectives:** Recent findings from experimental models suggests that an inflammatory response in the hypothalamus may contribute to obesity pathogenesis by disrupting key neurons involved in the regulation of caloric intake and energy expenditure. In obese adult humans, neuroimaging studies have shown a defective hypothalamic response to nutrients as well as have provided evidence for the existence of structural changes in the Medial Basal Hypothalamus (MBH) characterized by gliosis. Therefore, hypothalamic abnormalities, as assessed by different approaches, are present in the hypothalamus of obese adults and experimental animals. However, no previous studies have evaluated such abnormalities among obese children. So, the aim was to study, structurally and functionally, the hypothalamus of children and adolescents with obesity.

**Methods:** Twelve obese and 11 lean aged between 9 and 17 years agreed to participate and underwent fasting blood draws, body composition analysis by DXA, and brain magnetic resonance imaging (MRI) scans: quantitative MRI to measure T2 relaxation time to investigate hypothalamic tissue characteristics and functional MRI to verify hypothalamic response after oral glucose ingestion.

**Results:** Obese subjects had longer T2 relaxation times in the MBH when compared to lean group ( $P<.001$ ), consistent with gliosis. Moreover, there was a highly significant group\*region interaction ( $P=.0016$ ), demonstrating that signs of gliosis were specific to the MBH as compared to control brain regions. Longer T2 relaxation times were correlated with higher visceral body fat percentage ( $r=0.591$ ,  $P=.04$ ) and android fat percentage ( $r=0.676$ ,  $P=.009$ ), but not fasting insulin concentrations ( $r=0.125$ ,  $P=0.6$ ). In functional studies, the hypothalamus of obese children presented an impaired response to oral glucose ingestion, with lower mean signal change ( $P<.001$ ) and a lower general connectivity with brain gray matter ( $P=.013$ ). Finally, we found a negative correlation between MBH T2 relaxation and the mean hypothalamic BOLD signal change following glucose intake ( $r = -0.46$ ,  $P=.041$ ).





( $p=0.039$ ) than aTG, however, aTG had greater specificity than aTPO ( $p=0.008$ ). Use of aTG and aTPO combined (either positive) did not have greater sensitivity than TPO alone, and had lower specificity than either aTG or aTPO alone ( $p<0.001$ ). The combination of aTG and aTPO (both positive) provided the highest specificity ( $p<0.001$ ), but lowest sensitivity. For likelihood ratios (LR), the best +LR was seen with combined aTG and aTPO both being positive; while the best -LR was seen with aTPO alone or combination of either positive.

**Conclusions:** Addition of aTG to aTPO alone did not improve, and potentially worsened, sensitivity and -LRs, while the combination of both positive maximized specificity and +LR. Given ADA and ISPAD recommendations that clinically euthyroid T1D patients with negative antibodies be screened for hypothyroidism every 1-2 years, the specificity gained by addition of aTG becomes less clinically meaningful. As a result, use of aTPO alone is clinically effective and could reduce cost, however, further study is needed to see if TSH alone may obviate the need for antibodies.

Ability of Anti-Thyroid Peroxidase and Anti-Thyroglobulin Antibodies Alone and in Combination to Predict Subsequent Hypothyroidism in Newly Diagnosed Type 1 Diabetes Patients				
	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio
aTPO alone	89.5% (CI: 75.2-97.6%)	83.8% (CI: 81.2-86.3%)	5.53 (CI: 4.58-6.69)	0.13 (CI: 0.05-0.32)
aTG alone	66.7% (CI: 48.2-82.0%)	89.4% (CI: 86.7-91.6%)	6.27 (CI: 4.51-8.71)	0.37 (CI: 0.23-0.60)
aTPO & aTG (either positive)	90.9% (CI: 75.7-98.1%)	78.3% (CI: 74.9-81.4%)	4.18 (CI 3.49-5.02)	0.12 (0.04-0.34)
aTPO & aTG (both positive)	63.6% (CI: 45.12-79.6%)	93.8% (CI: 91.64-95.53%)	10.3 (6.90-15.22)	0.39 (0.25-0.61)

aTPO=anti-thyroid peroxidase antibody; aTG=anti-thyroglobulin antibody, CI=95% confidence interval

FC52

**QUALITY IMPROVEMENT IN THE PERIOPERATIVE MEDICAL MANAGEMENT OF PEDIATRIC THYROIDECTOMY**

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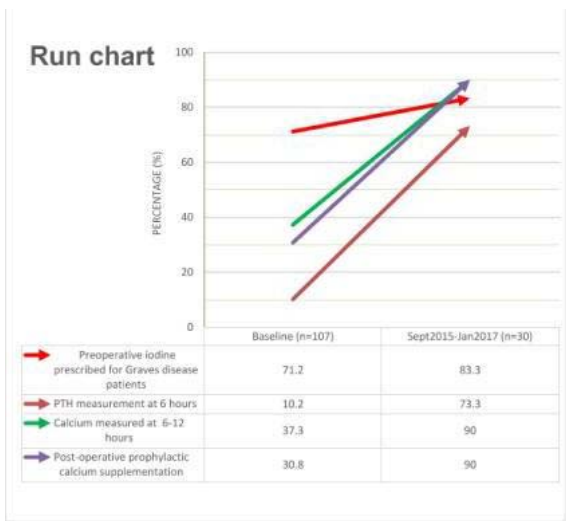
**Objectives:** The aim of this quality improvement project is to assess intuitional variability in perioperative medical management of pediatric thyroidectomy and to institute protocols to standardize practice and enhance quality of care.

**Methods:** A retrospective cross-sectional assessment was conducted to review the perioperative medical management of total thyroidectomy patients seen between January 2010 through October 2014 at two campuses of a pediatric tertiary care hospital system in Atlanta, GA. Baseline data was extracted from 107 patients. Indications for thyroidectomy included Graves disease (n=66), thyroid cancer (n=20), and other thyroid conditions (n=21). After the baseline data was

evaluated, we implemented standardized inpatient order sets, a written care pathway, and conducted education sessions with endocrinologists and surgeons. From September 2015 through January 2017, we collected post-intervention data on 30 patients (Graves disease (n=18), thyroid cancer (n=10), and other thyroid conditions (n=2)) to evaluate improvement in a practice bundle: prescribing preoperative iodine in Graves disease, measuring serum parathyroid hormone (PTH) and calcium levels at 6 hours post operation, and ordering universal postoperative prophylactic calcium carbonate. Feedback is being provided to both campuses.

**Results:** Rates of prescribing iodine in Graves disease showed a trend toward improvement (71.2% at baseline, 83.3% after the initiative,  $p=0.3$ ). Rates of postoperative monitoring of PTH rose from 10.2% to 73.3% ( $p <0.01$ ), and serum calcium monitoring rose from 37.3% to 90% ( $p <0.01$ ). Postoperative prophylactic calcium carbonate utilization improved from 30.8% to 90% ( $p <0.01$ ).

**Conclusions:** After the implementation of the quality initiative, we observed statistically significant improvement in 3 domains: PTH and calcium levels and prophylactic calcium carbonate. One barrier to universal implantation was the presence of multiple endocrine and surgical groups and 2 hospital sites. We plan additional PDSA cycles to improve our care pathway and increase utilization of the order sets, with the end goal to better standardize care and decrease transient postoperative hypocalcemia.



FC53

**URINARY STEROIDOMICS FOR THE MANAGEMENT OF CHILDREN WITH CONGENITAL ADRENAL HYPERPLASIA**

*Clemens Kamrath, MD; Lisa Wettstaedt, Medical Student, Justus Liebig University Giessen, Giessen, Germany; Michaela F Hartmann, PhD; Stefan A Wudy, PhD, Justus Liebig University, Giessen, Germany*

**Objectives:** Treatment of children with classic congenital adrenal hyperplasia (CAH) with glucocorticoids is a difficult balance of hypercortisolism and hyperandrogenism.

Biochemical monitoring of treatment is not well defined. Normal growth is an important objective of treatment.

**Methods:** We retrospectively analysed 123 24-hr urinary steroid hormone metabolite profiles determined by gas chromatography-mass spectrometry with their corresponding one-year height velocity (HV) z-scores of 63 children aged  $7.2 \pm 1.6$  years with classic CAH due to 21-hydroxylase deficiency treated with hydrocortisone and fludrocortisone.

**Results:** Multivariate linear mixed effects model analyses revealed positive influence of z-scores of summed daily excretions of all urinary androgen metabolites ( $B = 0.97 \pm 0.20$ ,  $t\text{-value} = 4.97$ ,  $P < 0.0001$ ) and negative influence of daily excretion of the cortisol metabolite tetrahydrocortisol ( $B = -1.75 \pm 0.79$ ,  $t\text{-value} = -2.20$ ,  $P = 0.03$ ) on HV z-scores. ROC analysis revealed that adrenal androgen excess, defined as  $HV > 1.5$  z, was best determined by a z-score of the sum of the daily excretion rates of all urinary androgen metabolites of  $> 0.644$  (accuracy 70.7%, sensitivity 81.6 %, specificity 53.2%, positive prediction values (PPV) 73.8%, negative prediction values (NPV) 64.1%, positive likelihood ratio 1.7), whereas 24-hr excretion of tetrahydrocortisol  $> 1.750 \mu\text{g}/\text{m}^2 \text{BSA}/\text{d}$  in conjunction with suppressed daily excretion of urinary androgen metabolites  $< 0.163$  z indicated cortisol excess and overtreatment, defined as  $HV < -1.5$  z (accuracy 89.4 %, sensitivity 37.5 %, specificity 97.2%, PPV 66.7%, NPV 91.2%, positive likelihood ratio 13.4).

**Conclusions:** Urinary steroid metabolomics distinguishes patients with adequate metabolic control from those who were over treated or revealed an insufficient adrenal suppression. Therefore, urinary steroid metabolomics is an appropriate method for the monitoring of management of children with CAH.

FC54

#### PREVENTION OF DIABETES KETOACIDOSIS BY IMPLEMENTATION OF INTENSIVE SICK DAY RULES

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**Objectives:** Diabetic ketoacidosis (DKA) is a life-threatening acute complication of diabetes due to suboptimal insulin administration and hydration commonly observed in patients with uncontrolled type 1 diabetes mellitus (T1DM) leading to hospitalization. In order to prevent DKA-related hospital admissions, a new intensive in-home sick-day protocol was initiated and its efficacy was evaluated over a period of one year.

**Methods:** New sick day rules were implemented in January 2016 and all clinic T1DM patients were educated about them during their clinic visits or hospitalizations. A laminated copy of the sick day rules was also given to patients for reference. Retrospective data over 12 month periods for 2015 and 2016 were collected with the 2015 data serving as control and 2016 as post-intervention study data. We collected demographic, clinic and hospital admission data on known

diabetes clinic patients with T1DM admitted to our hospital with DKA.

**Results:** The DKA-related admissions declined from 21.9 to 18.4 per 100 patients/year from 2015 to 2016, consistent with 16% reduction. The mean age, gender and HbA1c were not statistically different for the patient cohorts between the two years. While the number of admissions for patients with 3 or more admissions per year was similar (7.5 and 7.8/100 patients/year in 2015 and 2016, respectively), the number of DKA admissions for patients with  $< 3$  admissions/year declined from 14.4 to 10.6/100 patients per year, a 26% decrease ( $p=0.045$ ).

**Conclusions:** Educating patients on intensive sick day rules was associated with a 16% decrease in DKA admissions per 100 known T1DM patients. A significant decrease was seen in patients admitted  $< 3$  times per year. Further research is needed to identify interventions to reduce admissions for patients admitted more frequently.

FC55

#### HYDROCORTISONE GRANULES WITH TASTE MASKING ARE WELL ABSORBED AND TOLERATED IN NEONATES, INFANTS & CHILDREN WITH ADRENAL INSUFFICIENCY

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**Objectives:** There is no licensed dose appropriate formulation of hydrocortisone for pre-school children with adrenal insufficiency (AI) and they rely on compounded adult medication.

To evaluate the absorption, palatability and safety of Infacort, an immediate-release, multi-particulate formulation of hydrocortisone with taste masking.

**Methods: Setting:** Single investigator site with satellite sites attended by a “flying” doctor from the investigator site.

**Design:** Open-label, single-dose study in three consecutive cohorts of children ( $n=24$ ) with adrenal insufficiency; Cohort 1, aged 2-6 years ( $n=12$ ); Cohort 2, infants 1 month to 2 years ( $n=6$ ); Cohort 3, neonates 1 to 28 days ( $n=6$ ). Fasted children were given a single dose of Infacort dose as dry granules administered directly from capsule or spoon followed by a drink. The primary endpoint was serum cortisol concentration 60 min after Infacort administration. Secondary endpoints were palatability assessed by parents and (where possible) children, and adverse events (AEs).

**Results:** All children showed an increase in cortisol above baseline after administration of Infacort ( $p<0.0001$ ), with geometric mean  $\pm$  SD cortisol concentration at 60 min of  $575.8 \pm 299.5 \text{ nmol/L}$ . There were no difficulties with administration of Infacort and 95.5% of parents/carers

reported they preferred Infacort over their child's current medication. 6 children completed an age- appropriate palatability questionnaire with 80% responses were very good or neutral and 20% were bad or very bad. No serious or severe treatment-emergent AEs were reported.

**Conclusions:** Infacort is well tolerated, easy to administer to neonates, infants and children and shows a good absorption with cortisol levels at 60 min after administration being similar to physiological cortisol levels reported in healthy children.

## Free Communication Session, Saturday, September 16, 2017, 7:30-8:30am Growth and GH/IGF Axis #2 FC56 – FC60

FC56

### NOVEL DOMINANT-NEGATIVE GH RECEPTOR MUTATIONS EXPANDS THE SPECTRUM OF GHI AND IGF-I DEFICIENCY

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**Objectives:** Autosomal recessive mutations in the growth hormone receptor (GHR) are the most common causes of primary growth hormone insensitivity (GHI) syndrome. We evaluated the functional effects of novel heterozygous *GHR* variants (located in the intracellular domain) identified in three unrelated children with non-classical GHI phenotypes (normal or elevated GHBP, low serum IGF-I, low-normal IGFBP-3, significant but less severe growth failure than classical GHI), and report therapeutic responses to rhIGF-I and/or rhGH therapy.

**Methods:** Sanger sequencing of the *GHR* gene or whole exome sequencing analysis was performed. Two of the *GHR* variants, *c.964dupG* and *c.920\_921ins14*, were re-generated by site-specific mutagenesis and analyzed in HEK293 reconstitution studies (expression, GH-induced STAT5B phosphorylation and luciferase reporter assays). Patients were treated with rhGH, rhIGF-I, rhIGF-I/IGFBP-3 or combination rhIGF-I+rhGH

**Results:** All three variants identified (*c.964dupG*, *c.920\_921ins14*, and *c.945+2T>C*) are predicted to result in frameshift and early protein termination. *In vitro* functional analysis of variants *c.964dupG* and *c.920\_921ins14* demonstrated expression comparable to wild-type GHR, but an inability to activate GH-induced STAT5B signaling. When co-expressed with wild-type GHR, these variants significantly blunted GH signaling responses of wild-type GHR, similar to our previously described, dominant-negative *GHR c.899dupC*. We show that a combination therapy of rhGH and rhIGF-I optimally improved linear growth to within normal range for the patient carrying the dominant-negative *GHR c.899dupC* mutation.

**Conclusions:** Dominant-negative *GHR* mutations, all located in the intracellular GHR domain, are causal of the mild GHI, IGF-I deficiency, and significant growth failure observed in our patients. A combined therapy of rhGH plus rhIGF-I appears to be an effective treatment option, with some response seen in patients receiving rhIGF-I or rhGH alone. The possibility of heterozygous mutations in the *GHR* intracellular domain should be considered in patients presenting with low IGF-I concentrations and growth phenotypes less severe than seen in classical GHI syndrome.

FC57

### TRANSCON CNP, A SUSTAINED-RELEASE PRODRUG OF C-TYPE NATRIURETIC PEPTIDE, EXERTS POSITIVE EFFECTS ON BONE IN YOUNG CYNOMOLGUS MONKEYS AND IN A MOUSE MODEL OF ACHONDROPLASIA

Kennett Sprogoe, PhD; Vibeke Mil Breinholt, PhD; Rasmussen Caroline, PhD; Per H Mygind, PhD; Oliver Keil, PhD; Susanne Adermann, PhD; Ulrich Hersel, PhD, Ascendis Pharma, Heidelberg, Germany; Nabil Kaci, PhD; Cornille Maxence, PhD, Inserm U1163-Institut Imagine, Paris, France; Lars H Andersen, PhD, Ascendis Pharma, Hellerup, Denmark; Laurence Legeai-Mallet, PhD, Inserm U1163-Institut Imagine, Paris, France

**Objectives:** No FDA-approved treatment option exists for achondroplasia (ACH), the most common form of dwarfism. C-Type Natriuretic Peptide (CNP) has shown promising efficacy in both animal models and human subjects with ACH. TransCon CNP is a prodrug designed specifically to release free CNP at a slow rate resulting in a hemodynamically safe and efficacious drug levels following weekly dosing. The aim of these nonclinical studies was to compare the efficacy of the long-acting TransCon CNP to a daily administered CNP in normal and diseased animal models.

**Methods:** TransCon CNP was administered to newborn ACH mice harboring the *Fgfr3*<sup>Y367C/+</sup> mutation (5.6 mg/kg/day) and to young, healthy cynomolgus monkeys (N=4) (up to 100 µg/kg/week). Body, tail, and selected bones were measured by radiography/µCT and/or with a caliper. H&E and Collagen X staining were performed on the growth plate in order to address effects on the bone architecture. Cardiovascular

tolerability was studied by telemetry in both mice and monkeys.

**Results:** The administration of TransCon CNP to ACH mice resulted in positive effects on axial and appendicular bones and in an increased diameter of foramen magnum. Collagen type X and H&E staining showed an improvement of the growth plate architecture, including an increased size of the epiphysis and secondary ossification centers, compared to *Fgfr3*<sup>Y367C/+</sup> mice treated with vehicle. In young, healthy cynomolgus monkeys, TransCon CNP induced a dose-responsive effect on tibia growth, with increases up to 70% relative to the growth rate for control animals, without observed hypotension or increased heart rate. In cynomolgus monkeys TransCon CNP exhibited a  $T_{1/2}$  of 80-120 hours.

**Conclusions:** TransCon CNP exerted growth promoting effects on bone in both healthy animals and in a disease model of ACH resulting in improvement of the ACH phenotype. Additionally, TransCon CNP increased the diameter of the foramen magnum in ACH mice. In contrast to daily CNP, no apparent risk of hypotension was observed for TransCon CNP. These data supports further development of TransCon CNP as a potential therapy for ACH providing safe and efficacious CNP levels, with weekly administration.

FC58

### 3-YEAR UPDATE OF THE PHASE 2A AND LONG-TERM SAFETY STUDIES (VERTICAL AND VISTA) OF SOMAVARATAN (VRS-317), A LONG-ACTING RHGH FOR THE TREATMENT OF PEDIATRIC GROWTH HORMONE DEFICIENCY

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**Objectives:** Recombinant human growth hormone (rhGH) is the standard of care for pediatric growth hormone deficiency (GHD). Requirement for daily rhGH injections represents a treatment burden that can compromise adherence and efficacy in these patients. Somavaratan, a novel, long-acting rhGH fusion protein under development for pediatric and adult GHD, showed significant improvements in height velocity (HV) and IGF-I in a multicenter, randomized phase 1b/2a study in prepubertal children with GHD. We present preliminary efficacy and safety results of somavaratan in subjects receiving 3 years of treatment.

**Methods:** In the phase 2a VERTICAL study, 64 subjects were randomized to receive 5.0 mg/kg/month (weekly vs. twice monthly vs. monthly dosing) for 6 months; 60 elected to continue treatment in the VISTA long-term safety study. As initial IGF-I response supported a dose increase, all subjects transitioned to somavaratan 3.5 mg/kg twice monthly by the second treatment year. Data cutoff was December 8, 2016.

**Results:** Of 48 subjects (24 male, 24 female) in the third year of somavaratan treatment, mean baseline age ( $\pm$ SD) was  $7.6 \pm 2.4$  years. Mean IGF-I standard deviation score (SDS) increased from  $-1.8 \pm 0.8$  at baseline to  $1.0 \pm 1.6$  ( $n=45$ ) at peak (3–8 days postinjection) and  $-0.5 \pm 1.0$  ( $n=47$ ) at trough (end-of-dosing cycle). In years 1, 2, and 3, mean HV remained consistent at  $8.4 \pm 2.0$ ,  $8.3 \pm 1.6$ , and  $7.8 \pm 1.6$  cm/year, respectively, and height (HT) SDS showed continued increases from  $-2.6 \pm 0.6$  at baseline to  $-2.1 \pm 0.6$ ,  $-1.6 \pm 0.7$ , and  $-1.2 \pm 0.8$ . Mean bone age delay (years) was  $-1.48 \pm 0.81$  at baseline ( $n=48$ ),  $-1.34 \pm 0.89$  (year 1,  $n=48$ ),  $-1.09 \pm 1.02$  (year 2,  $n=47$ ), and  $-0.66 \pm 0.82$  (year 3,  $n=25$ ). Treatment-related adverse events were mild and transient.

**Conclusions:** At 3 years of somavaratan treatment, IGF-I, HV, HT SDS, and bone age showed continued improvement in prepubertal children with GHD. Increasing the somavaratan dose to 3.5 mg/kg twice monthly yielded consistent growth rates, with overall year 3 growth consistent with that of daily rhGH treatment reported in US registries. The somavaratan 3.5 mg/kg twice-monthly dose is being evaluated in treatment-naïve GHD children in an ongoing phase 3 trial.

FC59

### PHENOTYPICAL FEATURES OF PATIENTS WITH A MOLECULAR DEFECT OF THE IGF-1 RECEPTOR AND THE GROWTH RESPONSE TO GROWTH HORMONE TREATMENT.

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**Objectives:** To describe the phenotype and response to rhGH treatment of patients with an IGF-I receptor (*IGF1R*) defect and to develop a clinical score to select patients for genetic testing.

**Methods:** Between 2005-2016 41 patients were identified with an *IGF1R* defect. The 32 patients from whom clinical data were available were divided into 4 groups, based on in silico analysis and clinical data: group 1 ( $n=19$ ): pathogenic mutations; group 2 ( $n=7$ ): terminal deletions; group 3 ( $n=4$ ): non-pathogenic variants; group 4 ( $n=2$ ): digenic disorders (*IGF1R* + another defect). For groups 1 and 2 we analysed the 3-year height SDS and IGF-I SDS response to GH treatment in comparison to GH-treated children born small for gestational age (SGA).

**Results:** In total, 22 pathogenic mutations, 6 non-pathogenic variants, 9 deletions and 2 digenic defects were identified. The included patients (n=32) had a mean height SDS of -3.0 (range -5.5 to -1.7), birth weight (BW) SDS of -2.1 (range -3.7 to -0.4), and birth length (BL) SDS of -2.6 (-5.0 to -1.0). Head circumference (HC) was lower at presentation than at birth (-2.6 vs -1.6,  $p=0.02$ ). Mean serum IGF-1 was 1.1 SDS (range -1.3 to 3.2,  $p<0.001$ ). Fourteen out of 19 reported feeding problems. A scoring system with 100% sensitivity in our cohort and in reported patients was developed, based on a positive score on  $\geq 3$  of the following criteria: BW and/or BL  $< 0$  SDS; height  $< 0$  SDS. Of the 20 rhGH-treated patients (13 mutations; 7 terminal deletions), average height gain in group 1 was 0.5, 0.7 and 1.0 SDS during the first 3 years and 0.8, 1.1 and 1.3 SDS in group 2, while children born SGA gained 0.9, 1.5 and 1.8 SDS. Mean maximum IGF-I levels on treatment were 3.5 SDS (range 1.2-6.0 SDS).

**Conclusions:** We present the largest cohort of patients with an *IGF1R* defect so far and confirm that the phenotype is characterized by SGA in most cases, short stature, microcephaly, serum IGF-I  $> 0$  SDS and feeding problems, which we converted into a simple clinical score to select patients for *IGF1R* analysis. The growth response to GH treatment is clinically significant but lower than observed in SGA patients on a similar dose, in spite of increased serum IGF-I levels.

FC60

#### **BONE MINERAL DENSITY IN YOUNG ADULTS WITH PRADER-WILLI SYNDROME: RESULTS OF A 2-YEAR RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSS-OVER TRIAL**

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**Objectives:** Adults with Prader-Willi syndrome (PWS) are at risk to develop osteoporosis. Growth hormone (GH) treatment has beneficial effects on bone mineral density (BMD) in children with PWS. Cessation of GH treatment at attainment of adult height (AH) might deteriorate BMD in patients with PWS, while continuation might be beneficial. The objective was to investigate the effects of GH versus placebo on BMD in young adults with PWS who were GH-treated during childhood and had attained AH.

**Methods:** Two-year, randomized, double blind, placebo-controlled crossover GH study in 27 young adults with genetically confirmed PWS who were treated with GH during childhood for at least 2 years and had attained AH. Patients were stratified according to gender and BMI (below/above 25 kg/m<sup>2</sup>) and then randomly and blindly assigned to 1 year of subcutaneous injections once daily at bedtime of either 0.67 mg/m<sup>2</sup>/day GH (Genotropin®, 5 mg/ml, Pfizer) or 1 year of

identical appearing placebo, after which they crossed-over to the alternative treatment for another year.

**Results:** At AH, BMD<sub>TotalBody</sub>SDS was significantly lower compared to healthy peers ( $p=0.002$ ), while BMAD<sub>LumbarSpine</sub>SDS was similar ( $p=0.75$ ). Both were significantly lower in patients with a deletion than in those with an mUPD ( $p=0.036$  and  $p=0.035$ , resp.). Compared with GH, placebo did not significantly deteriorate BMD<sub>Tb</sub>SDS and BMAD<sub>L5</sub>SDS ( $p=0.71$  and  $p=0.14$ , resp.). In patients who did not receive sex steroid replacement therapy (SSRT) BMD<sub>Tb</sub>SDS decreased from -0.48 SDS at AH to -0.7 SDS after 2 years ( $p=0.036$ ), and BMAD<sub>L5</sub>SDS from 0.25 to -0.21 SDS ( $p=0.019$ ). In patients who received SSRT, BMD<sub>Tb</sub>SDS significantly increased from -1.03 to -0.76 SDS ( $p=0.01$ ).

**Conclusions:** This two-year cross-over GH trial in young adults with PWS who were treated with GH during childhood and had attained AH shows that, compared to GH, 1 year of placebo does not deteriorate BMD<sub>Tb</sub>SDS and BMAD<sub>L5</sub>SDS. BMD in patients who received SSRT during the RCT improved significantly compared to patients who did not. GH is not able to prevent a decline in BMD when patients need SSRT. This indicates that SSRT should be considered when BMD starts to decline due to incomplete pubertal development in PWS.

#### **Free Communication Session, Saturday, September 16, 2017, 7:30-8:30am Obesity, lipids, and co-morbidities #2 FC61 – FC65**

FC61

#### **THE ROLE OF SOLUBLE LIPID TRANSPORT PROTEINS IN MODULATING LIVER RECEPTOR HOMOLOG-1 (LRH-1) MEDIATED GENE EXPRESSION**

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**Objectives:** LRH-1 is a nuclear receptor that binds phosphatidylcholines (PCs) and regulates multiple metabolic pathways including hepatic glucose sensing and metabolism; however, mechanisms through which insoluble PCs access LRH-1 in the nucleus are unclear. We aim to test the role of lipid transport proteins in shuttling PCs from cytoplasmic membranes into the nucleus to regulate LRH-1 activity.

**Methods:** We identified four lipid transport proteins that bind PCs and localize to the nucleus: PCTP, PITP $\alpha$ , STARD7 and STARD10. We tested their effect on LRH-1 transactivation by a series of siRNA-mediated knockdown and transient overexpression experiments in human liver cell lines. The effects of knockdown and overexpression were measured by qRT-PCR against a panel of known LRH-1 target genes and by luciferase reporter assays. We subsequently explored mechanisms through which these candidate lipid transport proteins modulate LRH-1 transactivation. This was done by pulldown and split luciferase experiments to test for direct



interactions. We also introduced mutations in the pocket of the transport proteins to prevent PC binding or nuclear localization and measured the effect on LRH-1 target genes by qRT-PCR.

**Results:** The knockdown of PCTP as well as its inhibition using the synthetic agonist A1 both resulted in decreased LRH-1 transactivation by luciferase reporter assays. Knockdown of PITP $\alpha$ , STARD7 and STARD10 by siRNA resulted in decreased level of expression of SHP, a known target of LRH-1. Overexpression of PCTP led to a lower expression levels of some LRH-1 target genes. The split luciferase experiment did not capture a direct interaction between LRH-1 and any of the transport proteins indicating that the interactions may be transient or that transport proteins have an indirect effect on LRH-1 transactivation.

**Conclusions:** Alteration of lipid transport proteins expression has an impact on LRH-1 transactivation. This effect does not appear to be mediated by a stable direct interaction between LRH-1 and the transport proteins, but rather through an indirect pathway. Understanding the regulatory pathways governing LRH-1 activity is key to developing novel therapeutic approaches to prevent metabolic disease progression.

FC62

#### **BARIATRIC SURGERY DURING THE TRANSITION PHASE IN PRADER-WILLI SYNDROME: LONG-TERM OUTCOME AFTER BILIOPANCREATIC DIVERSION**

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**Objectives:** Improvement in weight control remains the most important goal of any treatment program in Prader-Willi syndrome (PWS). To date, bariatric surgery experience in PWS is limited, and different procedures have been used with varying success. Malabsorptive procedures, such as biliopancreatic diversion (BPD), are not always recommended for PWS due to safety lack of data and involves long-term complications.

**Methods:** We report 10 severely obese patients (6 males) with genetically confirmed PWS (7 del15, 3 UPD15), who underwent Scopinaro's BPD after inability to control food intake with the classical approaches. Surgery was performed on patients aged 18,8 $\pm$ 2,9 yrs (mean $\pm$ SD) (range: 15,4-24,3 yrs) and the BMI (kg/m<sup>2</sup>) was  $\geq$ 40 in all cases (49,3 $\pm$ 6,4). At baseline, severe co-morbidities were present, such as obstructive sleep apnea (OSAS), type 2 diabetes mellitus (T2DM), hypertension, metabolic syndrome and/or steatohepatitis.

**Results:** No perioperative complications were observed. After a follow-up period of 13,7 $\pm$ 7,4 yrs (range: 4.1-27 yrs; mean age at follow-up: 32.5 $\pm$ 6.8 yrs) the maximum weight loss% (MWL%) was 30,7 $\pm$ 10 (10,1-52,6). Following BPD, BMI decreased in 6 patients, stable in 3 subjects and increased in 1 individual. The mean BMI at the last visit was 40,5 $\pm$ 8.8

(28,9-51,6). After BPD, appetite was reduced in 7 cases; 6 subjects had hypochromic anemia and diarrhea; OSAS were present in 5 patients and osteoporosis/osteopenia in all individuals. T2DM disappeared and behavioural problems improved in some cases. One patient suddenly died at the age of 37.3 yrs. After surgery all patients received medical therapy to prevent nutritional deficiency.

**Conclusions:** The long-term outcome of BPD in our PWS seems to be favorable, with a significant reduction of weight excess in the majority of subjects. Thus, BPD seems to be a good option in the presence of severe comorbidity and in selected PWS patients, with co-operating families, when other classical approaches have failed. Due to the presence of specific side effects of the procedure, however, a careful long-term multidisciplinary follow-up is always necessary.

FC63

#### **TREATMENT OF TWO POMC DEFICIENT PATIENTS WITH THE MELANOCORTIN-4 RECEPTOR AGONIST SETMELANOTIDE LED TO SUCCESSFUL WEIGHT LOSS**

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**Objectives:** The rare condition of POMC deficiency is characterized by monogenic obesity due to early onset hyperphagia, red hair and ACTH insufficiency. We have recently described the first results of an investigator initiated phase 2 study in which two POMC deficient patients were treated with the Melanocortin-4 receptor (MC4R) agonist setmelanotide (Kühnen et al., NEJM, 2016).

**Methods:** The Phase 2, non-randomized, open label pilot study with the new MC4R agonist setmelanotide was conducted in two POMC deficient adult patients (EudraCT No. 2014-002392-28; clinicaltrials.gov identifier No. NCT02507492). Setmelanotide was injected with a single dose which gradually escalated from 0.5 to 1,5mg subcutaneously once per day. We now describe the follow-up results of the initially included two POMC deficient patients after a treatment period of over 24 months.

**Results:** Following over 24 months treatment for each patient, reductions in the body weight of 65.6 kg (42.3 % of the initial body weight) for patient 1 and 40.5 kg (27 % of the initial body weight) for patient 2 were achieved. So far, we observe no severe adverse events related setmelanotide treatment. Due to the activation of the melanocortin-1 receptor (MC1R) in the skin, the treatment was accompanied

by an increased tanning of the skin and a hair color change. Moreover, pre-existing hyperinsulinemia normalized during the study in parallel with the weight loss observed, which was based on a reduction in severe hyperphagia and accompanying increases in energy expenditure. Cardiovascular parameters significantly improved in each patient.

**Conclusions:** We present long term (> 24 months) setmelanotide treatment induced physiological results observed in two POMC deficient patients. The initiation of the treatment led to severe reduction of body weight caused by setmelanotide replacement of the defective MSH signal in the MC4 signaling pathway in these patients. The results point to a potential neuropeptide replacement therapy with this MC4R agonist, that can include other indications in which MSH deficiency might lead to the occurrence of severe hyperphagia as observed in LEPR deficient patients and potentially other MC4 pathway deficiency genetic disorders.

FC64

#### ADJUSTING FOR PUBERTAL STATUS REDUCES PREVALENCE OF OBESITY

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**Objectives:** Pubertal stage has been shown to distort body composition indicators of children based upon existing reference standards using calendar age. For instance, tall children are more likely to have higher body mass index, BMI and be misclassified as obese. This concept has been consistently observed in apparently healthy cohorts of children in Europe, United States, and elsewhere. We examined growth pattern differences Tanner-stage-age normed vs chronologic age BMI z scores for US children transitioning through puberty ages 8-18y and Tanner 2-5 and quantified maturation-chronologic age differences when estimating prevalence of obesity or overweight in US youths.

**Methods:** We performed secondary data analyses of anthropometry and Tanner staging data of 3206 US children ages 8 – 19 years from the National Health and Nutrition Examination Survey (NHANES III) (n=1606, 53% male, 72% Non-Hispanic White (NHW), 9% Mexican American (MA) and 19% Non-Hispanic Black (NHB). The semi-parametric LMS in GAMLSS technique of growth modeling was utilized to generate specialized age-conditioned growth functions within each Tanner stage. Overweight/obesity status were then defined based on resultant Tanner-stage-age and BMI-age z-scores.

**Results:** Highly variable patterns of prevalence of obesity and overweight (derived from BMI z-score-for chronologic age) were observed when results were examined by tanner stages by ethnicity and sex. For example, NHW (35%) and MA (33%) females had higher prevalence of overweight at early puberty relative to NHB (24%) females, yet at late-puberty NHB (46%) females had the highest prevalence (NHW 28%, MA 38%). A similar pattern was observed for obesity prevalence and for

males. Adjusting for Tanner stage significantly reduced the prevalence of overweight (males: from 27 – 38% to 16 – 22%; females: 25-36% to 15-19%; similar reduction magnitudes with obesity) across ethnicities and sex.

**Conclusions:** Differences in timing of puberty between ethnic groups can affect the estimated prevalence of overweight/obesity. Adjustment for pubertal development reduces the prevalence of overweight/obesity. This adjustment may be important when interpreting prevalence data and interventions aimed at reducing the public health impact of obesity.

FC65

#### IDENTIFICATION OF RARE GENETIC VARIANTS IN PATIENTS WITH NON-SYNDROMIC EARLY-ONSET OBESITY USING A POOLED DNA SEQUENCING APPROACH

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**Objectives:** Studies trying to elucidate the pathophysiology of obesity consistently describe a highly heterogeneous disorder both at a clinical and molecular level, with high heritability. At least 10 genes, mostly with recessive inheritance, have been reported to cause monogenic severe obesity, and there are few more candidates with strong effect identified in association studies. The aim of this study was to establish the contribution of rare sequence variants (RSVs) in candidate genes to severe early-onset obesity (BMI > +3SDS, onset < 3years).

**Methods:** Using a pooled DNA sequencing approach we screened 15 candidate genes for obesity in a cohort of 480 patients and 480 controls: 1) genes with reported alterations in patients with obesity (*LEP*, *LEPR*, *MC3R*, *MC4R*, *PCSK1*, *NTRK2* and *SIM1*) and 2) genes strongly associated to obesity by GWAS (*BDNF*, *FTO*, *NEGR1*, *GHSR*, *ADRB3*, *PPARG*, *PCSK2*, *PCSK1* and *TMEM18A*) We focused on RSVs found in single or few individuals per cohort.

**Results:** Seven of the 15 genes (*BDNF*, *FTO*, *MC3R*, *MC4R*, *NEGR1*, *PPARG* and *SIM1*) were differentially represented between patients and controls; we identified 30 RSVs in the mentioned subset of genes in 35 patients and 5 in 6 controls (p<0.0001). The difference of probably pathogenic RSVs (15 in 17 patients vs. 1 in 1 control) was also significant (p=0.0001); all were single allele changes and none of the individuals carried more than one variant.

**Conclusions:** Our data reveal a higher burden of probably pathogenic heterozygous RSVs in several candidate genes in patients with severe early-onset obesity compared to controls. Our results reinforce the role of the melanocortin pathway (including *MC3R*, *MC4R* and *SIM1*) and bring to light other genes with highly penetrant obesogenic single allele



RSVs like *PPARG*(regulator of adipocyte differentiation) and *BDNF* (regulator of stress response and appetite).

Free Communication Session, Saturday,  
September 16, 2017, 8:45-9:45am  
Type 2 diabetes and other carbohydrate  
metabolism #2  
FC66 – FC70

FC66

DIABETES MELLITUS IN THE LONG-TERM FOLLOW-UP OF  
NON-PANCREATECTOMISED PATIENTS WITH PERSISTENT  
HYPERINSULINAEMIC HYPOGLYCAEMIA OF INFANCY DUE TO  
LOSS-OF-FUNCTION MUTATIONS IN THE *ABCC8* GENE: A  
NEW FORM OF MONOGENIC DIABETES?

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**Objectives:** Mutations in the *ABCC8* gene are the most  
common cause of congenital hyperinsulinism (CHI). Diabetes  
has been observed in the evolution of several non-  
pancreatectomized patients.

To observe the evolution of glucose metabolism in non-  
pancreatectomised patients with CHI due to mutations in  
the *ABCC8* gene.

**Methods:** Twenty-three patients with CHI and mutations in  
the *ABCC8* gene followed up over the last 45 years.  
Nineteen patients were non-responders to diazoxide; 2  
patients were subtotally pancreatectomised and 4 totally  
pancreatectomised.

Continuous glucose monitoring (CGM) was performed  
periodically from 2003 in non-pancreatectomized patients.  
Oral glucose tolerance test (OGTT) was performed from the  
age of 5 years if hyperglycaemias were detected by CGM  
(glucose excursions>180 mg/dL). Diabetes was diagnosed  
according to ADA criteria. Normal CGM was defined as all  
glucose values< 140 mg/dL.

**Results:** Follow-up of 15 (8 girls) non-pancreatectomised  
patients (1 non-pancretectomised patient died from  
pulmonary hypoplasia and follow-up of other is not  
available). Current age: 17.04±9.03 years (2.8-42).  
Eight patients presented normal CGM; current age: 11.0 ± 4.8  
(16.2-2.9) years. Genetic study: 3 homozygous/compound  
heterozygous, 5 heterozygous. Four responded to diazoxide  
and only the youngest remains on this treatment.  
Seven patients presented hyperglycaemias during evolution:  
2 developed diabetes (previously published); 1 patient  
previously published as glucose-intolerant developed  
diabetes at the age of 26 years (hyperglycaemia and HbA1c

6.7%); one patient (patient 6) developed diabetes at the age  
of 6.5 years (first diabetic OGTT) and was insulinised at the  
age of 12; three patients presented hyperglycaemias by CGM  
from 13 to 1 years of age, one of whom had a diabetic OGTT  
(patient 4) with HbA1c of 6.1% and the other two have their  
OGTT pending (patients 6 and 9). Anti-GAD, -IA2 and -ICA  
antibodies were negative in all seven.

**Conclusions:** - A significant proportion (7 of 15) of patients  
with CHI due to mutations in the *ABCC8* gene who were  
medically treated developed hyperglycaemias and 4 of the 7  
diabetes mellitus.

- No relationship appeared to exist between diabetes  
occurrence and *ABCC8*.

- Responders to diazoxide did not present hyperglycaemias  
after treatment withdrawal.

Table: OGTT and CGM in hyperglycemic patients

Patient	Sex	Current age (years)	Age at diabetes diagnosis (years)	CGM(*)		OGTT 120'  Glucose (mg/dL)/insulin (mIU/L)
				n	%time glucose>140 mg/dL (mean and limits)	Maximum glucose (mg/dL) (mean and limits)
3	F	14.5		5	5.8 (3.5-9.9)	209/262- 194)
4	F	18.3	13	2	8.7 (5-12.5)	167/162-173)
6	F	14.9	6.5	7	23 (3-81)	250/165- 321)
9	F	6.7		2	(8-9)	224-220

(\*) before diabetes was diagnosed

FC67

SULPHONYLUREAS ARE A HIGHLY EFFECTIVE AND SAFE  
LONG-TERM TREATMENT FOR NEONATAL DIABETES DUE TO  
*KCNJ11* MUTATIONS: THE FIRST 10-YEAR FOLLOW-UP STUDY  
OF A LARGE INTERNATIONAL COHORT.

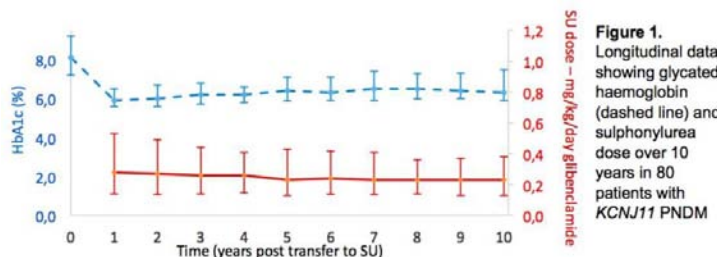
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**Objectives:** Mutations in *KCNJ11* cause permanent neonatal  
diabetes (PNDM) due to activation of the pancreatic

K<sub>ATP</sub> channel. 90% of patients can transfer from insulin to sulphonylurea therapy (SU) improving glycaemic control at 1 year. "SU failure", where SU no longer maintains good glycaemic control, is seen in ~50% of people with Type 2 diabetes after 5 years of treatment. No previous studies have assessed long-term efficacy and safety of SU in *KCNJ11* PNDM. We report the first 10-year follow-up of a large international cohort of patients with SU-treated *KCNJ11* PNDM.

**Methods:** We followed up all patients diagnosed with *KCNJ11* PNDM in laboratories in Exeter, Bergen, Rome, Paris and Poland and who successfully transferred from insulin to oral SU prior to 2007. Primary outcomes were sulphonylurea efficacy and metabolic control. Secondary outcomes were side effects, hypoglycaemia and complications. OGTT and IVGTT were done in six patients. **Results:** Long-term data were available for 81/91 eligible patients (89%). Median follow-up duration was 10.2 years. 75/81(93%) remained on SU alone at most recent follow-up: 6/81(7%) were on SU and daily insulin. Excellent glycaemic control was maintained long-term (fig. 1): in patients on SU alone, median(IQR) HbA1c pre-transfer to SU, at 1-year and at 10-years was 8.0(7.2-9.2)%, 5.9(5.5-6.4)% and 6.3(5.9-7.2)%. Median SU dose fell over the period of follow-up (1 year dose 0.28 mg/kg/day and 10 year dose 0.23 mg/kg/day,  $p=0.01$ ). There were no reported episodes of severe hypoglycaemia. Side-effects (diarrhoea/nausea/reduced appetite/abdominal pain) were reported in 10/81(12%); these were transient and no patients discontinued SU as a result. Microvascular complications were reported in 7/81(9%) patients; there were no macrovascular complications. Patients with complications were older at age of transfer to SU than those without complications (age at transfer 20.5 v 4.1 years,  $p=0.0005$ ). OGTT and IVGTT revealed good insulin response to glucose and maintained incretin effect after ten years.

**Conclusions:** SUs are a safe, highly effective treatment for *KCNJ11* PNDM, maintaining excellent glycaemic control over 10 years despite the dose of SU being reduced. In contrast to Type 2 diabetes "SU failure" is not seen with prolonged treatment in *KCNJ11* PNDM.



**Figure 1.** Longitudinal data showing glycated haemoglobin (dashed line) and sulphonylurea dose over 10 years in 80 patients with *KCNJ11* PNDM

FC68

## PSEUDOACROMEGALY AND INSULIN RESISTANCE, A RARE DISORDER OF DOWNSTREAM INSULIN SIGNALING

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**Objectives:** We report a case of a 12 year old female presenting to pediatric diabetes clinic with extremely tall stature, acanthosis nigricans, severe hirsutism, obesity, and acromegaloid features. Due to her unique presentation, we were concerned that she has an insulin resistance syndrome. However, most insulin resistance syndromes are associated with short stature.

**Methods:** The subject and her first-degree relatives underwent extensive metabolic phenotyping in addition to whole exome sequencing.

**Results:** The subject's IGF-1 was normal, however she was noted to have extremely elevated insulin (2446 uIU/mL) postprandially. She had biochemical hyperandrogenism with elevated free testosterone (16 pg/mL), and a relative leptin deficiency (19.0 ng/mL). The subject's bone age was 14 years, giving her a predicted adult height of 1.83m (+3.23 SDS). Two hour oral glucose tolerance testing indicated an undetectable growth hormone at 90 minutes, however her insulin was elevated to 799 uIU/mL at 60 minutes.

Whole exome sequencing identified no variants in insulin, insulin receptor, or the IGF-1 receptor. However it did identify 2 variants in genes critical to the FGF-21 signaling pathway. Fibroblast growth factor 21 (FGF-21) is a recently discovered peptide that has gained attention for its important effects on insulin sensitivity, growth hormone, and fertility. The mutated genes were Fibroblast Growth Factor Receptor 1 (*FGFR1*) and beta Klotho (*KLB*). *FGFR1* and *KLB* are transmembrane co-factors that bind FGF-21. These variants (p.V102I and p.S9Y) were inherited in trans from each parent. They are extremely rare, and are predicted to be damaging by the majority of *in-silico* variant prediction programs. The subject's FGF-21 level was elevated (391.3 pg/mL) compared to her father (104.3 pg/mL) and mother (225.2 pg/mL). Mutant and wild type *FGFR1* and *KLB* were transfected into various cell lines in order to assay downstream insulin signaling.

**Conclusions:** We hypothesize that, together, the *FGFR1* and *KLB* mutations act in a dominant and synergistic manner, resulting in this subject's severe insulin resistance, tall stature, and hirsutism. If true, this would represent a novel category of insulin resistance syndromes related to FGF-21.

FC69

## ADIPOCYTE GAMMA-SECRETASE INHIBITION ALTERS INFLAMMATORY CYTOKINE PRODUCTION

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**Objectives:** Adipose tissue-immune system interactions likely play a significant role in the pathophysiology of obesity and Type 2 diabetes mellitus. Expanding research suggests that adipocytes themselves may regulate inflammatory cascades. The gamma-secretase enzyme complex has an emerging role in regulation of both adipose insulin signaling as well as the immune system. Pathways regulated by gamma-secretase in a variety of cell types have also been implicated in obesity phenotypes. Previous data has suggested that adipocyte-

specific blockade of gamma-secretase leads to decreased macrophage recruitment and/or activation in adipose tissue. We therefore hypothesized that the gamma-secretase enzyme complex is required for adipocyte-mediated inflammatory signaling.

**Methods:** To explore this hypothesis in a controlled *in vitro* system, we examined the effect of gamma-secretase inhibition on fully differentiated 3T3-L1 adipocytes following exposure to lipopolysaccharide (LPS). We utilized qRT-PCR to follow changes in gene expression of a variety of inflammatory cytokines and immunoreceptors previously identified in adipocytes, including TNF- $\alpha$ , IL-6, MCP1, CD44, and TREM2. Cytokine secretion was also determined by ELISA.

**Results:** While baseline transcription of *TNFA*, *IL6*, and *CD44* were not significantly affected by g-secretase inhibition, *MCP1* and *TREM2* mRNA levels were significantly downregulated after overnight exposure to a g-secretase inhibitor (decreased 66% and 77%, respectively,  $p < 0.01$ ,  $n = 6$ ). Exposure to increasing amounts of LPS (range 0 to 10 ng/mL) for 6 hours led to an expected increase in IL6 and MCP1 secretion, which could be significantly attenuated by pre-treatment with a g-secretase inhibitor. MCP1 secretion was decreased 1.5 fold ( $p < 0.05$ ,  $n = 6$ /condition); surprisingly, IL-6 secretion was decreased 2.2 fold ( $p < 0.01$ ,  $n = 6$ /condition) despite the lack of change in *IL6* transcription.

**Conclusions:** This data suggests that the gamma-secretase enzyme complex plays a variety of roles in both the production and secretion of inflammatory cytokines in adipocytes. This may open new avenues of research into pathways regulating adipose inflammation, insulin resistance, and Type 2 diabetes mellitus.

FC70

#### THE PREVALENCE OF ABNORMAL LIPIDS AND PREDIABETES IS SIGNIFICANTLY INCREASED IN YOUTH WITH DOWN SYNDROME COMPARED TO TYPICALLY-DEVELOPING PEERS

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**Objectives:** Down syndrome (DS) is associated with increased obesity. Although previously thought to be protected from atherosclerosis, our group previously documented a more atherogenic lipid profile in DS youth compared to controls. However, the prevalence of abnormal glucose tolerance (AGT) and actual dyslipidemia in DS youth compared to controls is not known. We aimed to compare the prevalence of prediabetes and dyslipidemia in youth with DS compared to typically-developing controls, using current clinical thresholds.

**Methods:** DS and typically-developing youth (age 10-20y) of comparable age, sex, race, ethnicity, and BMI%ile were enrolled at two large children's hospitals. Fasting lipids and

oral glucose tolerance tests were performed. Lipid abnormalities were defined using NHLBI guidelines for children 10-19 years. Impaired glucose tolerance (IGT), impaired fasting glucose (IFG), and overall AGT(IGT and/or IFG) prevalence were measured in both groups, limited to those with BMI $\geq$ 85%ile on the CDC BMI chart. Unpaired t-test and/or Wilcoxon rank sum tests were used as appropriate to compare continuous variables, and Fisher's exact test was used for categorical variables.

**Results:** 144 DS youth (age  $14.6 \pm 3.3$ y, 56%F, 20% African American(AA)) were compared to 87 controls(age  $14.9 \pm 3.1$ y, 59%F, 27%AA) of similar BMI ( $27.0 \pm 7.9$  DS vs  $27.2 \pm 7.8$  controls,  $p = 0.9$ ). Compared to controls, DS youth had increased prevalence of total cholesterol  $\geq 170$ mg/dl (50.7% vs 23%,  $p < 0.0001$ ), triglycerides(TG)  $\geq 90$ mg/dl (49.3% vs 33.3%,  $p = 0.02$ ), TG $\geq 130$  mg/dl(26.4% vs 11.5%,  $p = 0.007$ ), LDL-C  $\geq 110$  mg/dl (45.5% vs 19.5%,  $p < 0.0001$ ), and non-HDL-C  $\geq 120$ mg/dl (58.3% vs 27.6%,  $p < 0.0001$ ). Among those with BMI  $\geq 85$ %ile (DS  $n = 72$ , control  $n = 51$ ), youth with DS had greater prevalence of AGT (26.4% vs 9.8%,  $p = 0.036$ ) and IFG(14.3% vs 3.6%,  $p = 0.049$ ). There was no difference in prevalence of HDL $\leq 40$  mg/dl or IGT.

**Conclusions:** Contrary to prior dogma, DS youth had significantly higher prevalences of abnormal lipid and glucose levels compared to typically developing controls, and should be carefully screened by clinicians. Future studies are needed to determine if these abnormalities in cardiometabolic risk during youth are predictive of later ischemic heart disease and type 2 diabetes.

#### Free Communication Session, Saturday, September 16, 2017, 8:45-9:45am

##### Thyroid

##### FC71 – FC75

FC71

#### BORDERLINE NEONATAL TSH LEVELS AND EDUCATIONAL AND DEVELOPMENT OUTCOMES: A POPULATION-BASED RECORD-LINKAGE STUDY

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**Objectives:** Newborn screening has almost eliminated intellectual disability in children with Congenital hypothyroidism however, clinical uncertainty remains about infants with TSH concentrations lower than the newborn screening cutoffs. We assessed the association between neonatal TSH concentrations and educational and developmental outcomes.

**Methods:** A population-based record-linkage study of all liveborn infants undergoing newborn screening from 1994 to 2008 in New South Wales, Australia. Developmental and educational outcomes were linked to individual records by the NSW Centre for Health Record Linkage. The primary educational outcome was the proportion of students with National Assessment Program Literacy and Numeracy results lower than the national minimum standard in reading or numeracy and the primary developmental outcome was the proportion of children assessed at high risk by the Australian Early Development Census at age 4–6 years. The proportions of infants with each outcome were calculated per percentile (0–100) of TSH concentration. Multivariable logistic regression was used to account for potential confounding by maternal and fetal variables known to affect neonatal TSH concentrations or neurodevelopmental outcomes.

**Results:** 503,706 infants had a newborn TSH result that linked to a developmental or educational outcome. As newborn TSH levels increase, from the 75–80<sup>th</sup> centile, the risk of having a poor neurodevelopmental outcome increased until the 99.95<sup>th</sup> centile. Infants with a newborn TSH  $\geq$ 99.95<sup>th</sup> centile, likely to have diagnosed and treated CH, had similar results to infants with a TSH <75<sup>th</sup> centile. Infants with a newborn TSH result between 99.5<sup>th</sup>–99.9<sup>th</sup> centile were more likely to have special needs (adjusted odds ratio (aOR) 1.68, 95% confidence interval (95%CI) 1.23–2.30), poor numeracy performance (aOR 1.57, 95%CI 1.29–1.90) and poor development (aOR 1.52, 95%CI 1.20–1.93).

**Conclusions:** We found an association between neonatal TSH concentrations lower than the present newborn screening thresholds and poor educational and developmental outcomes. This association needs further investigation to assess whether assessment and treatment of these infants might improve their long-term cognitive outcomes.

FC72

#### DETERMINATION OF CALCITONIN REFERENCE RANGES FROM HEALTHY INFANTS, CHILDREN AND ADOLESCENTS – AN IMPORTANT TOOL FOR THE EARLY DIAGNOSIS OF MEDULLARY THYROID CANCER

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**Objectives:** The aim of our study was to establish age-dependent reference ranges for calcitonin (CLCT) in serum of healthy infants, children and adolescents to enable the diagnosis of medullary thyroid cancer (MTC), to monitor MTC follow-up and to validate CLCT reference data in pediatric cohorts with thyroid diseases, asthma and multiple endocrine neoplasia type 2 (MEN2).

**Methods:** 3196 serum samples of children in the age range of 1 month and 17.9 years were collected. Reference ranges

were established between the 2.5<sup>th</sup> and the 97.5<sup>th</sup> percentile. CLCT concentrations of children with thyroid diseases (n=138), asthma (n=163) and MEN2 (n=49) were measured for comparison. All sera were quantified by the Cobas® Calcitonin ECLIA (Roche). The LMS-method was used to set up reference ranges.

**Results:** CLCT levels of healthy children demonstrated a dynamic course during childhood. For both gender the highest levels were detected in the first months of life. A decline was observed until the age of 3 years as well as a second minor decline during puberty. CLCT levels of boys were significantly higher compared to girls (p<0.01). 3.7% of patients with thyroid disease and 4.9% of patients with asthma had increased CLCT levels. From the MEN2 cohort every RET-protocogene carrier (n=10) revealed a detectable CLCT value. After thyroidectomy 78.9% of MEN2 patients had undetectable levels whereas 11.1% were suspicious of micrometastasis or relapse.

**Conclusions:** This is the first study to establish CLCT reference ranges for pediatric uses by the highly sensitive and precise ECLIA technology. The data suggests different regulation of this hormone within the first years of life. Cut-offs from the 97.5<sup>th</sup> percentile of infants were clearly higher than the respective cut-offs of adults which are frequently used for reference in pediatrics. Probably due to the higher thyroid volume boys revealed significantly higher CLCT values than girls. Thyroid disease and asthma that were investigated to be influencing factors for hypercalcitoninemia in adults, appear to have only a minor effect on CLCT level in pediatric patients. The ECLIA method was found to be a suitable tool to monitor CLCT in children with MEN2, also without stimulation by calcium or pentagastrin.

FC73

#### EPIDEMIOLOGY OF CHILDHOOD HYPERTHYROIDISM IN FRANCE: A NATIONWIDE POPULATION-BASED STUDY

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**Objectives:** Hyperthyroidism affects all age groups, but only limited epidemiological data are available for children. We therefore investigated the epidemiology of hyperthyroidism in children and adolescents in a nationwide study in France.

**Methods:** We used antithyroid drug reimbursement recorded in the French National Health Insurance database in 2015 as an indicator of childhood hyperthyroidism (patients aged 6 months up to < 18 years). We estimated incidence rates (IRs) and 95% confidence intervals with a non-linear model based on a Poisson distribution. We also performed a spatial analysis of the case distribution in France.

**Results:** We identified 670 cases of hyperthyroidism in children during the year 2015, with no evidence of month to month variation. Twenty patients (3%) had an associated autoimmune or genetic disease, type 1 diabetes and Down

syndrome being the most frequent. The annual IR for 2015 was 4.58/100,000 person-years (95% CI 3.00-6.99/100,000). The IR increased with age in both sex from approximately 5 years. This increase was particularly marked from eight years onwards in girls and 10 years onwards in boys. The increase was more pronounced in girls, and there was a female preponderance in all age groups (female to male sex-ratio 3.27:1). The observed interaction between age and sex revealed that the effect of being female increased with age: girls were 3.2 times more likely to be affected than boys in the [10-14 years] age group, and 5.7 times more likely to be affected in the [15-17 years] age group. About 10 % of the patients were affected very early (below the age of five years), with a sex ratio of 1:1.43. No conclusions could be drawn concerning a possible spatial pattern.

**Conclusions:** These original findings provide further insight into the IR of this condition and the impact of the sex of the patient during childhood and adolescence. They also reveal a higher IR than expected from data for other countries in Northern Europe, consistent with a possible increase in IR.

FC74

#### THE PARIS-IMAGINE “HYPOTHYSEQ NGS PANEL” IS NOW FUNCTIONAL AND BRINGS VALUABLE INFORMATION ON THE GENETICS IN A LARGE COHORT OF CHILDREN WITH CONGENITAL HYPOTHYROIDISM

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**Objectives:** Congenital hypothyroidism (CH) is mainly due to thyroid dysgenesis (TD) (65%) and dyshormonogenesis (DH) (35%). Genes implicated in DH are well known while causative mutations in TD account for less than 5% of all cases. Our aims were 1) to develop a custom targeted NGS strategy for the molecular diagnosis in CH of various causes and 2) to assess the possible molecular implication of candidate genes.

**Methods:** The HypothySeq NGS panel has been designed for different thyroid disorders. We included 78 genes: i) 23 known genes; causative genes for DH and TD, for defects in thyroid hormone, transport proteins, inborn errors of thyroid hormone membrane transport, metabolism or action and ii) 55 candidate genes, arising from invalidated animal models (n=27) or from human pathologies or experimental biology

(n=28). We performed targeted NGS using SureSelectXT Target Enrichment Reagent Kit. We have tested a cohort of 226 TD patients, 17 DH patients and 6 positive controls.

**Results:** In TD patients, we found 10 variants in known causative genes at the heterozygous state (6 mutations in *PAX8*, 3 in *NKX2-1* and 1 in *TSHR*) considered pathogenic. No mutation was found in *HHEX* and *FOXE1* genes. In patients considered DH, 12 mutations were identified in 8 patients (2 heterozygous mutations in *PAX8*, 1 homozygous mutation in *TG* and 1 in *DUOX2*, 2 composite heterozygous mutations in *TPO*, in *NIS* and 2 in *TG*). Interestingly, we found three coding heterozygous mutations in *TBX1*, 3 for *SALL1*, 1 for *NTN1*: 3 mutations may be pathogenic being in functional domains and *in silico* prediction. Surprisingly, we found several mutated candidate genes in the same patient and sometimes with a heterozygous variant of DH causative genes.

**Conclusions:** We designed and validated a targeted NGS panel for diagnosis of congenital thyroid disorders. The HypothySeq panel allowed the molecular diagnosis of 4,4% of TD patients and 47% of DH patients with causative genes. The analysis of results on candidate genes in TD patients will allow us to establish genotype-phenotype correlations. This first screening step of thyroid disorders improves molecular diagnosis for patients at a lower cost.

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FC75

#### MUTATIONS IN IRS4 ARE ASSOCIATED WITH CENTRAL HYPOTHYROIDISM

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**Objectives:** Congenital central hypothyroidism (CeH) may occur isolated, or in combination with other pituitary hormone deficiencies. Although a fourth causative gene for CeH was recently reported (*TBL1X*), the etiology of isolated CeH remains unsolved in many cases.

**Methods:** Using whole exome sequencing in two unrelated sets of brothers with idiopathic isolated CeH, we identified frameshift mutations in the insulin receptor substrate 4 (*IRS4*) gene. The IRS-family acts as an interface between tyrosine kinase receptors, including the leptin receptor, and multiple intracellular signalling pathways. Sanger sequencing of this gene in unrelated cases of idiopathic isolated CeH revealed two additional frameshift mutations in three families. We performed clinical and biochemical characterization of the probands and relatives with a mutation identified by family

screening. In additional experiments, we investigated *IRS4* mRNA expression in post-mortem human hypothalamus and pituitary tissue, and measured serum thyroid hormones, and *Trh* and *Tshb* mRNA expression in respectively hypothalamus and pituitary of *Irs4* knockout mice.

**Results:** Family screening detected mutations in 10 relatives (one male). All male mutation carriers (n=8) had CeH with plasma free thyroxine (FT4) concentrations below the reference interval in combination with thyrotropin concentrations within the reference interval. Female carriers had FT4 concentrations in the lower half of the reference interval. MRI of the hypothalamus and pituitary in 11 mutation carriers showed no structural abnormalities. 24-hour TSH secretion profiles were tested in two adult male patients and showed decreased basal, pulsatile and total secretion of TSH. *IRS4* mRNA was expressed in the several human hypothalamic nuclei, including the paraventricular nucleus, and the pituitary gland. *Tshb* mRNA expression in pituitaries of female *Irs4* knockout mice was clearly decreased while plasma T4 was unaltered.

**Conclusions:** Mutations in *IRS4* are associated with familial isolated CeH in men. As *IRS4* is responsible for mediating signalling by tyrosine kinase receptors, including the leptin receptor, we hypothesize that the CeH in these men is caused by impaired leptin signalling in hypophysiotropic TRH neurons.

## Free Communication Session, Saturday, September 16, 2017, 8:45-9:45am Neuroendocrinology including hypothalamic pituitary FC76 – FC80

FC76

### IDENTIFICATION OF GENETIC VARIANTS IN A LARGE COHORT OF PATIENTS WITH CONGENITAL HYPOTHALAMO-PITUITARY DISORDERS

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**Objectives:** Congenital hypothalamo-pituitary (HP) disorders, including congenital hypopituitarism (CH) and hypogonadotrophic hypogonadism (HH), are frequently associated with midline brain/craniofacial abnormalities. Phenotypic severity ranges from fatality, to holoprosencephaly (HPE), septo-optic dysplasia (SOD), and isolated CH or hormone deficiencies [GH deficiency (GHD), HH].

**Methods:** Our CH patient cohort (n=1,839 samples) has been screened for mutations in known causative genes specific to their phenotype. Those with unique complex phenotypes are undergoing whole exome sequencing (WES). Control databases are consulted for any identified variants. Expression studies of novel genes are performed on human embryonic tissue from the HP region and related tissues, followed by functional studies to show significance of variants.

**Results:** *HESX1* mutations were identified in <1% (7/724) and *SOX3* in 2% (7/354) of CH patients, including SOD. *SOX2* and *OTX2* accounted for 22% and 7% respectively of those with severe eye phenotypes (13/59, 4/59). Variants in Kallmann syndrome (KS) genes were identified in SOD patients; these included *PROKR2* (2%), *FGF8* (<1%) and *KAL1* (<1%) variants. In isolated CH patients, mutations in *PROP1* were present in 7% (18/253), *POU1F1* in 9% (12/139), *LHX3/LHX4* in 6% (7/110) and *GLI2* in 3% (3/106). *GH1* or *GHRHR* mutations were identified in 10% of IGHD patients (51/413). In HH/KS patients, 5% (4/84) had mutations in KS genes; *KAL1* (2), *FGFR1* (2). In HPE patients, 5/64 (8%) had an *SHH* (4) or *FGF8* (1) mutation. Screening is ongoing for all of these genes in CH patients. A total of 52 pedigrees with familial or unique phenotypes had WES, with 33 novel variants identified in 81 patients so far.

**Conclusions:** To date, we have identified mutations in 175/1,839 (10%) CH patients; the genetic cause remains unknown in the majority. Given the phenotypic variability, Sanger sequencing is not an optimal strategy; targeted sequencing using microarrays or next generation sequencing may identify more variants. Epigenetic factors may also need consideration. Phenotypic characterization and functional studies are essential to validate any novel variant.

FC77

### OXYTOCIN IN CHILDHOOD-ONSET CRANIOPHARYNGIOMA - FIRST EXPERIENCES WITH NEUROPSYCHOLOGICAL EFFECTS OF OXYTOCIN ADMINISTRATION

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**Objectives:** Quality of survival after childhood craniopharyngioma (CP) is frequently impaired by hypothalamic involvement (HI) and sequelae such as obesity and neuropsychological deficits. Oxytocin (OXY) is produced in the hypothalamus, secreted by posterior pituitary gland, and plays a major role in regulation of behavior and body composition.

**Methods:** In a cross-sectional study, OXY saliva concentrations were analyzed in 34 CP and in 73 healthy controls. OXY was measured in saliva before and after standardized breakfast and associations with gender, body mass index (BMI), HI, diabetes insipidus, and irradiation were analyzed. Furthermore in a pilot study, emotion recognition

abilities were analyzed with regard to OXY concentrations in saliva and urine before and after nasal administration of 24 IU OXY in 10 CP patients with hypothalamic lesions (4 grade I: limited to anterior hypothalamic areas; 6 grade II: involving mammillary bodies and posterior hypothalamic areas). Perception and identification of emotional expressions were tested using the Geneva Multimodal Emotion Portrayals (GEMEP) corpus. Current mental state was assessed by Multidimensional Mood Questionnaire.

**Results:** In cross-sectional analyses, CP with preoperative HI showed similar OXY levels compared to CP without HI and controls. However, CP with grade I surgical hypothalamic lesions presented with lower levels ( $p=0.017$ ) of OXY under fasting condition compared to CP with grade II surgical lesion and CP without hypothalamic lesions (grade 0). CP patients' changes in OXY levels before and after breakfast correlated ( $p=0.02$ ) with their BMI. In a pilot trial, nasal administration of OXY was well tolerated and resulted in increased OXY concentrations in saliva and urine. After OXY administration, CP with postsurgical grade I hypothalamic lesions showed improvements in emotional identifications compared to CP with grade 2 hypothalamic lesions. CP patients improved assignment to negative emotions.

**Conclusions:** CP patients continue to secrete OXY, especially when anterior hypothalamic areas are not involved, but OXY shows less variation due to nutrition. OXY might have positive effects on emotion perception in CP with specific lesions of anterior hypothalamic areas.

FC78

#### A NOVEL DENOVO FORKHEAD BOX A2 (FOXA2) MUTATION LEADS TO CONGENITAL HYPERINSULINISM, CRANIOFACIAL DYSMORPHIC FEATURES AND CONGENITAL HYPOPITUITARISM

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**Objectives:** FOXA2, located at the at the cytogenetic location 20p11.21, has been shown to play a role in the pancreatic  $\beta$ -cell development. FOXA2 knockout mouse has been shown to exhibit severe hyperinsulinaemia. Genes at 20p11.21 have been implicated to have a potential role in the pituitary development. We show for the first time that a de novo mutation in the developmantal transcription factor FOXA2 (formerly HNF3B) is associated with congenital hyperinsulinism (CHI) combined with hypopituitarism in humans.

**Methods:** A female baby born to non-consanguineous Caucasian parents at 42 weeks gestation with a birth weight of 4.185Kg (+1.72SDS) was noted to have high glucose requirement and a hypoglycaemia screen confirmed CHI. She also developed TSH, ACTH and GH deficiencies. Genetic analysis was negative for *ABCC8*, *KCNJ11*, *HNF4A* or *GCK* mutations. MRI brain showed a hypoplastic anterior pituitary, absent posterior pituitary, thin pituitary stalk and corpus callosum. 18F-DOPA PET-CT suggested diffuse pancreatic lesion. She has solitary median maxillary incisor, congenital nasal pyriform aperture stenosis, pulmonary stenosis, choroidal coloboma and hepatic portal bridging fibrosis.

**Results:** Whole exome trio sequencing identified a novel de novo heterozygous mutation in FOXA2 (c.505T>C, p.(S169P) in the child. The identified variant is highly conserved, not present in control databases and predicted to be deleterious to the protein function. We have demonstrated strong expression of FOXA2 mRNA in the pituitary of mouse embryos by *in situ* hybridisation. Expression profiling on human embryos by immunohistochemistry, showed strong expression in the neural tube, third ventricle, diencephalon and in the pancreas. Transient transfection of HEK293T cells with Wt (Wild type) hFOXA2 or mutant hFOXA2 showed an impairment in transcriptional reporter activity by the mutant hFOXA2. Further biochemical analyses demonstrated that the c.505T>C, p.(S169P) variant is pathogenic resulting in lower expression levels when compared with Wt hFOXA2

**Conclusions:** We describe, for the first time, the expression of FOXA2 in human pituitary and pancreatic development and the disruptive effect of the mutation on the protein function thereby demonstrating FOXA2 as a novel candidate gene in humans with pituitary and pancreatic  $\beta$ -cell disorders.

FC79

#### MOLECULAR ANALYSIS OF BRAZILIAN PATIENTS WITH COMBINED PITUITARY HORMONE DEFICIENCY (CPHD) AND ORTHOTOPIC POSTERIOR PITUITARY LOBE (OPP) REVEALS 8 DIFFERENT PROP1 ALTERATIONS WITH THREE NOVEL MUTATIONS

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**Objectives:** Mutations in *PROP1*, *HESX1* and *LHX3* are associated to CPHD and OPP. We aimed to identify mutations in *PROP1*, *HESX1* and *LHX3* in a large cohort of patients with CPHD and OPP (43 Brazilian, 2 Argentinian).

**Methods:** We studied 30 index patients with CPHD and OPP (7 familial and 23 sporadic) as well as 15 relatives. All index-patients presented GH deficiency, 28 had TSH deficiency, 25 had LH/FSH deficiency, and only 21 had ACTH deficiency. *PROP1* was sequenced by the Sanger method in all except one sporadic case studied by a candidate gene panel. Multiplex-ligation-dependent probe amplification (MLPA) was applied to 2 familial cases in whom *PROP1* failed to amplify by PCR. In the 13 patients without *PROP1* mutations, *HESX1* and *LHX3* were sequenced by the Sanger method and one case was studied by whole-exome sequencing (WES).

**Results:** Sanger sequencing identified mutations in *PROP1* in 13 index cases, with two novel mutations in compound heterozygous state in 2 index cases: c.1A>G and c.342+1G>C, respectively associated with c.263T>C (p.Phe88Ser) and c.218G>A (p.Arg73His). Mutation c.1A>G affects the initiation codon and abolishes the translation of the protein, while c.342+1G>C affects splicing of exon 2. The mutations already described c.150delA (p.Arg53Aspfs\*112), c.263T>C (p.Phe88Ser) and c.301\_302delAG (p.Leu102Cysfs\*8) were found in homozygous state in 11 index cases. The candidate gene panel identified the novel mutation c.109+1G>A in *PROP1* in compound heterozygous state with c.301\_302delAG (p.Leu102Cysfs\*8) in 1 sporadic case. MLPA confirmed complete *PROP1* deletion in two families. The homozygous *HESX1* mutation c.68T>C (p.Ile26Thr) was identified by WES in one sporadic case born to consanguineous parents. No *LHX3* mutation was detected. All mutations found in our cohort were classified as pathogenic according to the American College of Medical Genetics guideline.

**Conclusions:** *PROP1* mutations, including three novel mutations described herein, were detected in 53% (16/30) of this cohort with CPHD and OPP, with 7/7 of familial cases and 9/23 of sporadic cases harboring *PROP1* mutations. The high prevalence and diversity of *PROP1* mutations is probably associated to the ethnic background of this cohort.

FC80

#### DIABETES INSIPIDUS AFTER MODERATE-SEVERE TRAUMATIC BRAIN INJURY IN CHILDREN

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**Objectives:** Traumatic brain injuries (TBI) are a major cause of death and disability in children. There are limited pediatric data on the incidence and course of diabetes insipidus in the immediate period after TBI. In this study, we investigated the incidence of diabetes insipidus and assessed the relationship between diabetes insipidus and mortality after moderate to severe traumatic brain injuries in children.

**Methods:** Children less than 18 years of age who were hospitalized between January 2005 to April 2011 in a U.S. academic hospital with a Level 1 Trauma Center were screened for inclusion in this retrospective chart review. Children were identified using ICD-9 codes for traumatic brain injuries. Those with a Glasgow Coma Scale (GCS) score of  $\leq 12$  assessed in the emergency department were included and classified as having moderate to severe brain trauma. Diabetes insipidus was defined during hospitalization as a serum Na  $\geq 146$  mmol/L with increased serum osmolality  $> 300$  mOsm/kg and polyuria  $> 2$  L/ m<sup>2</sup>/ day as well as at least any 1 of the following: urine osmolality  $< 300$  mOsm/kg, diabetes insipidus diagnosed in the medical chart, or vasopressin administration during hospitalization.

**Results:** A total of 156 children were identified with moderate to severe traumatic brain injury during the study period. 18 children (11.5%) were diagnosed with diabetes insipidus during hospitalization. Overall mortality was 14% (22/156). Mortality in children who developed diabetes insipidus was 83% (15/18), while mortality in children without diabetes insipidus was 5% (7/138), ( $p < 0.001$ ).

**Conclusions:** Development of diabetes insipidus is relatively common after moderate-severe traumatic brain injury in children. The occurrence of diabetes insipidus is an ominous sign associated with high mortality. Further prospective studies are warranted in better clarifying the natural history of diabetes insipidus after traumatic brain injuries in children and effects of treatment in improving survival.

#### Free Communication Session, Saturday, September 16, 2017, 3:15-4:15pm

##### Type 1 diabetes #2 FC81 – FC85

FC81

#### CARDIOVASCULAR AUTONOMIC DYSFUNCTION PREDICTS INCREASING ALBUMIN EXCRETION IN TYPE 1 DIABETES

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**Objectives:** To determine the potential role of autonomic dysfunction in the development of renal complications of type 1 diabetes in the pediatric population

**Methods:** In this prospective study, 199 children and adolescents (47% female; median [IQR] age: 14.16 [11.02 – 17.02] years) in the Oxford Regional Prospective Study underwent assessment of autonomic function ~5 years after

diagnosis, and were subsequently followed with longitudinal assessments of HbA<sub>1c</sub> and urine albumin-creatinine ratio (ACR) over  $8.59 \pm 3.39$  years. Autonomic function was assessed with 4 standardized tests of cardiovascular reflexes: (i) heart rate response (HRR) to Valsalva Maneuver, (ii) HRR to deep breathing, (iii) HRR to standing, and (iv) blood pressure (BP) response to standing. Linear mixed models were used to assess the association between autonomic parameters and future rates of change in ACR.

**Results:** Independent of HbA<sub>1c</sub>, the rate of change in ACR over time was significantly influenced by: (i) HRR to Valsalva Maneuver: for every SD increase in HRR, ACR increased by 2.16% [95% CI: 0.08 – 4.28] per year, and (ii) diastolic BP response to standing (2.55% [95% CI: 0.37 – 4.77] per year per SD increase). There was also a strong trend for the effect of HRR to standing (-2.07% [95% CI: -4.11 – 0.01] per year per SD increase,  $p=0.051$ ). A lower HRR to standing in our cohort was associated with a higher minimum heart rate after standing ( $p<0.01$ ), instead of a diminished maximum heart rate ( $p=0.75$ ), indicating persistence of the known initial cardioacceleratory response.

**Conclusions:** In this cohort of young people with type 1 diabetes, future increases in urine ACR were predicted by enhanced cardiovascular reflexes at baseline, including HRR to Valsalva Maneuver and diastolic BP response to standing. This pattern of autonomic dysfunction implicates sympathetic overactivity in the pathogenesis of diabetic nephropathy.

FC82

#### EFFICACY AND SAFETY OF SWITCHING FROM INSULIN DETEMIR TO INSULIN DEGLUDEC WITH MEALTIME INSULIN ASPART IN PEDIATRIC PATIENTS WITH TYPE 1 DIABETES. AN OBSERVATIONAL PROSPECTIVE STUDY

*Nancy S Elbarbary, MD, Ain Shams University, Cairo, Egypt*

**Objectives:** Insulin degludec (IDeg; Tresiba®) is a novel basal insulin with an ultra-long, flat and stable action profile. The aim of the current study is to assess the long-term efficacy and safety of insulin degludec (IDeg) as a part of a basal-bolus therapy among children and adolescents affected by type 1 diabetes (T1DM) previously on insulin detemir (IDet).

**Methods:** In the present study, 43 T1DM patients ( $11.8 \pm 1.3$  years of age, duration  $4.6 \pm 1.9$  years) started on IDeg once daily as basal insulin after at least 1 year on IDet twice daily. The primary end-points were the changes in glycated hemoglobin (HbA<sub>1c</sub>) from baseline at 6 months. The secondary end-points were changes in insulin dose (basal and bolus), frequency of hypoglycemia and occurrence of adverse events.

**Results:** Both HbA<sub>1c</sub> and fasting plasma glucose (FPG) levels decreased significantly from  $8.2 \pm 0.3\%$  and  $139 \pm 4.2$  mg/dL at baseline to  $7.7 \pm 0.2\%$  and  $119 \pm 3.6$  mg/dL at 6 months after starting IDeg ( $P<0.001$  for both). The daily basal insulin dose was significantly reduced from  $0.67 \pm 0.04$  U/kg/day at baseline to  $0.55 \pm 0.02$  U/kg/day at the end of the study period ( $P<0.05$ ), which corresponded to 79.2% of the baseline value. Moreover, mealtime insulin aspart ( $0.64 \pm 0.15$  vs  $0.48 \pm 0.13$

U/kg/day,  $P<0.02$ ) were significantly reduced. The frequency of both overall and nocturnal hypoglycemia decreased significantly from  $4.9 \pm 0.7$  times/month to  $2.4 \pm 0.3$  times/month at 6 months after starting IDeg ( $P<0.05$ ). However, no severe hypoglycemia occurred during the study period. Rates of hyperglycemia with ketosis were significantly lower for IDeg vs. IDet ( $P<0.05$ ). Both treatments were well tolerated with comparable rates of adverse events.

**Conclusions:** In our cohort, switching from IDet treatment to IDeg was safe and seemed to improve metabolic control expressed by HbA<sub>1c</sub> and FPG levels with the added benefit of a reduced basal and bolus insulin dose while reducing the frequency of hypoglycemia episodes in young people with T1DM.

FC83

#### CAN AN ELECTRONIC CLINICAL TOOL IMPROVE COMMUNICATION AROUND EXERCISE IN YOUTH WITH TYPE 1 DIABETES?

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**Objectives:** Exercise is a risk factor for dysglycemia, especially hypoglycemia, in youth with type 1 diabetes (T1D). Previous work has shown that many youth with T1D do not exercise safely, especially with regard to the risk of post-exercise hypoglycemia. Many also report a desire for more education during diabetes clinic visits on how to manage insulin and fuel intake around exercise. We created an electronic clinical tool to survey management of T1D during and after exercise with generation of a report for providers to use with patients. The objective was to assess its feasibility and effectiveness in the clinic setting.

**Methods:** We recruited 50 T1D youth, ages 10-18 (mean  $14.8 \pm 2.4$  years). 60% used an insulin pump. Subjects completed the T1D Report of Exercise Practices (T1D-REPS) on an electronic tablet prior to a clinic visit. Participant responses were flagged if contrary to ISPAD exercise guidelines and a report of behaviors with personalized recommendations was produced for providers prior to seeing the patient in clinic. Post-clinic assessment surveys were completed.

**Results:** A mean of 4 ( $\pm 0.9$ ) responses per patient flagged as potentially unsafe. 91% of providers reported it took  $< 10$  minutes to review and discuss the report with patients; 62% of youth reported their providers used the report to discuss exercise in the clinic visit. Responses were rated on a 5-point scale (1 = not at all; 5 = very much so). Providers rated the tool's utility highly in facilitating education regarding exercise guidelines at that clinic visit (mean rating  $4.2 \pm 0.8$ ); 91% of providers rated the tool  $\geq 4$ . When asked whether its use altered management plans around exercise, 58% of youth rated the tool  $\geq 4$ . When asked if such a tool should be used

routinely in diabetes clinic, 64% of provider responses and 62% of patient responses were  $\geq 4$ .

**Conclusions:** This electronic tool identified frequent and multiple deficits in exercise safety in youth with T1D, and improved education in the clinic visit regarding exercise. Both providers and patients reported the tool frequently prompted specific behavior recommendations, and a majority felt it feasible and desirable to include in routine outpatient diabetes care.

FC84

#### PERSISTENT ELEVATIONS IN BETA CELL DEATH AMONG INDIVIDUALS WITH LONGSTANDING TYPE 1 DIABETES

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**Objectives:** Because beta cells contain increased unmethylated *preproinsulin* (*INS*) DNA compared to other cell populations, DNA release by dying beta cells leads to increased circulating levels of unmethylated *INS* DNA. Consistent with the classic paradigm of large-scale beta cell destruction early in the course of Type 1 Diabetes (T1D), this novel biomarker is elevated before and at the time of T1D onset. However, recent studies have identified persistence of beta cells years after T1D diagnosis. It is unclear whether these persistent beta cells continue to undergo destruction, or whether circulating *INS* DNA levels are linked to persistent endogenous C-peptide secretion in later stages of T1D.

**Methods:** We assayed fasting and stimulated banked sera from subjects enrolled in the T1D Exchange registry ( $n=90$ , median age: 33.5 yrs, median T1D duration: 9 yrs), determined to be either Cpep (-) or (+) based on mixed-meal tolerance testing (MMTT). Results were compared to adult nondiabetic controls ( $n=12$ ). Levels of unmethylated and methylated *INS* DNA were analyzed by droplet digital PCR using a dual fluorescent probe-based multiplex assay detecting methylation or unmethylation at bp -69 of the *INS* gene.

**Results:** Fasting and stimulated circulating unmethylated *INS* DNA levels were increased among both Cpep (-) and Cpep (+) subjects with longstanding T1D compared to non-diabetic controls ( $p<0.01$ ). Circulating fasting *INS* DNA concentrations were negatively associated with age and T1D duration ( $p=0.04$ ). Consistent with prior reports, unmethylated *INS* DNA values correlated with methylated *INS* DNA values, which were also elevated among T1D subjects ( $p<0.001$ ). Although fasting *INS* DNA concentrations correlated with stimulated concentrations, there was wide variation in the effects of meal-stimulation on DNA levels, with fasting values in the highest quartiles decreasing with stimulation ( $p<0.001$ ).

**Conclusions:** These results confirm ongoing beta cell death in individuals with longstanding T1D, even in the absence of detectable C-peptide production, suggesting that therapies targeting beta cell survival could be beneficial among patients

with longstanding T1D. Future studies in longitudinal samples will better elucidate the natural history of beta cell death after T1D diagnosis.

FC85

#### GLUCOSE CONTROL IN ADOLESCENTS WITH T1D DURING THE MEDTRONIC HYBRID CLOSED-LOOP PIVOTAL TRIAL

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**Objectives:** The MiniMed<sup>®</sup> 670G hybrid closed-loop (HCL) insulin delivery system was evaluated in a 3-month in-home pivotal trial, in adolescents (14-21 years,  $n=30$ ) and adults (22-75 years,  $n=94$ ) with T1D. For adolescents, a 0.6% reduction in glycated hemoglobin (A1c) levels (7.7% to 7.1%,  $p<0.001$ ) and increased time in target range of 71-180mg/dL (60.4% to 67.2%,  $p<0.001$ ) was observed. To further quantify HCL impact on glycemic control, an exploratory analysis was conducted in adolescents aged 14-17 years ( $n=20$ ) and 18-21 years ( $n=10$ ), during the 24-hour, night (10pm-7am) and early morning (3am-6am) periods.

**Methods:** Participants wore the system (MiniMed 670G insulin pump, Guardian<sup>®</sup> Sensor 3 glucose sensor and Guardian Link 3 transmitter) in Manual Mode for a baseline 2-week run-in phase followed by a 3-month study phase with HCL control enabled (Auto Mode), during which HCL was utilized 75.8% of the time. Distribution of sensor glucose (SG) values during the aforementioned time periods was compared between the run-in and study phases.

**Results:** The table shows the mean $\pm$ SD percent of SG values for each time period. Both age groups had increased time in target range and reductions in hypo- and hyperglycemia. The greatest percent of time in target for both groups was in the early morning, a period when the HCL algorithm functioned, for the most part, with minimal subject-delivered meal boluses and physical activity. During the early morning, the HCL algorithm-determined insulin delivery (at 5-minute intervals) led to insulin suspension 28.4 $\pm$ 8.4% and 31.5 $\pm$ 17.8% of the time, for the younger and older cohorts. Mean A1c decreased in both cohorts (14-17 year olds: 7.8 $\pm$ 0.7% to 7.2 $\pm$ 0.5%; 18-21 year olds: 7.4 $\pm$ 1.0% to

6.8±0.6%). There were no severe hypoglycemic or diabetic ketoacidosis events during the entire study.

**Conclusions:** Both adolescent groups experienced improved glycemia (increased time in target, reduced A1c, reduced exposure to hypoglycemia) during the study phase, compared to baseline. Findings from the MiniMed 670G HCL system pivotal trial suggest that the automated and dynamic delivery of basal insulin every 5 minutes might improve T1D outcomes for the difficult to manage adolescent group.

Pediatric Endocrinology Society 2017

Glucose control in adolescents with T1D during the Medtronic hybrid closed-loop pivot

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Table

	14-17 years old (n=20)		18-21 years old (n=10)	
	Run-in Phase	Study Phase	Run-in Phase	Study Phase
Percent of 24-hour SG values in reference glucose ranges, mg/dL				
≤50	0.7±0.6 (0.6, 0.1-1.1)	0.4±0.3 (0.3, 0.2-0.5)	0.7±0.6 (0.5, 0.2-1.2)	0.6±0.6 (0.5, 0.3-0.6)
≤70	4.1±2.9 (4.4, 1.8-5.6)	2.5±1.1 (2.2, 1.7-2.8)	4.6±3.0 (4.2, 3.1-5.2)	3.4±1.5 (3.2, 2.3-4.1)
71 - 180	57.9±8.3 (58.5, 53.1-63.2)	65.5±6.0 (66.4, 59.5-71.4)	65.5±13.9 (68.2, 60.9-73.1)	70.5±11.1 (70.0, 63.8-77.9)
>180	38.0±9.0 (38.9, 32.1-42.4)	32.0±5.8 (31.8, 26.2-37.4)	29.9±14.0 (29.1, 21.2-31.8)	26.1±10.4 (27.4, 19.6-33.4)
>300	4.2±3.8 (3.0, 1.8-4.9)	3.0±1.8 (2.3, 1.8-4.0)	3.1±5.3 (1.6, 0.2-2.8)	2.4±2.6 (1.4, 0.6-3.1)
Percent of night (10:00 pm-7:00am) SG values in reference glucose ranges, mg/dL				
≤50	1.1±1.4 (0.4, 0.0-1.7)	0.5±0.4 (0.4, 0.1-0.7)	1.0±1.2 (0.6, 0.0-1.3)	0.8±0.8 (0.6, 0.3-1.0)
≤70	6.3±5.9 (5.9, 1.9-9.3)	2.5±1.5 (2.4, 1.7-3.3)	4.7±3.5 (4.5, 1.5-6.6)	3.7±1.8 (3.2, 2.7-4.0)
71 - 180	63.5±12.3 (64.5, 55.8-72.5)	72.4±8.3 (71.6, 68.8-77.5)	65.7±17.9 (69.1, 60.8-72.5)	69.6±13.8 (66.7, 61.0-83.0)
>180	30.2±14.4 (28.5, 17.9-41.1)	25.0±7.9 (25.2, 20.4-28.7)	29.6±18.8 (27.0, 19.3-30.8)	26.7±13.2 (29.8, 14.3-36.3)
>300	2.7±4.1 (1.6, 0.6-3.2)	1.9±1.9 (1.5, 0.9-2.7)	3.0±5.5 (0.8, 0.0-4.2)	2.9±3.8 (1.2, 0.5-4.7)
Percent of early morning (3:00 am-6:00 am) SG values in reference glucose ranges, mg/dL				
≤50	1.1±2.3 (0.1, 0.0-1.4)	0.3±0.5 (0.1, 0.0-0.5)	1.7±2.3 (0.5, 0.0-2.1)	1.0±1.1 (0.6, 0.2-2.1)
≤70	8.0±9.7 (5.2, 1.5-11.8)	2.1±1.8 (1.7, 0.9-2.8)	6.1±5.2 (6.8, 0.0-7.9)	4.2±2.6 (3.9, 2.3-5.0)
71 - 180	65.7±15.7 (67.3, 53.8-76.6)	82.2±8.0 (83.1, 79.0-85.8)	66.4±21.4 (69.9, 62.7-79.7)	73.4±15.8 (71.7, 60.8-91.1)
>180	26.3±17.4 (23.9, 12.2-37.5)	15.7±7.6 (14.3, 13.0-19.6)	27.5±22.4 (22.9, 13.5-29.2)	22.5±14.8 (24.2, 6.8-36.8)
>300*	1.1±2.2 (0.0, 0.0-1.5)	1.2±1.6 (0.6, 0.2-1.6)	4.2±8.4 (0.1, 0.0-4.2)	3.4±4.7 (0.9, 0.2-7.1)

Values are expressed as mean±SD (median, IQR)  
\*At this range, an increase in percent of SG values was observed in younger cohort

Free Communication Session, Saturday,  
September 16, 2017, 3:15-4:15pm  
Fetal and neonatal endocrinology and  
metabolism, including hypoglycemia  
FC86 – FC90

FC86

RESTORATION OF STEM CELL DERIVED BETA-CELL FUNCTION  
FROM PERMANENT NEONATAL DIABETES PATIENT BY  
CRISPR/CAS9

Shuangyu Ma, BS/BA; Ryan Viola, Lab Manager, Columbia University, New York, NY, United States; Valentino Cherubini, MD, Salesi Hospital, Ancona, Italy; Fabrizio Barbetti, MD, University of Rome Tor Vergata, Rome, Italy; Dieter Egli, PhD, Columbia University, New York, NY, United States

**Objectives:** Permanent Neonatal Diabetes Mellitus (PNDM) can be caused by heterozygous, gain-of-proteotoxic function mutations of the insulin (*INS*) gene or -rarely- by recessive, loss-of-function *INS* mutations. Currently, insulin injection is the only treatment available for these patients. With this study we wanted to verify the feasibility of restoring pancreatic beta-cell function by mutation correction in induced pluripotent stem cells (iPSC) from a patient with PNDM due to a homozygous *INS* mutation.

**Methods:** iPSCs were generated by reprogramming somatic cells from a skin biopsy of the patient. We corrected the mutation (*INS* p.0? c.331C>A) in patient iPSCs with CRISPR/Cas9-mediated ssDNA replacement.

**Results:** Using differentiation to stem cell derived beta cells (sc-beta cells), we confirmed the absence of insulin production in sc-beta cells expressing MAFA, Nkx6.1, and synaptophysin. Upon iPSC gene correction by CRISPR/Cas9 and differentiation to sc-beta cells, we found that insulin production and stimulated secretion was restored to levels comparable to IPSc from *INS* wildtype cells. The functional testing of gene-corrected sc-beta cells in mice is ongoing.

**Conclusions:** Our study provides proof of principle for the generation of genetically corrected sc-beta cells for patients with PNDM. Because of the lack of auto-immunity, insulin dependent diabetes caused by single gene mutations should be amenable to cell therapy.

FC87

A NOVEL SYNDROME OF HYPERINSULINAEMIC  
HYPOGLYCEMIA AND POLYCYSTIC KIDNEYS DUE TO A  
PROMOTOR MUTATION IN PMM2  
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**Objectives: Background:** Hyperinsulinaemic hypoglycemia (HH) occurs due to the dysregulation of insulin secretion from the pancreatic beta cell and leads to hypoglycemia. Polycystic kidney disease (PKD) is characterized by multiple cysts in the kidneys and is either autosomal recessive or dominant. No previous association has been reported between HH and PKD.

**Methods:** We identified 18 children from 12 families with the combination of HH and PKD. Homozygosity mapping, non-parametric linkage analysis, whole genome sequencing, and in-vitro studies were undertaken to understand the molecular basis of this association

**Results:** Homozygosity and linkage data in a consanguineous family with 3 affected members revealed a homozygous 2.5Mb region on chromosome 16p13.2. Whole genome

sequencing in this and 4 other informative families confirmed this to a single significant locus of 2.3Mb that includes 14 genes. No mutation were found in the coding regions of these 14 genes but a *PMM2* promoter variant (c.-167G>T) in all patients. This variant was either homozygous or *in trans* with *PMM2* coding variants, including mutations previously reported in patients with congenital disorder of glycosylation (CGD) type 1a. Patients had no other features of GCD type 1a and the transferrin isoelectric focusing was normal. *In vitro* studies in patient cells revealed decreased transcription activity of the mutant promoter. Electrophoretic mobility shift assay demonstrated impaired binding of the transcription factor ZNF143. *In silico* analysis revealed the importance of ZNF143 for the structural confirmation of a chromatin loop including *PMM2* to enable tissue-specific transcription.

**Conclusions:** We report a novel disorder of HH and PKD due to promoter variant in *PMM2* that appears to exert a critical tissue-specific effect on transcription, leading to an organ-specific phenotype.

FC88

#### MODELING CONGENITAL HYPERINSULINISM IN PATIENT STEM CELL DERIVED BETA-LIKE CELLS

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**Objectives:** Mutations in the genes encoding the potassium-sensitive ATP (K-ATP) channel of the pancreatic beta cell are the most common cause of congenital hyperinsulinism (CHI). In Finland, the most common single cause is the *ABCC8* mutation V187D which leads to a trafficking defect of the SUR1 protein, causing a drug resistant, severe form of the disease. Our objective was to recapitulate the CHI phenotype with patient induced pluripotent stem cell (iPSC)-derived beta-like cells, to enable future studies in testing novel pharmaceuticals and PET tracers for improved management and diagnostics of CHI.

**Methods:** iPSCs were derived from a patient with severe, diazoxide unresponsive diffuse CHI caused by homozygous *ABCC8*-V187D. iPSCs from a healthy donor were used as a control. The cells were differentiated towards beta-cell fate, using a 7-stage, 30-day protocol which yielded islet-like clusters containing 20-40% insulin-positive monohormonal beta-like cells. These were studied *in vitro* or transplanted to immunocompromised NSG mice.

**Results:** Insulin secretion was studied *in vitro* by static 30-min sequential exposure to glucose and pharmaceuticals acting on K-ATP channels. Mutant beta-like cells failed to shut down secretion when exposed to diazoxide as compared to healthy control cells (fold change  $1.00 \pm 0.19$  vs.  $0.44 \pm 0.11$ ; mean  $\pm$  95% CI;  $p=0.0005$ ) and did not increase secretion in response to tolbutamide (fold change  $0.91 \pm 0.25$  vs.  $1.56 \pm 0.31$ ,  $p<0.0001$ ,  $n=5$ ). Four months post transplantation the mice were subjected to an insulin tolerance test. The CHI-mice had

lower fasting blood glucose ( $5.2 \pm 2.1$  vs.  $8.4 \pm 2.7$  mmol/l,  $p=0.09$ ) and higher human C-peptide ( $704 \pm 328$  vs.  $155 \pm 67$  pmol/l,  $p<0.01$ ). Most importantly, human C-peptide secretion was not inhibited by insulin-induced hypoglycemia in the CHI-mice (reduction at 40 min after insulin administration  $17.6 \pm 23.3\%$   $n=6$  vs.  $67.8 \pm 11.8\%$   $n=6$ ,  $p<0.01$ ). Quantitative immunohistochemical analysis of the grafts is ongoing to assert differences in endocrine cell populations and the rates of apoptosis and proliferation.

**Conclusions:** In conclusion, we have successfully recapitulated the CHI phenotype in beta-like cells derived from patient-iPSC and created a humanized mouse model for CHI.

FC89

#### EFFECT OF EXENDIN-(9-39) ON GLUCOSE AND INSULIN RESPONSES TO A MIXED MEAL AND A PROTEIN LOAD IN CHILDREN WITH HYPERINSULINISM

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**Objectives:** Congenital hyperinsulinism due to inactivating mutations of the  $K_{ATP}$  channels ( $K_{ATP}HI$ ) is frequently unresponsive to available medical therapy. We have strong preclinical and clinical data supporting a novel therapeutic approach employing exendin-9-39 (Ex9). Our objectives were to: 1) examine the effect of Ex9 on glucose and insulin responses to a mixed meal (MMTT) and a protein load (OPTT) in children with  $K_{ATP}HI$ ; 2) apply a novel model of insulin secretion to analyze these responses.

**Methods:** Eight children with  $K_{ATP}HI$  (3-15 yrs) underwent 2 experiments on 2 separate days; on each day, subjects received either vehicle or Ex9 (0.1mg/kg/hr) intravenously during a MMTT and an OPTT (1 gm/kg protein). Blood glucose (BG), insulin (Ins), and C-peptide were measured at multiple time points. The applied mathematical model relies on C-peptide and insulin plasma levels to resolve relevant indices of whole-body insulin kinetics.

**Results:** Area under the curve (AUC) BG for the MMTT was significantly elevated by 28% with the administration of Ex9 ( $26259 \pm 3204$  vs  $33469 \pm 3204$  mg\*min/dL,  $P \leq 0.0001$ ). AUC BG for the OPTT was significantly greater during Ex9 compared to vehicle ( $12612 \pm 1414$  vs  $18504 \pm 1323$  mg\*min/dL,  $P=0.002$ ). AUC insulin secretion rate (ISR) was not significantly different during Ex9 compared to vehicle infusion for the MMTT ( $P=.5$ ) or the OPTT ( $P=.3$ ). Fractional clearance rate of insulin (FCR) was not affected by Ex9 treatment during the MMTT ( $P=.9$ ) or OPTT ( $P=.9$ ). While the fraction of insulin that survives First Pass Hepatic Extraction of Insulin (FPHEI) estimated from the MMTT data did not show any difference during treatment with Ex9 ( $P=.3$ ), FPHEI estimated from OPTT data show statistical trend for 60% increase ( $47 \pm 12$  vs  $75 \pm 16\%$ ,  $P=.08$ ). FPHEI during treatment with Ex9 was significantly different

between the MMTT and the OPTT ( $P=0.002$ ). During the MMTT there was a significant reduction in insulin sensitivity (SI) by 30% in Ex9 vs vehicle ( $13.3 \pm 5.5$  vs  $9.3 \pm 1.7 \times 10^{-4} (\mu\text{I})^{-1} \cdot \text{min}^{-1}$ ,  $P=0.015$ ).

**Conclusions:** Based on our results, it appears that Ex9 exerts its effect by decreasing the hepatic extraction of insulin but only during OPTT. Furthermore, the significant reduction of SI with Ex9 during MMTT suggest that its effects are extra-pancreatic.

FC90

#### RISK FACTORS FOR PERINATAL STRESS-INDUCED HYPERINSULINISM.

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**Objectives:** Hyperinsulinism (HI) is a disorder that may result in severe hypoglycemia, which may lead to seizures, brain damage, and increased morbidity. Most of the current literature on hyperinsulinism focuses on forms caused by genetic disorders; however, a more common form of hyperinsulinism is perinatal stress-induced hyperinsulinism (PSHI). PSHI presents itself in the neonatal period in association with risk factors such as birth asphyxia, intrauterine growth retardation, hypertension, maternal toxemia, meconium and prematurity. Recent recommendations from the Pediatric Endocrine Society (PES) suggest that more patients should be screened for hypoglycemia that the previous AAP guidelines. Aim: To evaluate the PSHI patient population and to determine the risk factors associated with PSHI.

**Methods:** A retrospective chart review was conducted of all PSHI patients from January 1, 2004 to February 1, 2017 at Cook Children's Medical Center. Data was abstracted from the patients' electronic medical record, recorded, and stored in a password-secured REDCap database. Data was exported to SPSS and analyzed using basic descriptive statistics.

**Results:** There are currently 71 PSHI patients who have been evaluated of whom 61% are male, 76% Caucasian race and 32% of Hispanic ethnicity. 64% were delivered by C-section at a mean gestation 35.6 weeks (range 24.7 to 41) with mean birth weight 2177 (452 to 4762g). Of these 44% were SGA. Hypoglycemia was diagnosed by day 3 in 87% but the median day of diagnosis of hyperinsulinism was day 13. 24% of the mothers had pregnancy induced hypertension and 8% had preeclampsia. 21% reported meconium being present during delivery. All 71 patients responded to diazoxide. Currently 54 patients are >2 years old and having prospective neurological outcome data collected.

**Conclusions:** Currently, this report is the largest descriptive analysis of PSHI patients in the current literature. Infants with maternal or fetal risk factors for PSHI should be screened at birth and treated to determine if early diagnosis and treatment can improve long term neurological outcome. This paper supports the PES recommendation that infants of mothers with Pregnancy induced hypertension and

meconium should be screened. Further analysis of long-term neurological outcome of our cohort is underway.

#### Free Communication Session, Saturday, September 16, 2017, 3:15-4:15pm

##### Adrenals #1 FC91 – FC95

FC91

#### A MIRAGE SYNDROME PATIENT WITHOUT HEMATOLOGICAL PHENOTYPES: INACTIVATION OF A GERMLINE ACTIVATING SAMD9 MUTATION BY A SOMATICALLY ACQUIRED NONSENSE MUTATION IN HEMATOPOIETIC CELLS.

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**Objectives:** MIRAGE syndrome is a newly-recognized form of syndromic adrenal hypoplasia. Germline heterozygous *SAMD9* mutations, which are usually observed as *de novo* mutations, cause the syndrome. Mutant *SAMD9* proteins have augmented growth-restricting capacity *in vitro*. We report a MIRAGE syndrome patient that had one germline and one somatic *SAMD9* mutations on a same allele. Significance of the somatic mutation ("adaptation by inactivation") is discussed.

**Methods:** A 10-year-old girl was born at gestational age 33 weeks with a birth weight 1,058 g ( $-3.3$  SD). She was diagnosed as having adrenal hypoplasia based on hormone measurements and adrenal ultrasonography. She was treated with hydrocortisone and fludrocortisone. She had female-type external genitalia despite 46, XY karyotype. She had short limbs and joint contracture in her wrists and ankles. The growth was stunted with height 81 cm ( $-8.7$  SD) at age 10 years. Chronic diarrhea, recurrent respiratory infection and severe intellectual disability were observed, but no significant hematologic abnormalities were noted throughout the course. We extracted genomic DNA samples from her lymphocytes and hair follicles. *SAMD9* was analyzed with next-generation sequencing and/or Sanger sequencing. Pathogenicity of the detected germline *SAMD9* mutation (p.Ala722Glu) was verified *in vitro*.

**Results:** Analysis of the lymphocytic DNA showed two heterozygous mutations on one allele (p.[Arg685\*; Ala722Glu]). The p.Arg685\* mutation was not detected in hair follicles, suggesting that the p.Arg685\* mutation was somatically acquired. Parents of the patient did not carry the two mutations. Expression of the p.Ala722Glu-*SAMD9* protein caused strong growth-restriction in HEK293 cells.

**Conclusions:** We identified a MIRAGE syndrome patient who had a germline *SAMD9* mutation with growth-restricting



capacity, and had an additional somatic inactivating mutation on the same allele. Somatic inactivation of the deleterious *SAMD9* allele likely caused expansion of the clone with two mutations (“adaptation by inactivation”), and was possibly associated with the absence of hematologic abnormalities.

FC92

**HIGH DHEAS AT AGE 7 ARE ASSOCIATED TO HIGHER GLYCEMIA DURING PUBERTY BUT NOT METABOLIC SYNDROME**

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**Objectives:** Premature adrenarche (PA) has been recently identified as a risk factor for metabolic diseases. This risk may depend on ethnic background, birthweight and infancy weight gain. In a longitudinal cohort (Growth and Obesity Cohort, GOCS n=969 both sexes) children with high DHEAS (HD=biochemical adrenarche) at 7 y, were fatter and more centrally obese than their counterparts (ND) (AJCN, 2013). Aim: To determine whether HD at age ~7yr in girls determines a higher prevalence of metabolic Syndrome or its components during puberty.

**Methods:** Girls from the GOCS cohort with anthropometry since birth (2003). From 2006, a clinical evaluation and a complete metabolic profile at Tanner B2/B4. HD defined by DHEAS (RIA, µg/dl) >75<sup>th</sup> percentile (girls >42.0 µg/dl). Metabolic syndrome according to IDF 2007. Statistics: Generalized linear models and survival analysis were used to assess the relation between HD and anthropometric and metabolic profile at B2 (n=401) and B4 (n=357). Adjusting by infancy weight change (>0.67), mother’s age at menarche, maternal height and education.

**Results:** Girls who displayed HD, at Tanner B2 were taller, had higher BMI and were younger (8.8 (CI 95%CI; 7.9-9.3) vs. 9.3 (95%CI; 9.1-9.6) than girls with normal DHEAS (ND). None of the girls met the blood pressure criteria. No differences were observed in the risk of metabolic syndrome or its components (Summarized in Table). However, glycemia > 100 mg/dl was present in higher percent of HD girls at Tanner II and Tanner IV. \*p<0.05 \*\*p>0.005

	Tanner II		Tanner IV	
	ND	HD	ND	HD
Metab. Synd. n(%)	2 (0.7)	3 (3.8)	2 (0.8)	2 (2.6)
WC > 90 <sup>th</sup> perc.	27 (8.6)	11 (12.9)	34 (11)	11 (13.2)
TG > 150 mg/dl	34 (12)	12 (15)	40 (16.6)	16 (20.7)
HDL < 40 mg/dl	57 (20.0)	19 (23.8)	36 (14.4)	10 (12.5)
Glycemia > 100 mg/dl	4 (1.4)	5 (6.3)*	4 (1.7)	7 (9.1)**
BMI > 2SDS	37 (12.2)	20 (20.4)*	32 (12.5)	18 (18)
mean glycemia mg/dl	88.3 ± 7.1	89.9 ± 7.8*	86 ± 6.6	87 ± 8.7*

**Conclusions:** HD conferred a risk of higher glycemia and the rest of the components of metabolic syndrome appeared to

ameliorate with advanced pubertal stage. Follow-up of this cohort is necessary to address prospectively the interrelationships of HD, early growth, adiposity, sex steroids and markers of metabolic risk (Fondecyt 1140447 & 1120326, WCRF:2010/245).

FC93

**ALTERED STEROID AND DRUG METABOLISM BY A P450 OXIDOREDUCTASE VARIANT FOUND IN APPARENTLY NORMAL POPULATION**

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**Objectives:** A broad spectrum of human diseases, including abnormalities in steroidogenesis, is caused by mutations in the NADPH P450 oxidoreductase (POR). POR transfers electrons from NADPH to several small molecules, non-P450 redox partners and microsomal cytochrome P450 proteins (CYPs). Our aim was to check if POR variations from non-clinical samples, by seeking 1000 genomes database, can be disruptive. Y607C variant (rs72557954, NM\_000941.2:c.1820A>G) has been reported in population studies and prevalent in south Asians, but was predicted to be likely pathogenic. We performed detailed enzymatic and biochemical characterizations of Y607C variant to study its effect on different substrate and redox partners.

**Methods:** We analysed the ability of POR wild type (WT) and Y607C variant to reduce ferricyanide, MTT, cytochrome c and drug, and steroid metabolizing CYP450. POR WT and Y607C were expressed and produced as recombinant proteins while CYP19A1 and CYP3A4 were produced as His-tagged recombinant proteins and purified by affinity chromatography. The effect of mutation on cofactor (FAD/FMN) binding and activity under varying substrate and cofactor conditions was performed.

**Results:** We found varied effects of Y607C mutation on reduction activity of different substrates. As compared to WT, Y607C variant showed 66% cytochrome c and 91 % ferricyanide reduction activity but had only 13 % MTT reduction activity. Y607C did not affect POR flavin content but NADPH binding was severely affected. With varying NADPH concentration, Y607C showed ~95% decrease in supporting CYP19A1 and CYP3A4 activity. This mutation was later identified in patients with POR deficiency.

**Conclusions:** Identification of severe effects of this mutation on both drug and steroid metabolizing CYP450s indicates that likely pathogenic mutations may be found in apparently normal (non-clinical) population. Their combination as compound heterozygotes or homozygous may lead to severe impact on both steroid and drug metabolism by modification of its redox partners activities. Variations in POR need to be evaluated individually. Most importantly, advanced identification of disease causing variants in POR will help in



understanding the POR deficiency in patients if the same mutations are later identified.

FC94

#### BIOAVAILABILITY OF ORAL HYDROCORTISONE CORRECTED FOR BINDING PROTEINS AND MEASURED BY LC-MS/MS USING SERUM CORTISOL AND SALIVARY CORTISONE

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**Objectives:** The assessment of absolute bioavailability of oral hydrocortisone is complicated by its saturable binding in the therapeutic range to cortisol binding globulin (CBG). Ninety percent of serum cortisol circulates bound to CBG, 5% to generic binding proteins, such as albumin and  $\alpha$ -1 glycoprotein, and only 5% is unbound or 'free' (1). CBG has high affinity for cortisol but lower capacity whereas albumin has a lower affinity and higher capacity (2). An increase in the free fraction results in an increase in clearance with dose and therefore less than dose proportional increases in C<sub>max</sub> and AUC (3). Derendorf reported absolute bioavailability to be 0.96 (CI 0.82 to 1.09) using a radioimmunoassay to measure cortisol in serum (3); however immunoassays give variable results and LC-MS/MS is now becoming the gold standard method for measuring steroids. We have measured absolute bioavailability of hydrocortisone using serum cortisol and salivary cortisone measured by LC-MS/MS.

**Methods:** 14 healthy male dexamethasone suppressed volunteers were administered 20mg hydrocortisone either intravenously or orally by tablet. Samples of serum and saliva were taken and measured for cortisol and cortisone by LC-MS/MS. Serum cortisol was corrected for saturable binding using published data (2) and PK parameters derived using the program WinNonlin.

**Results:** The mean (95% CI) bioavailabilities of oral hydrocortisone calculated from serum cortisol, corrected serum cortisol and salivary cortisone were 1.00 (0.89-1.14); 0.89 (0.75-1.05); and 0.93 (0.83-1.05), respectively.

**Conclusions:** The data confirm that after oral administration hydrocortisone is completely absorbed (3). The data derived from serum cortisol corrected for protein binding and that from salivary cortisone are similar supporting the concept that salivary cortisone reflects serum free cortisol levels and that salivary cortisone can be used as a non-invasive method for measuring the pharmacokinetics of hydrocortisone.

**Refs:** 1. Lewis JG, et al. Clin Chim Acta 2005; 359:189-194. 2. Lentjes & Romijn. J Clin Endocrinol Metab 1999; 84:682-687. 3. Derendorf et al. Journal of Clinical Pharmacology 1991; 31:473-476

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**Conflicts:** Martin Whitaker and Richard Ross are Directors of Diurnal PLC.

FC95

#### SIMULTANEOUS PROFILING OF 17 STEROID HORMONES USING LIQUID CHROMATOGRAPHY TANDEM MASS SPECTROMETRY IN NEWBORN AND EARLY INFANCY

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**Objectives:** Many of the steroidogenic disorders present in newborn or early infancy with ambiguous genitalia and/or salt-wasting. Quantification of endogenous hormonal steroids and their precursors is essential for the diagnosis. Rapid changes in steroid hormone concentrations due to fetal adrenal zone involution, low-concentration analytes and assay interference by endogenous or placental steroids are main diagnostic challenges of this critical life period. Analysis of serum steroids by liquid chromatography tandem mass spectrometry (LC-MS/MS) can provide rapid, highly specific, and sensitive simultaneous analysis of multiple steroid analytes.

**Methods:** We employed LC-MS/MS to measure a panel of 17 steroids of 300 healthy full-term newborns and babies (150 males, 150 females) grouped in five age groups (3-7th, 8-14th, 15-28th, 29-90th, 91-180th days). Nonparametric statistical approaches were used to generate the mean, 2.5th-97.5th percentile distributions for age groups. 17OH-Progesterone+21-deoxycortisol/cortisol, 11-deoxycortisol/cortisol, 17OH-pregnenolone/cortisol, cortisol/cortisone and testosterone/dihydrotestosterone (only in boys) ratios were calculated as biomarkers of specific enzyme deficiencies.

**Results:** Reference intervals of 17 steroids measured simultaneously by LC-MS/MS were established. 17-hydroxylated C21-glucocorticoids, non-17-hydroxylated C21-mineralocorticoid precursors (pregnenolone and progesterone) and C19-androgens (dehydroepiandrosterone, dehydroepiandrosterone-sulphate,  $\Delta$ 4-androstenedione) showed most significant age-related changes from 3 to 180 days of life. However C21-mineralocorticoids (aldosterone, corticosterone, 11-deoxycorticosterone) remained constant during the first 6 months of life. Biomarkers of 21- $\alpha$ -hydroxylase, 11- $\beta$ -hydroxylase, 3- $\beta$ -hydroxylase activities were in favor of cortisol increase.

**Conclusions:** Implementation of LC-MS/MS based steroid panel will provide shortly correct diagnosis. Therefore, the establishment of age-related reference intervals for newborn babies and early infancy in this study will allow rapid, noninvasive, accurate diagnosis and differential diagnosis, guide sex assignment, genetic counseling, predicting prognoses and prevent the potential life-threatening outcomes of impaired steroidogenesis.

**Free Communication Session, Sunday, September 17, 2017, 7:30-8:30am**  
**Adrenals #2**  
**FC96 – FC100**

FC96

**LOW VITAMIN D RECEPTOR (VDR) IMPACTS PEDIATRIC ADRENOCORTICAL TUMOR BEHAVIOR WHILE VDR ACTIVATION REPRESSES WNT/ $\beta$ -CATENIN SIGNALING AND ADRENOCORTICAL CELL PROLIFERATION**

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**Objectives:** We investigated the role of the vitamin D receptor (VDR) in adrenal development and pediatric adrenocortical tumorigenesis, and its interaction with Wnt/ $\beta$ -catenin pathway and adrenocortical cell proliferation.

**Methods:** Clinicopathological features, VDR (qPCR and immunohistochemistry) and cyclin D1 (CCND1; qPCR) expression were evaluated in 74 pediatric ACTs and 44 fetal/pediatric normal adrenals. In vitro, we evaluated in NCI-H295 cells the effects of VDR activation by  $1\alpha,25$ -dihydroxyvitamin D3 (VitD3,  $10^{-7}$ M) or inhibition (siRNA) on the expression of Wnt/ $\beta$ -catenin components and cell cycle progression-governing complexes (qPCR, immunoblotting and immunofluorescence), cell cycle (flow cytometry) and viability (MTS). We also evaluated the effect of TCF/ $\beta$ -catenin blockage (PNU-74654,  $10^{-4}$ M) over VDR expression.

**Results:** We demonstrate important nuclear VDR immunostaining in normal human adrenal cortex since midgestation, and its protein and mRNA underexpression in pediatric ACTs. In these tumors, VDR expression correlated negatively with Wnt/ $\beta$ -catenin components expression *AXIN1* and *MYC*, positively with *WNT4* and *DKK3*, and especially with cell cycle regulator *CCND1*, which was associated with poor patient outcome. In vitro, VitD3 treatment directly inhibited  $\beta$ -catenin/*CTNNB1* expression, nuclear accumulation, and reduced the expression of its targets *CCND1*, *MYC* and *GLI1*. Moreover, the expression of *CDK4*, *CDK2*, *CCNE1*, and *MDM2* was also declined. Concomitant cell cycle impairment with  $G_0/G_1$  accumulation was observed. In line, VDR knockdown elicited opposite results, with upregulation of  $\beta$ -catenin expression and abrogation of the inhibitory

effect VitD3 over Wnt/ $\beta$ -catenin pathway. Decline of cells in  $G_0/G_1$  phase, but increase in sub- $G_1$ /apoptotic was also observed. The inhibition of TCF/ $\beta$ -catenin importantly increased VDR expression and nuclear accumulation.

**Conclusions:** VDR plays an important role in normal adrenal differentiation and maintenance, which is lost in pediatric ACTs. VDR underexpression associates with tumor progression and poor prognosis. VitD3/VDR activation represses Wnt/ $\beta$ -catenin signaling and adrenocortical cell proliferation. VDR activation may emerge as an adjuvant therapy for patients with ACT.

FC97

**WOULD MOLECULAR TESTING IDENTIFY CASES OF CONGENITAL ADRENAL HYPERPLASIA MISSED BY NEWBORN SCREENING?**

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**Objectives:** To prepare for the first prospective trial in the USA using a molecular assay as a 2<sup>nd</sup> tier newborn screening (NBS) test for congenital adrenal hyperplasia (CAH), our objectives were: 1) to characterize the *CYP21A2* mutation spectrum in a large cohort of Minnesota CAH patients; 2) to evaluate whether a mass screening assay developed by the Centers for Disease Control (CDC) was accurate and reproducible in identifying mutations causing CAH disease from dried blood spots; 3) to examine the genotypes and phenotypes of the probands and their original NBS result.

**Methods:** Blood specimens from probands and their parents were spotted on to filter paper to approximate NBS dried blood spot specimens. Genotyping was done by the CDC using a CDC-developed rapid high-throughput assay. Medical charts were reviewed to identify phenotypes and original NBS results.

**Results:** Gene sequencing results of 97 families with 109 CAH affected children identified the 12 common mutations found in diagnostic panels as well as large 30kb deletions, large gene conversions, and 10 other *CYP21A2* mutations, including nine rare and one novel. The CDC assay showed 100% accuracy and reproducibility on 900 dried blood spot samples tested. CAH subtypes of probands (n=109) were 61 salt-wasting (SW); 28 simple-virilizing (SV); 20 non-classic (NC). The original NBS for CAH results (n=82) identified 61 affected newborns (51 SW, 10 SV) and missed 21 (7 SW, 14 SV); 27

probands were excluded from NBS analysis (17 NC-CAH, 1 adopted, 9 with no NBS results available). There were 3 *CYP21A2* mutations (H62L-P453S, L307V and G424S) found only in the missed NBS cases.

**Conclusions:** A high fraction (26%) of CAH-affected newborns are missed by the current NBS method, an immunoassay measuring 17-hydroxyprogesterone (17OHP), a metabolite elevated due to the enzymatic block, from blood samples taken at 24-36 hours of life. This suggests that some newborns with CAH have a delayed rise in 17OHP that is not captured by early NBS sampling but would be by molecular assay as it is not time dependent.

FC98

#### MUTATION IN *SAMD9* EXTENDS THE GENETIC AND CLINICAL SPECTRUM OF TRIPLE A SYNDROME

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**Objectives:** Triple A syndrome is a rare autosomal recessive disorder characterized by adrenal failure, alacrima, achalasia and a variety of neurological features. It is caused by mutations in the *AAAS* gene. We recently described two triple A-like disorders caused by mutations in *GMPPA* and *TRAPPC11* being responsible for 4 % of *AAAS* mutation-negative cases. However, about 26 % of patients with suspected triple A syndrome are still genetically undiagnosed. This study aims to summarize genotypes and phenotypes of triple A syndrome including a novel case caused by *SAMD9* mutation.

**Methods:** Clinical and genetic analyses of more than 300 patients with suspected triple A syndrome.

**Results:** In classic triple A syndrome due to *AAAS* mutations adrenal insufficiency occurs in 77.1 %, achalasia in 85.1 % and alacrima in 89.7 % of all patients. Most patients (72.8%) display neurological impairment, most frequently distal muscular weakness, hyperreflexia, nasal speech and autonomic dysfunction. Recently a new form of syndromic adrenal hypoplasia termed MIRAGE syndrome (Myelodysplasia, Infection, Restriction of growth, Adrenal hypoplasia, Genital phenotypes and Enteropathy) caused by germline de novo heterozygous *SAMD9* mutations was described. *SAMD9* has a role in growth factor signal transduction and is involved in endosome fusion. We identified a novel heterozygous *SAMD9* mutation (c.2306A>G, p.Asp769Gly) in a girl with adrenal insufficiency, dysautonomia, diarrhea, proteinuria and delay in intellectual, motor and speech development. Hypolacrima and achalasia extended the MIRAGE phenotype in this patient. She died at age 12 years from multiorgan failure due to severe infection.

Family segregation analysis confirmed the de novo status of this mutation.

**Conclusions:** There are at least three novel disorders who display overlapping features with classic triple A syndrome. Protein products of the mutated genes are involved in different cellular pathways. Clinicians should be aware of this genetic heterogeneity in terms of genetic and clinical counselling. Mutation analysis in *SAMD9* and the presence of MIRAGE syndrome should be taken into consideration in patients with adrenal insufficiency, achalasia, alacrima and lack of mutations in *AAAS*, *GMPPA* and *TRAPPC11*.

FC99

#### SERUM CORTISOL AND SALIVARY CORTISONE AND FREQUENCY OF SAMPLING TO ESTIMATE CORTISOL EXPOSURE

Richard J Ross, MD; Robert F Harrison, MD; Miguel Debono, PhD, University of Sheffield, Sheffield, United Kingdom; Martin J Whitaker, PhD, Diurnal Ltd, Sheffield, United Kingdom; Brian G Keevil, MD, University Hospital of South Manchester, Sheffield, United Kingdom; John Newell-Price, MD, University of Sheffield, Sheffield, United Kingdom

**Objectives:** Measuring cortisol exposure is important as excess is associated with increased mortality. Salivary cortisone provides a non-invasive method. To validate the relationship between serum cortisol and salivary cortisone and examine measurement frequency required to estimate cortisol exposure.

**Methods:** Serum cortisol and salivary cortisone measured by LC-MS/MS in 2 cohorts hourly over 24hrs: Cohort 1, 14 volunteers; Cohort 2, 8 volunteers, 12 patients with adrenal adenomas (6 non-functioning, 6 functioning). The relationship was analysed in Cohort 1 using linear mixed effects model and the resulting fixed effects component applied predictively to Cohort 2. The relationship between estimated AUC (eAUC) and absolute AUC (AUC<sub>24</sub>) was investigated by deriving the standard deviation of the per subject percentage error (SDPE, similar to coefficient of variation) for the use of 1 to 3 equi-spaced sampling points in 24 hours.

**Results:** The fixed effects model:  $\log_{10}$  serum F = 1.24+0.89  $\log_{10}$  salE best described the relationship between serum cortisol and salivary cortisone in cohort 1 and gave similar results when applied to cohort 2: model predictions  $r=0.93$  and  $0.91$   $p<0.001$ , respectively. For a single measurement of serum cortisol used to derive eAUC the mean SDPE of the different time points for cohort 1 and 2 respectively was: 20% (range 7.4% - 39%) & 27% (range 16% - 56%); highest at 07:00h and lowest at 01:00h; for 2 samples at 12hrs 14% (range 8.7% - 23%) & 16% (range 9.8% - 23%); for 3 samples at 8hrs 10% (range 5.2 - 14%) & 12% (range 6.4% - 15%). A sensitivity analysis using 3 samples but shifting each sample time by 1 to 2 hours either side of nominal showed the mean deviation from the on time value was within 5.5%.

**Summary:** salivary cortisone as a measure of serum cortisol is confirmed in patient population. A single cortisol sample is a poor measure of AUC<sub>24</sub> especially in the morning, but 3 x 8

hourly gives an eAUC within 5-15% of the AUC<sub>24</sub> and samples taken up to two hours off nominal time a variation of only 5.5%.

**Conclusions:** Three ~8 hourly salivary cortisone samples provide a non-invasive method for estimating cortisol exposure. EUP7-281654

**Conflicts:** MJW & RJR Directors of Diurnal Plc

FC100

### 17OH-PREGNENOLONE SEEMS A MAJOR DRIVE OF ANDROGEN EXCESS IN PATIENTS WITH 11 $\beta$ -HYDROXYLASE DEFICIENCY

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**Objectives:** Biallelic mutations in the *CYP11B1* gene causes 11 $\beta$ -hydroxylase deficiency (11 $\beta$ -OHD) which is a rare form of congenital adrenal hyperplasia (CAH) with reported prevalence of 1 in 100.000 live births. However, a higher frequency of 11OHD in Turkey is estimated most likely due to the higher rate of consanguineous marriages. Our aim was characterization of clinical features and liquid chromatography tandem mass spectrometry (LC-MS/MS)-based steroid metabolome analysis of 11 $\beta$ -OHD. This would give us a further understanding of pathways leading to accumulation of steroid metabolites with mineralocorticoid and androgen function besides an opportunity to make a better differential diagnosis with far more common 21-hydroxylase deficiency and 3 $\beta$ -hydroxysteroid dehydrogenase deficiency.

**Methods:** A clinical questionnaire was used to describe previously unreported patients with genetically confirmed 11 $\beta$ -OHD. We employed LC-MS/MS to measure a panel of 17 plasma steroids in patients (n=25; 13F, 12M) and healthy controls aged 0-18 yrs (n=160; 76F, 84M).

**Results:** There were 2 missense, 2 nonsense, 2 frameshift homozygous mutations of the *CYP11B1* gene, 2 of them being novel. Affected patients were severely virilized, 4 of them had salt-wasting and other 6 had hypertension at presentation. All patients had significantly advanced bone age, 4 were treated for precocious puberty, one was given letrozol for severely advanced bone age, 3 boys had adrenal rest tumors. Seven patients were initially misdiagnosed with 21-hydroxylase deficiency and one girl with 3 $\beta$ -hydroxysteroid dehydrogenase deficiency. Four patients were treated with

mineralocorticoids before definitive diagnosis. 17OH-Pregnenolone/cortisol and 17OH-progesterone/cortisol ratios were significantly higher in patients than in controls ( $p < 0.0001$ ). However significantly elevated 11-deoxycortisol/cortisol ratios as well as high 11-deoxycorticosterone and corticosterone concentrations established the diagnosis.

**Conclusions:** Deep clinical phenotyping together with LC-MS/MS-based steroid metabolome analysis will guide accurate diagnosis and treatment, and predicting prognosis in CAH. Excessive androgen biosynthesis seems to be regulated mainly by 17OH-Pregnenolone accumulated upstream of 11 $\beta$ -hydroxylase.

### Free Communication Session, Sunday, September 17, 2017, 7:30-8:30am Multisystem endocrine disorders FC101 – FC105

FC101

#### UNDERSTANDING WOLFRAM SYNDROME: GENETICS, FUNCTIONALITY & ALLELIC VARIATIONS

*Melissa Riachi, MS/MA; Mark Kristiansen, PhD, University College London Great Ormond Street Institute of Child Health, London, United Kingdom; Sebahat Yilmaz, Associate Prof; Zehra Aycan, Prof; Erdal Kurnaz, MD, Dr Sami Ulus Training and Research Children's Hospital, Istanbul, Turkey; Nanna Dahl Rendtorff, PhD; Lisbeth Tranebjaerg, Prof, University Hospital / University of Copenhagen, Copenhagen, Denmark; Robert Kleta, Prof, University College London Faculty of Medical Sciences, London, United Kingdom; Detlef Bockenhauer, Prof, University College London, Faculty of Medical Sciences, London, United Kingdom; Maria Bitner-Glindzicz, Prof, University College London Great Ormond Street Institute of Child Health, London, United Kingdom; Khalid Hussain, Division chief, Sidra Medical and Research Center, Doha, Qatar*

**Objectives:** Wolfram syndrome (WS), also known as (DIDMOAD), is a progressive neurodegenerative disease characterized by diabetes insipidus, diabetes mellitus, optic atrophy and sensorineural deafness. The heterogeneity of this syndrome entails its wide spectrum of symptoms which can include abnormal sexual development, urinary tract complications, neurological and psychiatric abnormalities. This phenotypic spectrum of Wolfram Syndrome type 1 (WS1) is caused by mutations in the *WFS1* gene, which encodes for Wolframin, a protein essential for the mediation of the endoplasmic reticulum stress response. There are currently two types of WS that are mainly differentiated by their genetic cause. Despite their many overlapping clinical features, Wolfram type 2 (WS2) is distinguished by its lack of diabetes insipidus and is caused by mutations in the *CISD2* gene.

**Aims:** To understand the genetic and functional mechanisms behind recessive and dominant WS and WS – like syndromes in a cohort of 12 patients.

**Methods:**

- Homozygosity Mapping
- Linkage Analysis
- Whole Exome Sequencing
- Sanger Sequencing
- Western Blotting

**Results:** WS1 was identified in 42% of the cohort. Protein expression was performed, and decreased and/or absent levels of Wolframin were detected in the patients compared to healthy age matched controls. Heterozygosity in *WFS1* was previously detected by Eiberg H et al. (2006) and Rendtorff ND et al. (2011) in 17 % of the cohort. Protein expression is still being analyzed using the fibroblasts of these patients with dominant Wolfram. Moreover, WS2 was detected in 9 % of the cohort and Western Blotting revealed decreased levels of the *CISD2* protein.

As for the remaining 32% of the patients with a WS-like phenotype, compound heterozygosity in *WFS1* is still being examined and *WFS1* and *CISD2* homozygosity has been ruled out. Also, potentially new candidate genes are being explored through whole exome sequencing analyses.

**Conclusions:** So far this study has identified novel and rare autosomal recessive mutations in the Wolfram genes. These genetic findings were combined with the respective protein expression analyses which in turn showed altered levels of protein.

Also, protein expression analyses in dominant Wolfram has neither been previously examined nor reported in the literature.

FC102

**UNCOVERING A NEW MECHANISM IN THE PIGMENTARY HYPERTRICHOSIS AND NON-AUTOIMMUNE DIABETES MELLITUS (PHID) SYNDROME INVOLVING THE 3'UTR.**

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**Objectives: Background:** H syndrome, formerly known as histiocytosis – lymphadenopathy plus syndrome, is a cluster of autosomal recessive auto - inflammatory disorders characterized by histiocytosis and prominent cutaneous presentations. Pigmentary hypertrichosis and non-autoimmune immune insulin dependent diabetes mellitus (PHID) is one of the rare H syndrome diseases mainly characterized by hyperpigmentation, hypertrichosis, sensorineural hearing loss, cardiac complications, developmental delay and diabetes mellitus. Mutations in the coding regions of the *SLC29A3* gene that encodes for an equilibrative nucleoside transporter (ENT3), have been reported to cause the phenotypic spectrum of the H syndrome. Disease causing mutations in the untranslated

regions of the *SLC29A3* gene have not been previously described in the literature. The importance of the untranslated region (UTR) of the mRNA in the post transcriptional regulation of gene expression makes it a 'hotspot' for pathologies, as mutations in this region can be very consequential.

**Objectives:** To determine whether a novel 3'UTR mutation in the *SLC29A3* gene is disease causing in two Turkish patients that presented with a PHID phenotype.

**Methods:** The mutation was identified by a targeted gene approach using Sanger Sequencing. In order to understand the functionality of this 3'UTR mutation, mRNA expression studies were performed by using the quantitative real time Polymerase Chain Reaction (rtPCR) method. Also, protein expression analyses were performed by Western Blots on the fibroblasts cultured from the patients' skin biopsies

**Results:** The rtPCR results showed a decrease in the patients' *SLC29A3* expression levels compared to seven controls matched for passage numbers and RNA extraction methods. Also, the Western Blots showed a decrease in the expression of the ENT3 protein in the patients compared to six controls.

**Conclusions:** The mRNA and protein expression analyses proved that the novel 3'UTR mutation in the *SLC29A3* gene is indeed disease causing, highlighting a new pathological mechanism for the PHID syndrome. The involvement of the 3'UTR has not been previously established in any of the H syndrome disease cluster.

FC103

**PROGRESSION OF DIABETES MELLITUS IN WOLFRAM SYNDROME**

*Bess A Marshall, MD; Neil H White, MD; Tamara Hershey, PhD, Washington University in St. Louis, St. Louis, MO, United States*

**Objectives:** Wolfram Syndrome is a rare multisystem degenerative disease caused by mutations in the *WFS1* gene. Features include neurodegeneration, diabetes insipidus, diabetes mellitus, optic atrophy, loss of vision, hearing loss, bladder dysfunction, and other endocrinopathies. Detailed natural history information is needed to improve patient care and to design intervention trials.

**Methods:** Thirty-seven persons with Wolfram, (age 5-30, average age 16.0±0.5 years, 14 male) have participated in a seven-year natural history study collecting detailed phenotypic data. In 30 subjects, C-peptide was obtained 30 min after ingestion of a standard mixed meal after an overnight fast (Boost, Nestle; 6 ml/kg, max 360 ml; 240 ml = 240 kcal, 41 g carbohydrate, 4 g fat, 10 g protein). Subjects with fasting glucose over 250 mg/dl (13.9 mmol/L) were not given Boost but C-peptide was collected. Subjects on insulin were instructed to continue their usual insulin dosing.

**Results:** Three subjects (7.2 to 15.8 years) did not have diabetes mellitus and their 30 min C peptide did not change over three annual visits (year 1: 8.0±2.3, year 2:7.2±4.0, and year 3 8.5± 3.4 ng/ml, data shown as mean±SEM). The other 27 subjects had an average age of onset of diabetes of

5.6±0.5 years (range 2.2-13.9 years) and an average duration of diabetes of 10.7±0.5 years (range 1-27 years). Their stimulated C peptide declined with the duration of their diabetes. C-peptide in ng/ml at 30 min after Boost or with glucose >250 mg/dl: at 1 year, 1.8±0 (n=2), year: 2: 1.0±0.1 (n=3), year 3: 1.2±0.2 (n=7), year 4: 1.2±0.3 (n=7), year 5 0.7±0.2 (n=8), year 6: 0.7±0.1 (n=8), year 7: 0.7±0.2 (n=6), year 8: 0.4±0.1 (n=9), year 9: 0.7 ±0.3 (n=8), year 10: 0.4±0.1 (n=7), year 11: 0.6±0.3 (n=6), and years 12-23: 0.2 or 0.3 ±0.1 (n=4, 5, 6, 6, 9, 5, 4, 1, 0, 1, 2, 2 for years 12-23, respectively), years 24-27: less than 0.2, all single subjects.

**Conclusions:** In conclusion, C-peptide stimulated by mixed meal challenge or by fasting hyperglycemia in subjects with Wolfram Syndrome falls with duration of diabetes mellitus over approximately 10 years after diagnosis, with the largest decline occurring in the first 5 years after diagnosis.

FC104

# A REVIEW OF GENOTYPE-PHENOTYPE PRESENTATIONS IN PATIENTS WITH PSEUDOHYPOALDOSTERONISM TYPE 1 FOLLOWING THE IDENTIFICATION OF NOVEL MUTATIONS

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**Background:** There is limited data available in the literature on the genotype-phenotype correlation and the management of patients with Type I pseudohypoaldosteronism (PHA1), a rare condition characterised by hyponatremia, hyperkalemia and metabolic acidosis.

**Objective:** Our aim is to study the clinical presentation and management in relation to the underlying genetic abnormality of patients with PHA1.

**Methods:** A Questionnaire-based, cross-sectional survey, of all the paediatric consultants in the United Kingdom was undertaken through the British Society of Paediatric Endocrinology and Diabetes (BSPED) in January 2015. The questionnaire collected information on patients with genetically confirmed PHA1: Number of PHA1 patients, Demographics (including ethnicity), Clinical features of PHA1 (vomiting, weight loss, dehydration, drowsiness, seizures), Investigations – Biochemistry, imaging, genetic analysis, Management at presentation, Duration, clinical course and other complications.

**Results:** A total of 17 patients with PHA1 were identified from 6 tertiary paediatric endocrine centres. Genetic confirmation

of the diagnoses was made in 12 patients (9 males and 3 females). Out of 12 patients, 4 had autosomal dominant renal type PHA (PHA1a), including one novel mutation. Eight had autosomal recessive multi-system type PHA (PHA1b), of which 2 are novel mutations in the *SCNN1A* and 1 novel mutation in *SCNN1B*. Detailed phenotypic information was collected and analysed from this cohort. Depending on the type and location of mutation, a clear difference in clinical phenotype was difficult to distinguish in our patient cohort (table) in line with the existing evidence.

**Conclusions:** PHA being a rare condition there is limited genotypic and descriptive phenotypic data available in the current literature. Within our cohort and review of the literature, there appears to be no obvious genotype – phenotype correlation for both PHA1a and 1b. We recommend establishing a national database incorporating detailed genotypic and phenotypic data for such rare life-threatening conditions. This may enable identification of genetic subgroups that would have the potential to develop personalised patient care.

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**Table: PHA1: Genotype –Phenotype correlation**

	PHA1a- Renal type (Autosomal Dominant)				PHA1b- Systemic type (Autosomal recessive)							
	NR3C2				SCNN1A				SCNN1B			
Patient Number	4th	1st	2nd	3rd	1st	2nd	3rd	4th	5th	6th	7th	8th
Gender	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Ethnicity	White Caucasian	Asian Pakistani	Asian Pakistani	Asian Pakistani	Asian Pakistani	Asian Pakistani	Asian Pakistani	Asian Pakistani	Asian Pakistani	Asian Pakistani	Asian Pakistani	Asian Pakistani
Consanguinity	No	No	No	No	No	No	No	No	No	No	No	No
Age at presentation	12y	1y	2y	1y	12y	1y	1y	1y	1y	1y	1y	1y
Clinical features	Vomiting, weight loss, dehydration, electrolyte imbalance	Vomiting, weight loss, dehydration, electrolyte imbalance	Vomiting, weight loss, dehydration, electrolyte imbalance	Vomiting, weight loss, dehydration, electrolyte imbalance	Vomiting, weight loss, dehydration, electrolyte imbalance	Vomiting, weight loss, dehydration, electrolyte imbalance	Vomiting, weight loss, dehydration, electrolyte imbalance	Vomiting, weight loss, dehydration, electrolyte imbalance	Vomiting, weight loss, dehydration, electrolyte imbalance	Vomiting, weight loss, dehydration, electrolyte imbalance	Vomiting, weight loss, dehydration, electrolyte imbalance	Vomiting, weight loss, dehydration, electrolyte imbalance
Sodium (mmol/L)	128	134	133	133	126	110	120	125	126	114	118	118
Potassium (mmol/L)	7.4	6	7.8	6.2	10	8	6	7.6	7.6	10	7.8	7.8
Alkaline phosphatase (U/L)	<1000	<1000	<1000	<1000	<1000	<1000	<1000	<1000	<1000	<1000	<1000	<1000
Affected family members	Maternal	Paternal	-	Maternal	-	Maternal	-	Maternal	Paternal	Paternal	-	-
Complications	None	None	Unilateral myopia	None	Recurrent hypotension	None on day 10 post presentation	Documented severe infections	Documented severe infections	Documented severe infections	Documented severe infections	Documented severe infections	Documented severe infections

FC105

# PANCREATIC INSULINOMAS IN CHILDHOOD: CLINICAL, MORPHOLOGICAL AND GENETIC CHARACTERISTICS OF 16 CHILDREN.

Maria Melikyan, PhD, Endocrine research center, Moscow, Russian Federation; Sergey Makarov, MD, Russian Children's Clinical Hospital, Moscow, Russian Federation; Larisa Gurevich, PhD, M. F. Vladimirsky regional clinical institute, Moscow, Russian Federation; Youriy Sokolov, PhD, paediatric municipal clinical hospital, Moscow, Russian Federation; Henrik t Christesen, PhD, Odense University Hospital, Odense, Denmark

**Objectives:** Insulinomas are extremely rare tumors in children. An early clinical and genetic diagnosis is very important for the appropriate medical assessment. There are only few reports of malignant insulinomas in children. We aim to investigate clinical features, biochemical, genetic and histopathological characteristics of 16 children with pancreatic insulinomas.

**Methods:** Insulinomas were diagnosed biochemically and by imaging and verified histopathologically. Detailed clinical and biochemical examination was performed in all children. Sequencing of the MEN1 gene was performed in 15 patients using the bidirectional direct sequencing and MLPA deletion analysis. Follow up (mean age 15,3 y) included screening for signs of MEN1, neurodevelopmental examination and screening for the metastasis in case of malignant cases.

**Results:** Sixteen children (8 boys and 8 girls) aged 8-16 years were diagnosed to have primary pancreatic insulinoma. Seizures and weight gain were the most common symptoms of hyperinsulinaemic hypoglycemia (68,7% and 57,2% respectively). Six children (37,5%) had hypoglycemic coma before the diagnosis was established. Ten patients (62,5%) were erroneously diagnosed with epilepsy and treated with anticonvulsants. Seven out of fifteen children (46,6%) were found to have mutations in MEN1 gene, multiple pancreatic tumors were found in five of them. The mean tumor size was 2,8 cm. There was no predominance in tumor localisation within the pancreas. Histopathological studies revealed G2 differentiation stage (ENETs grade) in seven of sixteen cases (43,7%). Distant metastases were seen during follow up in two patients. Neurologic examination revealed hypoglycemic brain damage in four out of 15 patients.

**Conclusions:** Late diagnosis of insulinoma is typical, probably to unspecific symptoms and the disease rareness, what may lead to neurodevelopmental impairment. MEN1 syndrome should be suspected in all cases of paediatric insulinomas.

## Free Communication Session, Sunday, September 17, 2017, 8:45-9:45am

### Puberty

#### FC106 – FC110

FC106

#### PATERNALLY INHERITED DLK1 DELETION AS A NOVEL CAUSE OF FAMILIAL CENTRAL PRECOCIOUS PUBERTY

Andrew Dauber, MD, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States; Marina Cunha-Silva, MD; Delanie Macedo, MD; Vinicius Brito, MD, Universidade de São Paulo, São Paulo, Brazil; Ana Paula Abreu, MD, Brigham and Women's Hospital, Boston, MA, United States; Stephanie Roberts, MD, Boston Children's Hospital, Boston, MA, United States; Luciana Montenegro, PhD, Universidade de São Paulo, São Paulo, Brazil; Melissa Andrew, BS/BA, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States; Andrew Kriby, BS/BA, Massachusetts General Hospital, Boston, MA, United States; Matthew Weirauch, PhD; Guillaume Labilloy, MS/MA, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States; Danielle Bessa, MD, Universidade de São Paulo, São Paulo, Brazil; Rona Carroll, PhD, Brigham and Women's Hospital, Boston, MA, United States; Dakota Jacobs, MS/MA; Patrick Chappell, PhD, College of Veterinary Medicine, Oregon State University, Corvallis, OR, United States; Berenice B Mendonca, PhD, Faculdade de Medicina da Universidade de São Paulo, São

Paulo, Brazil; David Haig, PhD, Harvard University, Cambridge, MA, United States; Ursula Kaiser, MD, Brigham and Women's Hospital, Boston, MA, United States; Ana Claudia Latronico, MD, Universidade de São Paulo, São Paulo, Brazil

**Objectives:** We sought to identify the genetic etiology of CPP in a three-generation family with familial CPP.

**Methods:** We studied a three-generation family in which two sets of sisters and their paternal grandmother were affected by CPP. We performed whole exome sequencing, followed by linkage analysis and whole genome sequencing in selected family members. Serum levels of DLK1 were measured via ELISA. Expression of *DLK1* was measured in mouse hypothalamus and in kisspeptin-secreting neuronal cell lines *in vitro*.

**Results:** CPP first manifested with thelarche in all four girls (age of onset 4.6-5.9 years). CPP was confirmed based on elevated baseline and GnRH-stimulated LH levels. Brain MRIs were normal. The fathers of the affected girls were brothers and had normally timed puberty. This pattern of inheritance suggested an imprinted disorder. Whole exome sequencing was performed in the 5 affected individuals and an unaffected sister but no candidate variants were identified, including no mutations in *MKRN3*. Linkage analysis identified 5 regions of maximal linkage. One of these regions (chr14q32) harbored a cluster of imprinted genes; defects in this region are known to cause Temple Syndrome, a complex developmental syndrome, which includes CPP. Additionally, prior GWAS studies have identified a SNP in this region that affects timing of menarche when paternally inherited. Whole genome sequencing identified a complex defect in the paternally expressed imprinted gene *DLK1* (~14 Kb deletion and 269 bp duplication). The deletion included the 5'UTR and the first exon of *DLK1*, including the translational start site. Only family members who inherited the defect from their father had precocious puberty, consistent with the known imprinting of *DLK1*. The patients did not demonstrate additional features of Temple syndrome except for increased fat mass. Serum DLK1 levels were found to be undetectable in all affected individuals when compared to healthy controls. Furthermore, we demonstrated that *DLK1* was expressed in mouse mediobasal hypothalamus and in kisspeptin neuron-derived cell lines, supporting a link between *DLK1* and the regulation of pubertal timing.

**Conclusions:** We identified the first genomic defect in *DLK1* causing nonsyndromic familial CPP. Loss of *DLK1* expression is the likely cause of CPP in Temple syndrome.

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**Table 1.** Clinical and hormonal features of affected girls with familial CPP associated with deletion of c I of *DLK1* at initial diagnosis and last visit.

	Patient III.3	Patient III.2	Patient III.1	Patient III.
<b>Initial Diagnosis</b>				
Clinical manifestation (yr)	Thelarche (5.5) Pubarche (6.0)	Thelarche (5.0)	Thelarche (4.6)	Thelarche (5.5) Pubarche (6.4)
Age at first visit (yr)	6.7	8.0	6.4	6.9
Height cm (SD)	129.5 (2.5)	136.3 (1.2)	125.5 (1.7)	127.5 (1.6)
BMI Kg/m <sup>2</sup> (percentile)	17.9 (87%)	19.5 (95%)	16.8 (83%)	17.3 (78%)
Breast development (Tanner stage)	4	4	3	4
Pubic hair (Tanner stage)	2	1	1	3
Bone age (yr)	11	11	7	10.6
Basal and stimulated LH levels (U/L) ‡	1.9/31.5	1.7/26.9	<0.6/11.4	1.6/23.5
Estradiol (pg/ml) *	53.3	34.9	<13	29
<b>Last Visit</b>				
Age (yr)	22	21	18	16
Duration of GnRHa treatment (yr)	4.2	3.0	4.2	3.6
Weight (Kg)	71.6	55.5	84	56.1
Target Height cm (SD)	166 (0.6)	158.5 (-0.6)	158.5 (-0.6)	166.5 (0.7)
Height (cm)	156.5	159.7	159.3	160.5
BMI (kg/m <sup>2</sup> )	29.2	22	33.1	22.1
Age of menarche (yr)	12	12	12	10.8
Basal LH/FSH (U/L) ‡	3.3/5.1	2.9/2.5	5.5/7.0	0.2/0.6
Estradiol (pg/mL) *	83	170.1	<15	26.5

‡Immunofluorometric assay; \* Fluoroimmunoassay Abbreviations: yr, years; BA, bone age; BMI: b mass index;

E<sub>2</sub>, estradiol; SD: standard deviation. Breast and pubic hair Tanner stage and bone age were assessed at time of first visit.

FC107

# **DELETION OF THE URIDINE DIPHOSPHATE GLUCURONYLTRANSFERASE UGT2B17 GENE IS ASSOCIATED WITH DELAYED PUBARCHE IN HEALTHY BOYS**

Annette Mouritsen, MD, PhD; Alexander S Busch, MD; Lise Aksglaede, MD, PhD; Ewa Rajpert-De Meyts, PhD, Rigshospitalet, Copenhagen, Denmark; Anders Juul, PhD, Rigshospitalet, Copenhagen, Denmark

**Objectives:** Urinary excretion of testosterone (T) as water-soluble conjugate depends on the sulfation and glucuronidation capacity. One of the essential glucuronidases is encoded by the *UGT2B17* gene. We previously reported that homozygous deletion of *UGT2B17* in boys was associated with lower urinary excretion of T. The objective was to study whether boys with less glucuronidation capacity may have altered androgen action affecting pubarche, representing an androgen-dependent pubertal event.

**Methods:** A cross sectional study of 668 healthy Danish boys aged 6.1 to 21.9 years. 65 of the boys were followed every 6 months in a longitudinal study. *UGT2B17* copy number variation (CNV) genotyping was performed using quantitative PCR. Reproductive hormone levels were measured.

**Results:** In the cross-sectional study, 59 of the 668 boys (8.8%) presented with a homozygous deletion of the *UGT2B17* (del/del). These boys experienced pubarche at a mean age of 12.73 years (12.00–13.46), which was later compared to a mean age of 12.40 years (12.11–12.68) in boys heterozygous for *UGT2B17* (del/ins) and a mean age of 12.06 years (11.79–12.33) in boys with the wildtype genotype (ins/ins), even after correction for BMI z-score ( $p = 0.029$ ). The effect accounted for 0.34 years delay per allele (95% CI: 0.03–0.64). A comparable trend was observed in genital development and testicular volume but did not reach

statistical significance. No significant differences were observed in circulating levels of FSH, E<sub>2</sub>, LH, T, SHBG, DHEAS or androstenedione between genotype groups after correction for age.

**Conclusions:** CNV of *UGT2B17* is a genetic factor contributing to the timing of male pubarche.

FC108

# **EXTREME HYPERANDROGENISM WORSENS METABOLIC BUT NOT DERMATOLOGIC FINDINGS WITHIN OBESE ADOLESCENTS WITH POLYCYSTIC OVARIAN SYNDROME**

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**Objectives:** Hyperandrogenism and polycystic ovarian syndrome (PCOS) are associated with an increased risk of cardiometabolic disease in adolescents, yet it is unclear if androgen concentrations per se relate to the risk of disease. **Methods:** Overweight or obese control girls without PCOS (OC, N=34) and with PCOS per NIH criteria (PCOS, N=78) were included. Anthropometric data and personal and family history were assessed. Hirsutism and acne were evaluated as dermatologic hyperandrogenism. Exercise and activity was quantified by questionnaire, and hepatic fat % and body fat % were assessed by MRI and DEXA, respectively. Fasting measurements included: glucose, insulin, leptin, adiponectin, A1c, lipids, c-reactive protein, hepatic transaminases, estradiol, progesterone, total testosterone, free testosterone (FT) and sex-hormone binding globulin (SHBG). Free androgen index (FAI) and HOMA-IR were calculated.

**Results:** OC and PCOS groups had a median age of 15 years, BMI%ile of 98, were equally sedentary and had a similar family history of type 2 diabetes. The PCOS group had severe acne and hirsutism and higher androgens, as expected (FAI  $9.9 \pm 6.3$  vs  $3.2 \pm 2.1$ ,  $p < 0.0001$ ; FT  $8.9 \pm 4.9$  ng/mL vs  $3.7 \pm 2.1$ ,  $p < 0.001$ ). Cardiometabolic risk was worse in PCOS vs. OC, including: fasting insulin ( $28 \pm 17$  uIU/mL vs  $19 \pm 7$ ;  $p = 0.005$ ), HOMA-IR ( $5.5 \pm 1.8$  vs.  $3.9 \pm 1.2$ ;  $p = 0.002$ ), ALT ( $38 \pm 16$  U/L vs  $32 \pm 12$ ;  $p = 0.023$ ), LDL ( $98 \pm 31$  mg/dL vs  $80 \pm 20$ ;  $p = 0.007$ ), and visceral fat ( $80.0 \pm 27$  cm<sup>2</sup> vs  $63.8 \pm 24$ ;  $p = 0.006$ ). Within PCOS, higher FT concentrations directly related to higher insulin, C-peptide concentrations and thus HOMA-IR. When the PCOS cohort was divided by a FT above or below 10 ng/mL, those with FT >10 had higher HOMA-IR ( $p = 0.003$ ), serum triglycerides ( $p = 0.002$ ) and hepatic fat percent ( $p = 0.017$ ).

**Conclusions:** Compared to OC, PCOS have higher androgens and worse metabolic and dermatologic findings. Within the PCOS group, girls with higher FT have worse metabolic markers, but physical attributes including BMI and adiposity, acne and hirsutism are similar. Our results suggest that obese PCOS adolescents with very high FT have a greater risk for

metabolic disease and may require more frequent screening for serum lipids, hepatic steatosis and development of type 2 diabetes.

	PCOS FT<10 N=50	PCOS FT>10 N=24	P value
BMI (kg/m <sup>2</sup> )	35.1 (30.5, 38.9)	36.4 (34.3, 37.4)	0.318
Acne score (0-3)	1 (1,2)	1 (1,2)	0.928
FGS (0-32)	4 (2,9)	7 (4,12)	0.112
Waist (cm)	103±12	106±9	0.318
Liver fat (%)	4.4 (2.4, 8.4)	7.8 (4.7, 10.9)	0.017
SBP (mm/Hg)	119 (110,129)	119 (111,129)	0.729
DBP (mm/Hg)	67±1	66±1	0.608
HDL (mg/dL)	36±6.5	37±8	0.370
TG (mg/dL)	106 (75,134)	150 (111,179)	0.002
SHBG (ng/mL)	19 (14, 25)	13 (12,18)	0.002
TT (ng/mL)	36 (28, 47)	59 (53,68)	0.001
HbA1C (%)	5.4±0.3	5.4±0.4	0.306
HOMA	5.2 (3.3, 6.8)	6.6 (5.2, 10.4)	0.003
C-Peptide	2.9±1.0	3.8±1.3	0.005

FC109

DISCOVERY OF MUTATIONS IN MULTIPLE GENES CONTROLLING GNRH NEURONAL MIGRATION AND DEVELOPMENT IN PATIENTS WITH SELF-LIMITED DELAYED PUBERTY

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**Objectives:** Abnormal pubertal timing affects >4% of adolescents and is associated with adverse health outcomes. Up to 80% of variation in the timing of pubertal onset is genetically determined. Self-limited delayed puberty (DP) segregates in an autosomal dominant pattern, but in the majority the neuroendocrine pathophysiology and genetic regulation remain unclear. Mis-regulation of the embryonic migration of GnRH neurons has been implicated in the pathogenesis of DP (Howard et al 2016). We aim to identify new candidates for the genetic basis of DP using expression data on genes up- or down-regulated during GnRH neuronal migration.

**Methods:** We performed whole exome sequencing (WES) in 115 members of 18 families from our self-limited DP patient cohort, and filtered the data for genes with rare, predicted deleterious variants that segregated with trait within families. These data were firstly examined for overlap with gene expression data from microarray analysis of GnRH:GFP primary rat neurons at E14, E17 and E20. Secondly the data were compared to a microarray analysis of genes differentially expressed in GN11 (immature and migratory) and GT1-7 (mature and non-migratory) immortalised GnRH neurons.

**Results:** After WES, 1765 genes contained rare, predicted deleterious variants that segregated with trait. Microarray analysis identified 677 genes with significant (fold change > 2) up- or down-regulation during the time period of embryonic GnRH neuronal migration, and 102 differently expressed

between GN11 and GT1-7 cells. 48 genes identified as significantly up- or down-regulated between GnRH:GFP primary rat neurons at E14 and at E20, and 15 genes reaching statistical significance for differential expression between GN11 and GT1-7 cells, were also identified as potentially pathogenic in self-limited DP patients. These include the G-protein coupled receptor *LGR4* and the neuronal growth regulator *NEGR1*.

**Conclusions:** This analysis has yielded several interesting new rare, potentially pathogenic variants in genes implicated in GnRH neuronal migration and development in 7 families from our cohort. Whilst these candidates need to be functionally validated, these data provides further evidence for the importance of GnRH neuronal migration in the timing of puberty onset.

FC110

USE OF TESTOSTERONE GEL COMPARED TO INTRAMUSCULAR FORMULATION FOR PUBERTY INDUCTION IN MALES WITH CONSTITUTIONAL DELAY OF GROWTH AND PUBERTY

Danilo Fintini, MD, Bambino Gesù Children's Hospital, Rome, Italy; Laura Chioma, MD; Giulia Papucci, MD, Bambino Gesù Children's Hospital, Rome, Italy; Marco Cappa, MD, Bambino Gesù Children's Hospital, Rome, Italy

**Objectives:** Delayed puberty may include hypo- or hypergonadotropic hypogonadism, and constitutional delay of growth and puberty (CDGP) that represents the most common cause (up to 65%) of delayed puberty in boys. CDGP can be considered an extreme of the normal spectrum of pubertal timing, it remains a diagnosis of exclusion and can only be confirmed when puberty occurs spontaneously. CDGP treatment include expectant observation or therapy with intramuscular low-dose of testosterone (IMTT) while there are no data available regarding its use of transdermal testosterone gel (TTG). The aim of our observational study was to analyze the use of TTG for pubertal induction compared to IMTT in males with CDGP.

**Methods:** 75 adolescent boys with CDGP were recruited Endocrinology Unit of Bambino Gesù Pediatric Hospital between 2010 and 2016, divided into three homogeneous groups: Group 1 (N=25) treated with 50 mg i.m. enanthate testosterone (IMTT) every 4 weeks for three months; Group 2 (N=26) treated with 10 mg daily 1% testosterone transdermal gel (TTG) for three months, and Group 3 (N=22) only observed as control group (CNT). All the subjects were observed at baseline and after 6 months.

**Results:** The Height Velocity (HV) were statistically higher after 6 months in both IMTT and TTG groups compared to CNT, while in the CNT group showed significant increase of the testicular volume compared to IMTT and TTG groups. No other differences were recorded between IMTT and TTG group.

**Conclusions:** To our knowledge this is the first study that investigate the role of TTG on treatment of pubertal

activation on CDGP population compared to conventional treatment. Despite the small sample size, our preliminary data confirm the efficacy of short-term Testosterone gel treatment to induce the growth spurt with a rapid improvement on HV such as to approach to pubertal values.

**Free Communication Session, Sunday, September 17, 2017, 8:45-9:45am**  
**Late Breaking Abstracts**  
**FC111 – FC115**

FC111

**BIG FAT SECRET: DISRUPTION OF T CELL HOMEOSTASIS BY CYCLIN DEPENDENT KINASE 5 ACTIVITY IS CRITICAL IN THE PATHOGENESIS OF INFLAMMATION-INDUCED OBESITY**

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**Objectives:** A decline in regulatory T cells ( $T_{regs}$ ) and an increase in pro-inflammatory T cells in adipose tissue (AT) characterize the low-grade chronic inflammation of obesity and insulin resistance. Signal transducer and activator of transcription 3 (STAT3) is a critical mediator in this process; however, other regulators of this inflammatory cascade remain unclear. Cyclin-dependent kinase 5 (CDK5), primarily a neuronal kinase, was recently reported as necessary for STAT3 phosphorylation. With this pilot project, we aimed to investigate the T cell-specific function of CDK5 in age- and diet-induced obesity.

**Methods:** Male and female mice with T cell lineage-restricted deletion of the *Cdk5* gene ( $Cdk5^{TKO}$ ) and their Wild Type ( $Cdk5^{WT}$ ) littermates fed standard chow diet were compared at 1 year of age. 4 week old  $Cdk5^{TKO}$  and  $Cdk5^{WT}$  mice were fed high-fat diet (45kcal % fat, HFD) or low-fat control diet (10kcal% fat, LFD) for 16 weeks.

The effects of HFD on the metabolic phenotype were observed by serial measurements of body weight and food intake, histopathology, MRI with IDEAL imaging, and intraperitoneal glucose tolerance test (GTT).

To identify the pathogenic role of CDK5 in HFD-mediated alteration of T cell repertoire, T cells isolated from spleen and AT were analyzed by flow cytometry.

**Results:** We noted that  $Cdk5^{TKO}$  mice were resistant to age-induced obesity and visceral adiposity at 1 year of age.  $Cdk5^{TKO}$  mice also remained lean on HFD, gaining significantly less weight than  $Cdk5^{WT}$  mice. MRI showed that  $Cdk5^{TKO}$  mice were protected against visceral and hepatic adiposity. GTT

revealed better glucose tolerance in  $Cdk5^{TKO}$  mice. The percentage of  $T_{regs}$  was significantly higher in AT (but not spleen) of  $Cdk5^{TKO}$  mice on HFD. The proportion of CD8 T cells, Th1 cells, Th17 cells, and effector-memory T cells trended lower in  $Cdk5^{TKO}$  mice fed HFD.

In the LFD group, no difference was noted between  $Cdk5^{TKO}$  and  $Cdk5^{WT}$  mice.

**Conclusions:** 1) The pathogenesis and complications of inflammation-induced obesity (propagated by aging and HFD) depend on the impaired T cell homeostasis resulting from constitutive activation of CDK5 in T cell lineage. 2) T cell-specific CDK5 activity may be targeted for treatment of obesity and insulin resistance.

FC112

**HISTONE PHOSPHORYLATION BY THE KINASE OF TRANSIENT RECEPTOR POTENTIAL MELASTATIN 6 (TRPM6) ATTENUATES ADJACENT ARGININE METHYLATION IN DISORDERED PEDIATRIC MINERAL METABOLISM**

Nora Renthal, PhD, Boston Children's Hospital, Boston, MA, United States; Grigory Krapivinsky, PhD; David E Clapham, PhD, Boston Children's Hospital, Boston, MA, United States

**Objectives:** Melastatin-related Transient Receptor Potential 6 (TRPM6) is a cation channel kinase, "chanzyme," highly expressed in intestinal mucosa and kidney. TRPM6 and its sister chanzyme, TRPM7, are the only known examples of single polypeptides containing both an ion channel pore and a serine/threonine kinase. Deletion of either gene in mice is embryonically lethal. Human mutations in TRPM6 cause Familial Hypomagnesemia with Secondary Hypocalcemia (HSH), a rare autosomal recessive disease, characterized by severe hypomagnesemia with hypomagnesemic parathyroid failure. Affected individuals suffer neurologic symptoms of hypomagnesemic hypocalcemia, beginning in infancy, including tetany, refractory seizures, and death. Our study aimed to uncover the function of the TRPM6 kinase, its phosphorylation targets, the roll of these targets in the cell, and the interdependence of the TRPM6 channel and TRPM6 kinase.

**Methods:** This study employed techniques such as protein immunoprecipitation, western blotting, tandem affinity purification and mass spectrometry, CRISPR-Cas9 tag and mutation incorporation, immunofluorescence microscopy, autoradiography, and qPCR.

**Results:** Our laboratory has uncovered a signaling pathway mediated by TRPM6, whereby its C-terminal kinase is cleaved from the channel in a cell type-specific, channel-dependent fashion, and remains active. The cleaved kinase translocates to the nucleus where it phosphorylates specific histone serine and threonine (S/T) residues. TRPM6 cleaved kinases (M6CKs) bind subunits of the PRMT5 molecular complex responsible for the methylation of histone arginine residues, an important epigenetic modification. Histone phosphorylation by M6CK results in a dramatic decrease in methylation of arginines adjacent to M6CK-phosphorylated amino acids.

Knockout of *TRPM6* or inactivation of its kinase results in global changes in histone S/T phosphorylation and changes the transcription of hundreds of genes.

**Conclusions:** M6CK associates with the PRMT5 molecular complex to provide site-specific histone phosphorylation, which regulates transcription by attenuating the effect of local arginine methylation. These investigations provide a better understanding of cation-directed intracellular signaling and shed light on the pathophysiology of patients with HSH.

FC113

#### INFLUENCE OF GROWTH HORMONE THERAPY IN THE OCCURRENCE OF SECOND NEOPLASM IN SURVIVORS OF CHILDHOOD CANCER.

*Cecile Thomas-Teinturier, MD, AP-HP Hopitaux Paris-Sud Site Bicêtre, Le Kremlin-Bicêtre, France; Isabelle Oliver-Petit, MD, Hôpital Purpan, Toulouse, France; Helene Pacquement, MD, Institut Curie, Paris, France; Odile Oberlin, MD, Institut Gustave Roussy, Villejuif, France; Martine Munzer, MD, American Memorial hospital, Reims, France; Florent De Vathaire, PhD, Institut Gustave Roussy, Villejuif, France*

**Objectives:** Growth hormone (GH) deficiency is a common endocrine late effect of cranial irradiation for childhood cancer and needs GH treatment to achieve normal adult height. But concerns have been raised that GH treatment might lead to an increased risk of secondary neoplasms (SN).

To study the role of GH therapy in the risk of occurrence of SN, we used the database from the retrospective French cohort of 5-year survivors of childhood cancer treated before 1986, in which radiation dose-volumes to each organ had been estimated. 80% of survivors sent back a questionnaire. SN and GH therapy were validated.

**Methods:** Analysis of SN incidence was done using time-dependent Cox regression model. Then, we undertook a cohort-nested case-control study on 45 case patients with secondary meningioma and 173 controls matched for radiation dose distributions to meninges, sex, age at first cancer and duration of follow-up.

**Results:** Among 2852 survivors born after 1958, median age at cancer 4 years, with a median follow-up of 26 years, 196 received GH therapy. 376 survivors had a SN, including 40 who had received GH therapy: 17 meningioma (11 in females), 9 brain cancer, 14 non brain cancer. In a multivariate analysis, adjusting for age at diagnosis, gender, neurofibromatosis, brain tumor as first cancer, chemotherapy and radiation dose, GH treatment did not significantly increase the risk of secondary non brain cancer (RR=0.86, 95%CI:0.48-1.55, p=0.6), secondary brain cancer except meningioma (RR=0.69, 95%CI:0.27-1.77, p=0.4) or secondary meningioma (RR=2.01, 95%CI:0.93-4.34, p=0.07).

The case-control study confirmed a slight but non-significant excess risk of meningioma (OR=1.94, 95%CI: 0.82-4.6, p=0.2), greater in females (OR=4.26, 95%CI: 0.95-19.04, p=0.06).

**Conclusions:** Our study confirms the safety of GH use in survivors of childhood cancer with no significant influence in the occurrence of SN. The non-significant slight excess risk of meningioma, in particular in women does not justify a restriction on the use of GH therapy for GH deficient patients but life-long MRI follow-up of all survivors, especially women, who received brain radiation. Study on other confounding factors in women, such as oestrogen use is still ongoing.

FC114

#### IMPROVING OUTCOMES IN ADOLESCENTS WITH POORLY CONTROLLED TYPE 1 DIABETES

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**Objectives:** We conducted a randomized controlled trial to assess the efficacy of a web-delivered multi-component intervention to improve blood glucose control in adolescents with poorly controlled type 1 diabetes mellitus. We targeted self-monitoring of blood glucose levels (SMBG), working memory, and parental supervision.

**Methods:** Adolescents (N=61) with poorly controlled T1DM were randomized to usual care or to a 25-week/15 session web-delivered intervention (WebRx). The intervention included behavioral economic incentives for teens and parents, motivational and cognitive behavioral therapy and working memory training for the adolescent, and parent training. Outcome measures, including frequency of SMBG, visual spatial working memory, family conflict and HbA1c were assessed at baseline, at the end of the intervention period and 6 months thereafter (12 months after entering the study).

**Results:** Retention was very high, with 28 of 30 families completing more than 12 of 15 online counseling sessions and 25 of 30 teens completing at least 20 of the 25 working memory sessions. Adolescents who participated in WebRx had higher rates of SMBG at 6 months (5.51 vs 3.97, p<0.01) and at 12 months (4.75 vs 3.76, p<0.05). Parental monitoring was also higher in the intervention at 6 months (3.78 vs 2.28, p<0.01), but was not statistically different at 12 months. The teens who participated in WebRx achieved higher scores of working memory both at 6 months (62.1 vs 48.77, p<0.05) and at 12 months (70.96 vs 52.82, p<0.01). The experimental group had lower HgbA1c (8.57 vs 9.10, p <0.05) at the end of the intervention and this effect persisted at 12 months (8.73 vs 9.29, p<0.05). We also observed decreased family conflict and improved inhibition in the WebRx group.

**Conclusions:** This innovative, web-delivered intervention improved targeted behaviors as well as glycemic control in teenagers with poorly controlled type 1 diabetes. The beneficial effects were evident at the end of the intervention and were still demonstrable 6 months after the end of the

active behavioral treatment. Because the intervention can be completed online, it may be particularly helpful for patients who have limited access to diabetes centers.

FC115

**RAPID MULTISTEROID MASS SPECTROMETRY (MS) PROFILING COMBINED WITH SIMULTANEOUS GONADAL PEPTIDE MEASUREMENT ALLOWED FOR IMMEDIATE DIAGNOSIS OF MAJOR DISORDERS OF SEX DEVELOPEMENT (DSD) AND EARLY GENDER ASSIGNMENT IN A COHORT OF 92 NEONATES**

*Fatma Chebbi, MD; Marie-Christine Temple, MD, CHU COCHIN, PARIS, France; Cyril Amouroux, MD, CHRU Montpellier, MONTPELLIER, France; Françoise Paris, MD, PhD, CHRU de Montpellier, MONTPELLIER, France; Laetitia Martinerie, MD, University of Paris, Robert Debré Hospital, Paris, France; Karine Braun, MD; Hélène Bony, MD, CHU Amiens, AMIENS, France; Jean-Claude Carel, MD, University of Paris, Robert Debré Hospital, Paris, France; Najiba Lahlou, MD, PhD, University Paris Descartes, Paris, France*

**Objectives:** As DSD constitute a heterogeneous group, our diagnostic strategies were based on assessment of both adrenal and gonadal secretion. Molecular diagnosis is limited by accessibility, delay and the small number of genes known to cause DSD. Multisteroid MS offers higher specificity, sensitivity and quicker results in smaller volume than immunoassays.

**Methods:** We developed a rapid liquid chromatography-tandem MS assay for simultaneous quantification of 10 steroids, targeting, in combination with gonadal peptides, the DSD underlying etiologies. Cortisol, 11-Deoxycortisol, Corticosterone, Deoxycorticosterone, Testosterone, Dihydrotestosterone, Androstenedione, Dehydroepiandrosterone, 17-hydroxyprogesterone and Progesterone were quantified by triple-quadrupole MS Quattro Premier (Waters, StQuentin-en-Y, Fr). On the same samples AMH and inhibinB were simultaneously assayed using ultrasensitive ELISA (AnshLabs, Houston, Tx). All results were obtained within 5 hours.

**Patients:** Over the last 3 years, 92 neonates with DSD detected at birth were investigated in the first week of life and retrospectively classified after karyotyping as XX and XY DSD.

**Results:** Among 43 neonates with XX DSD, were diagnosed or suspected within one day: three 21-hydroxylase blockades, two 11 $\beta$ -hydroxylase blockades, 1 case of ovotestis, and 15 cases of isolated clitoris hypertrophy related to transient persistence of adrenal fetal zone.

Among 49 neonates with XY DSD, were diagnosed or suspected within one day : one 3 $\beta$ -dehydrogenase defect, 2 cases of 5 $\alpha$ -reductase defect, 2 cases of androgen insensitivity, 1 case of SF1 defect, 1 case of SOX9 defect and 5 cases of AMH defect responsible for Mullerian duct persistence.

In all cases the biological diagnosis was confirmed later on by molecular biology, showing several not yet reported mutations. All other patients from the cohort were free from any endocrine or genetic abnormality.

**Conclusions:** The applied strategy for evaluating at the same time both adrenal and gonadal functions allowed for fast and reliable diagnosis and therapy of acute situations such as congenital adrenal hyperplasia, and helped to swiftly assign the appropriate gender in all DSD cases.

**POSTER SESSION 1**

**Thursday, September 14, 2017, 5:45-6:45pm**

**P1 - Adrenals**

**P1-100 – P1-135**

P1-100

**IDENTIFICATION OF A FOUNDER EFFECT OF THE STAR P.Q258\* NONSENSE MUTATION IN KOREAN PATIENTS WITH CONGENITAL LIPOID ADRENAL HYPERPLASIA**

*Eungu Kang, MD; Yoon-Myung Kim, MD; Gu-Hwan Kim, PhD; Beom Hee Lee, MD; Han-Wook Yoo, MD; Jin-Ho Choi, MD, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic Of*

**Objectives:** Congenital lipid adrenal hyperplasia (CLAH) is the most severe form of congenital adrenal hyperplasia, caused by defects in the steroidogenic acute regulatory protein (STAR) or, rarely, the cholesterol side-chain cleavage enzyme (P450<sub>sc</sub>). The most common STAR gene mutation is c.772C>T (p.Q258\*), which was identified in 65 to 90% of Japanese and Korean patients with CLAH, suggesting a founder effect. This study aimed to investigate the phenotypic and mutation spectrum of STAR defects and identify a founder effect of the p.Q258\* mutation in Korean patients with CLAH.

**Methods:** For 45 patients from 42 independent pedigrees, haplotype analysis was performed in 10 unrelated trio families, including patients with the p.Q258\* mutation whose DNA samples were available, using 1,972 single nucleotide polymorphism (SNP) and six short tandem repeat (STR) markers. An Illumina Infinium® Human Omni2.5-8 v1.3 performed the SNP genotyping.

**Results:** Among 84 alleles from 42 unrelated families, mutation p.Q258\* was found in 74 alleles (88.1%) from 41 families. A shared haplotype was identified in 17 of 20 alleles from 10 patients (size, 198 kb). The age of the founder mutation was estimated as 4,875 years (95% credible set: 3,575–7,925 years) assuming an intergenerational time interval of 25 years.

**Conclusions:** A haplotype analysis showed that the 198-kb region was shared by most individuals with CLAH, indicating the existence of a founder effect. The STAR p.Q258\* mutation is the most common in Korean patients with CLAH, suggesting a founder effect. The age of the mutation corresponded with the date when the Korean people settled in the Korean peninsula. The high prevalence of p.Q258\* in

Japan and China also suggests a founder effect in Asian countries.

P1-101

#### **GONADAL FUNCTION IN ADULT MALE PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA**

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**Objectives:** Reported fertility problems in men with congenital adrenal hyperplasia (CAH) range from normal to severely impaired. Previous studies are most often based on data from a single center. Mechanisms for fertility impairment include primary, secondary and tertiary gonadal dysfunction or psychosexual problems. Primary gonadal dysfunction may be due to benign testicular adrenal rest tumors (TART). In addition, central gonadal dysfunction may be caused by the suppressive effects of elevated adrenal androgens or their metabolites on the HPG axis. Aim of the study is to determine gonadal function in male CAH patients in the European DSD life cohort.

**Methods:** The DSD LIFE database contains data of 1161 patients with different forms of disorders of sex development (DSD) including 121 male CAH patients from 14 European centers. Indirect markers of gonadal function were collected including hormone concentrations, serum analysis (n=43-90) and ultrasound testes (n=67). Patient characteristics, biochemical parameters and treatment in patients with and without gonadal dysfunction were evaluated.

**Results:** 121 male CAH patients were available for the study. In 118 patients, median age 28 (range 15-68) years, gonadal function could be evaluated, 3 were excluded due to longstanding testosterone treatment. 2 patients had 11 $\beta$ -hydroxylase deficiency, 116 patients suffered from 21-hydroxylase deficiency (genotype O=23 pts, A=36 patients, B=32 pts, C=3 pts, no mutation=22 pts). Low testosterone concentrations (according to range variable lower than reference range) were reported in 19/97 (19.6%), low LH in

12/90 (13.3%), low FSH in 9/90 (10%), and low inhibin B in 8/43 patients (18.6%). Pathologic semen parameters (according to WHO 2010) were observed, considering low sperm count (15/39 patients), decreased motility (13/37 patients), abnormal morphology (4/28 patients). TARTs were present in 27 of 67 patients (in 2 patients unilaterally). 26 patients had fathered a total of 43 children.

**Conclusions:** Gonadal function in male CAH patients can be compromised with a high prevalence of TART. Further analyses are necessary to compare TART and non TART patients and to determine other contributing pathogenetic factors.

P1-102

#### **ADRENOCORTICAL CARCINOMA IN CHILDREN: A CLINICO-PATHOLOGIC ANALYSIS OF 41 PATIENTS AT MAYO CLINIC FROM 1950-2016**

*Nidhi Gupta, MD; Michael Rivera, MD; Paul Novotny, MS/MA; Vilmarie Rodriguez, MD; Irina Bancos, MD; Aida Lteif, Associate Professor, Mayo Clinic College of Medicine, Rochester, MN, United States*

**Objectives:** Adrenocortical carcinoma (ACC) is an aggressive rare childhood cancer. No definite histopathological criterion exists to differentiate pediatric ACC from adrenocortical adenoma. The aim of this study was to describe the clinico-pathologic data of children with ACC and identify prognostic factors. Performance of Weiss score, modified Weiss score and Wiencek-index was evaluated.

**Methods:** Retrospective chart review of patients with histologically proven ACC from 1950-2016 at the Mayo Clinic was done (age at onset of symptoms  $\leq$  21y). Archived pathology slides were reviewed.

**Results:** Forty-one patients met inclusion criteria. Median age at onset of symptoms was 15.7y (range, 0.2-21y). Female-male ratio was 3.6:1. Mixed symptomatology with >1 hormonal abnormality was the most common presentation (54%, n=22) followed by virilization alone (17%, n=7). Sixty-seven percent of patients (26/39) underwent total adrenalectomy and 56% (23/41) received adjuvant therapy. Patients aged <4y had smaller median tumor diameter and lower median tumor weight as compared to those >12y (tumor diameter: 6.4cm vs. 10.8cm; tumor weight: 80 grams vs. 435 grams). Metastatic disease was reported in 63% of patients (n=26). Most common sites of metastases were liver (74%, n=20) and lungs (67%, n=18). The majority of patients (63%, n=26) were classified as Stage IV (T<sub>1-4</sub>N<sub>0-1</sub>M<sub>1</sub>) by ENSAT system. Recurrent disease was reported in 24% patients (n=10). At a median follow-up of 1.8y (range 0.1-37y), 46% of patients (13/29; SE 0.095) remained alive. The 2-year and 5-year survival rates were 34.8% (SE 0.092) and 26.5% (SE 0.087) respectively. In a multivariate analysis, age at onset of symptoms and disease stage were independently associated with overall survival. The Wiencek scoring system ( $\geq$  4) was most accurate in predicting death or recurrence of ACC (sensitivity 100%, specificity 83.3%, Fisher's Exact Test p=0.0014).

**Conclusions:** Younger age at onset of symptoms (<4y) and less advanced stage of disease (Stage I or II) are favorable prognostic factors for survival in children with ACC. The Wieneke scoring system was most closely associated with patient outcomes. This is the largest single institution report on pediatric ACC.

Table 1: Macroscopic features of 41 pediatric patients with adrenocortical carcinoma

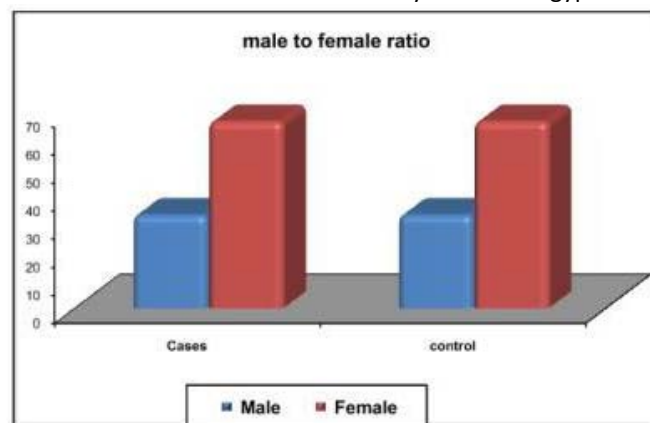
Macroscopic feature	Age < 4 y n = 10	Age ≥ 4 to ≤ 12 y n = 4	Age > 12 y n = 27	All patie n = 41
<b>Surgery (n)</b>				
Partial adrenalectomy	1	0	2	3
Total adrenalectomy	7	2	17	26
Radical resection	1	1	4	6
Inoperable	0	0	4	4
Other	1 <sup>a</sup>	1 <sup>b</sup>	0	2
<b>Primary site (n)</b>				
Right	5	0	11	16
Left	4	3	16	23
Other	1 <sup>a</sup>	1 <sup>b</sup>	0	2
<b>Maximum tumor diameter (cm) <sup>c</sup></b>				
Median	6.4	12.0	10.75	10.0
Range	2.0-11.0	6.0-14.0	4.0-20.0	2.0-20.0
<b>Tumor weight (grams) <sup>d</sup></b>				
Median	80	348	435	250
Range	20-250	180-515	25-1046	20-1046
<b>Tumor extension (n)</b>				
Localized to adrenal gland	4	1	7	12
Extending into adjacent tissue	4	2	11	17
Extending into adjacent organ	0	0	5	5
Other	2 <sup>a,b</sup>	1 <sup>b</sup>	4 <sup>b</sup>	7
<b>Vena cava invasion (n)</b>				
Present	0	0	5	5
Absent	7	2	10	19
Other	3 <sup>a,b</sup>	2 <sup>b</sup>	12 <sup>b</sup>	17
<b>Metastatic disease (n)</b>				
No metastases	8	2	5	15
Lung only	0	0	3	3
Liver only	1	0	4	5
Lung and liver only	0	1	3	4
Multiple sites	1 <sup>d</sup>	1 <sup>e</sup>	12 <sup>a</sup>	14
<b>Recurrent disease (n) <sup>f</sup></b>				
Present	1	1	8	10
Absent	9	3	19	31
<b>Tumor stage (n) <sup>g</sup></b>				
Stage I	2	0	0	2
Stage II	5	2	4	11
Stage III	1	0	1	2
Stage IV	2	2	22	26

## Methods:

- This is a prospective study that has studied 30 infants and children with CAH due to 21 hydroxylase deficiency attending to Tanta and Cairo Universities either at initial diagnosis or follow up visits, and 20 infants and children as a control group matched with age and sex of patients. Paired salivary and serum samples have been collected at the same time either at initial presentation for new cases or before the morning dose of hydrocortisone for previously diagnosed cases. Specimens were collected by sterile pipettes with at least 30 minutes between eating and sampling. Specimens were capped and frozen at -20 C till assay. Salivary samples were estimated by 17 OHP Saliva ELISA (RE52271), IBL, Germany. Serum samples were estimated by 17 OHP ELISA (RE52071), IBL, Germany.

**Results:** Female patients were 20 cases (66.7%) and male patients were 10 (33.3%). Unexpalined sibling death were found in 26.7% of paients. There was significant positive correlation between serum and salivary 17 OHP in cases( P 0.001) but there was non significant positive corralation in control (P 0.731). All salivary samples (100%) obtained at diagnosis were insuffient and those patients were excluded from the study, while only 10% of salivary samples at follow up were insufficient and their patients were excluded from the study. Duration of salivary samples in infants aged less than 2 years were significantly longer than salivary sampling in children aged more than 2 years(P <0.05).

**Conclusions:** CAH in Egypt has unbalanced male female ratio which indicate underdiagnosis of this condition in male cases and highlights the importance of neonatal screening in Egypt. Salivary 17OHP is a reliable method for assessment of CAH patients and as effective as serum 17OHP that should be used in follow up, not in diagnosis of CAH. Difficulties during sampling might limit the use of salivary 17OHP in infancy. More training of medical personnel is required before recommendation of wide use of salivary 17OHP in Egypt.



P1-103

## PROS AND CONS OF SALIVARY 17 HYDROXY PROGESTERONE IN CONGENITAL ADRENAL HYPERPLASIA CHILDREN, AN EGYPTIAN EXPERIENCE

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### Objectives:

- Study the value of salivary 17 OHP in diagnosis and follow up of CAH children.
- Record the advantages and difficulties of using salivary 17OHP.
- Evaluate possibility of recommendation for wide use of salivary 17OHP in diagnosis and follow up of CAH in Egypt.



# ADRENOMEDULLARY FUNCTION DECREASES AFTER BIRTH IN CLASSICAL CONGENITAL ADRENAL HYPERPLASIA AND PREDISPOSES TO ACUTE ILLNESS

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**Objectives:** Youth with classical congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD) exhibit abnormal morphology and function of the adrenal medulla. We have shown decreased epinephrine (Epi) levels in newborns and young infants with CAH, indicating that impaired adrenomedullary function may occur during fetal development and be present from birth. Little is known about adrenomedullary function in older infants and toddlers with CAH when they are at high risk for illness-related morbidity and mortality. Our objective was to quantify catecholamine levels in very young children with CAH and to correlate adrenomedullary function with frequency of acute illness.

**Methods:** We studied 34 newborns, infants and toddlers with CAH due to biochemically confirmed 21OHD, and 28 age-matched unaffected controls. Plasma catecholamine [Epi and norepinephrine (NE); pg/mL] levels and NE:Epi were determined at newborn, 1-yr, 2-yr, and 3-yr visits. We also quantified the frequency of acute illness for 22 CAH newborns/young infants compared to 17 controls. Data are presented as mean  $\pm$  SD, or median (IQR).

**Results:** Epi levels were lower in CAH newborns and young infants [80 (40-104)] vs. controls [127 (77-173.5);  $p < 0.05$ ], with a decrease in Epi between birth and 1 year in CAH [newborn 81 (45.5-102.5), 1-yr 40 (40-80.7);  $p < 0.05$ ]. Epi levels remained similar at 2 and 3 year in CAH toddlers. NE:Epi at birth was higher in CAH [12.3 (7.8-16.9)] vs. controls [6.7 (5.4-9.3);  $p < 0.01$ ] and increased over the 1st year in CAH [newborn 11.5 (8.3-15), 1-yr 23.8 (17-26);  $p < 0.05$ ], reflecting either the decline in Epi and/or overcompensation by the sympathetic nervous system for impaired adrenomedullary function. CAH infants had more illness in the 1st year (CAH  $2.0 \pm 2.8$ , controls  $0.4 \pm 1$ ;  $p < 0.05$ ) and 2nd year (CAH  $1.2 \pm 1.4$ , controls  $0.2 \pm 0.4$ ;  $p < 0.01$ ). CAH infants with lower Epi ( $< 100$ ) had a higher frequency of illness ( $1.4 \pm 1.7$ ) in the 1st year of life compared to those with Epi  $\geq 100$  ( $0.3 \pm 1$ ;  $p < 0.05$ ).

**Conclusions:** Epi levels are lower in newborns and young infants with CAH, and decline further over the first year of life, when CAH youth are prone to acute illnesses. CAH infants with lower Epi may be at even higher risk for more frequent illness.

# DISSOLUTION AND COMPATIBILITY OF HYDROCORTISONE GRANULES FOLLOWING EXPOSURE TO COMMON PAEDIATRIC ADMINISTRATION FLUIDS AND FOOD MATRICES

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**Objectives:** The objective of the present work was to study the biorelevant dissolution and compatibility properties of hydrocortisone granules (Infacort® development formulation Diurnal Ltd.) following exposure to typical administration fluids including breast milk, artificial milk, whole milk, water, apple-, orange- and tomato juice and semi-solid dosing vehicles such as apple sauce and yoghurt.

**Methods:** Dosing conditions were assessed for a representative patient collective, ranging from neonates to school children. Hydrocortisone doses applied in the *in vitro* experiments were in the dose range of 0.5 to 5 mg. Test media and volumes were adapted to simulate gastric contents of children of different ages immediately after administering a single dose of hydrocortisone together with an age appropriate volume of the different fluids (50-200 ml), or immediately after mixing and administering a single dose with a dosing vehicle (1 teaspoon) followed by some water intake. Dissolution experiments were performed at 37 °C with the Mini-Paddle apparatus. The total duration of the dissolution experiments was 120 or 240 min to screen both dissolution and compatibility with the different media. Samples were taken at predetermined time points and analyzed by HPLC.

**Results:** In all dosing scenarios simulating initial gastric conditions after administering age-related hydrocortisone doses to children of different age groups, *in vitro* drug release was fast and complete, i.e.  $\geq 75$  or 80 % of the dose was released in within 30 min. This was despite the dosing matrices differing significantly in pH and other physicochemical parameters. Moreover, in all experiments no drug precipitation or degradation could be observed over the entire test duration.

**Conclusions:** Results from the present study confirm the compatibility and chemical stability of hydrocortisone granules with commonly used dosing matrices over a 120 or 240 min time period, respectively. Results from the biorelevant *in vitro* dissolution experiments suggest that *in vivo* dissolution and bioavailability of the granules will not be affected by the composition of the co-administered fluids and vehicles studied.

## Acknowledgements

Dr. Anja Lange, Hospital for Pediatrics, University of Greifswald, is gratefully acknowledged for her support.

# CLINICAL AND GENETIC CHARACTERIZATION OF A COHORT OF PATIENTS WITH ALGROVE SYNDROME (AS)

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**Objectives:** Allgroves syndrome, AS (also called Triple-A syndrome, OMIM #231550) is a rare autosomal recessive disorder characterized by adrenocorticotrophic hormone resistant adrenal insufficiency, alacrima, achalasia, neurological and dermatological abnormalities. Mutations in the AAAS gene on chromosome 12q13 encoding the nuclear pore protein ALADIN have been reported in these patients. **Methods:** Over the period 2006 and 2016, we evaluated five patients with the clinical diagnosis of triple A syndrome, based on the presence of at least two symptoms, usually adrenal insufficiency and alacrimia.

**Results:** Patients underwent genetic analysis revealing homozygous mutations in the AAAS gene in all of them. One novel mutation was detected: homozygous deletion of 10bp (c. 1262\_1272del, p.Q421NfsX126) in the exon 14 of the AAAS gene that causes a frameshift with introduction of an aberrant stop codon after 126 amino acids. This genetic variant, due to significant alterations in the protein structure, are highly probable pathogenic. A precise genotype-phenotype correlation was impossible to be established.

**Conclusions:** Based on our experience, we recommend that in the presence of alacrima and at least one more symptom of AS, molecular analysis should be performed. Our cases share many clinical features with AS and underline the variability in this syndrome and the need for thorough investigations following a multidisciplinary approach.

# MANAGEMENT OF CUSHING SYNDROME IN CHILDREN WITH MCCUNE-ALBRIGHT SYNDROME IS A CHALLENGING TASK.

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Center, Moscow, Russian Federation; Natalya Zubkova, PhD; Maria Kareva, PhD, Endocrinology Research Centre, Moscow, Russian Federation; Valentina Peterkova, MD-PhD, Institute of Pediatric Endocrinology, Moscow, Russian Federation

**Objectives:** McCune-Albright syndrome (MAS) is a rare genetic disorder caused by somatic mutations of GNAS with mosaic distribution of activated Gas subunit in various tissues. Clinical features include café-au-lait spots, hyperfunctioning endocrinopathies and fibrous dysplasia. Cushing syndrome (CS) is a rare life-threatening manifestation of MAS associated with bilateral adrenal hyperplasia. In most of cases, bilateral adrenalectomy is required but in selected cases spontaneous remission was described.

**Methods:** We present three cases of Cushing syndrome in children with MAS and describe different treatment approaches.

**Results:** All the patients with MAS manifested with CS in neonatal period. ACTH-independent hypercortisolism was diagnosed based on clinical features and laboratory findings. Abdominal CT identified bilateral adrenal hyperplasia in all cases. Patients (P) 1 and 2 were admitted because of severe recurrent pneumonia since birth. They have "moon face", growth retardation and café-au-lait spots since birth and were diagnosed with CS at 4th and 5th months old respectively. Adrenalectomy was performed just after diagnosing because of the severity of symptoms. P1 underwent unilateral adrenalectomy of the larger gland with complete remission during next seven years of follow up, she did not develop adrenal insufficiency. In P2 bilateral adrenalectomy was performed following by substitutive therapy with hydrocortisone and fludrocortisone. P3 had milder clinical phenotype than patients 1 and 2 and was diagnosed with CS at the age of two, but clinical features of CS ("moon face", growth retardation, bone delay and obesity) and café-au-lait spots were presented since birth. Treatment with steroid synthesis inhibitor (ketoconazole) during a year was not effective. Unilateral adrenalectomy of the larger gland was performed at the age of three but the remission hadn't been achieved, so the second adrenal was removed six months after. There were no cases of adrenal crisis after surgical treatment.

**Conclusions:** Treatment approach to CS in MAS is challenging. Unilateral adrenalectomy sometimes could be effective but in others bilateral adrenalectomy is necessary. We need more experience to create clinical recommendations and to determine factors that could be predictable for unilateral adrenalectomy success.

# METFORMIN FOR RAPIDLY MATURING GIRLS WITH CENTRAL ADIPOSITY: NORMALIZATION OF ACCELERATED BONE MATURATION RELATES TO LIVER FAT

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**Objectives:** Girls with a history of prenatal growth restraint and postnatal weight catch-up tend to develop an excess of visceral and hepatic fat. Such central adiposity may be accompanied by an upregulated adrenarche with precocious pubarche (PP), and by a rapidly progressive puberty leading to early menarche and relatively short stature. A pilot study suggested that metformin treatment for 4 yr can reduce central adiposity in low-birthweight (LBW) girls with PP, and normalize pubertal milestones and adult height. We studied the relationships among metformin treatment, bone maturation and body composition in LBW-PP girls of this pilot study.

**Methods:** Longitudinal hand X-rays (0-4 yr, analysed by BoneXpert) were available from 34 randomized non-obese LBW-PP girls (89% of original cohort; N=17 untreated, N=17 metformin-treated; mean age at start 8 yr) along with body composition (0-4 yr, by DXA), hepatic fat and abdominally subcutaneous and visceral fat (post-treatment, by MRI).

**Results:** At start, bone age was ahead of chronological age. The tempo of bone aging was accelerated in untreated girls ( $\approx 16\%$  faster vs chronological aging) and normal in metformin-treated girls ( $\approx 20\%$  slower vs untreated girls). Metformin-treated girls gained more height per bone-age year. Metformin treatment was accompanied by lower gains of fat, particularly of visceral and hepatic fat. The tempo of bone maturation associated most closely ( $R=0.55$ ;  $P<0.001$ ) with hepatic fat.

**Conclusions:** Metformin treatment in rapidly maturing LBW-PP girls with central adiposity was found to normalize the accelerated bone maturation; this normalization was accompanied by less central fat, and it related most closely to hepatic fat.

P1-109

#### EFFECT OF MEGESTROL ACETATE ON ADRENAL FUNCTION WHEN USED AS AN APPETITE STIMULANT AMONG CHILDREN.

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**Background:** Adrenal insufficiency has been reported as an adverse effect of treatment with megestrol acetate in few case reports and few case series. In adults, hyperglycemia and features of Cushing syndrome have been described. The effect of cortisol synthesis on body mass index (BMI) has not been well described in children.

**Objectives:** To evaluate the effect of megestrol acetate on BMI and to describe its adverse events when used as an appetite stimulant in children.

**Patients and methods:** The study included patients  $< 21$  years of age, who were treated with megestrol acetate at Mayo Clinic between 1996 and 2014. These individuals had to have documentation of weight and height at initiation and at discontinuation of the therapy.

**Results:** 73 patients were treated with megestrol acetate (Mean age:  $10.07 \pm 4.84$  years Male: 63%;). Mean length of treatment was  $3.91 \pm 3.54$  months. Mean starting dose of Megestrol acetate was  $7.8 \pm 4.44$  mg/kg/day. Mean BMI z score before and after the treatment were statistically different (Before:  $-0.76 \pm 1.52$ ; After:  $-0.07 \pm 1.40$ ; ( $p < 0.001$ )). After adjusting for age and gender, we found that the change in BMI z-scores were positively related to the dose ( $\beta: 0.1 \text{ kg/m}^2$ ;  $p=0.008$ ) and duration ( $\beta: 0.07 \text{ kg/m}^2$ ;  $p=0.03$ ) of treatment. 11 patients (15%) had a cortisol level checked while on Megestrol. Additional 3 patients had cortisol level measured at completion of treatment. Cortisol was low in all 11 patients, at least once during the treatment period. Suppression was seen as early as 25 days post initiation of megestrol acetate treatment. In 9 patients cortisol levels had normalized when checked 12 days to 6 months after discontinuation of the megestrol acetate therapy. One patient had hyperglycemia but this was around the time of death. Mild hyponatremia was noted ( $131\text{-}134$  mg/dL) in 2 patients who did not have a cortisol level checked.

**Conclusions:** Megestrol acetate causes adrenal suppression at the standard treatment dose. Electrolyte abnormalities are uncommon. Megestrol is effective in improving BMI z score. We recommend that cortisol level be measured in all patients treated with megestrol acetate in the first 4 weeks of initiating therapy.

P1-110

#### ASSESSMENT OF HEALTH-RELATED QUALITY OF LIFE IN EGYPTIAN CHILDREN AND ADOLESCENTS WITH CONGENITAL ADRENAL HYPERPLASIA.

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**Objectives:** To assess health-related quality of life (HRQOL) in Egyptian children and adolescents with congenital adrenal hyperplasia (CAH) and to study different factors affecting QOL in CAH.

**Methods:** This cross-sectional study included 200 children and adolescents with CAH due to 21hydroxylase deficiency (21OHD) regularly attending Diabetes, Endocrine and Metabolism Pediatric Unit (DEMPU) at Cairo University Children's hospital. Enrolled patients were evaluated regarding age, sex of rearing (initial and final), family history, clinical type (salt wasting, simple virilizing or late onset), timing of genitoplasty, number of hospital admissions in the last year, compliance to treatment, regularity of follow up, presence of complications (hirsutism, precocious puberty,

hypertension, complications related to genitoplasty) as well as hormonal control. HRQOL was assessed using WHOQOL-BREF questionnaire with four domains analysed independently including physical, psychological, social and environmental domains with higher scores indicating better QOL.

**Results:** The study included 140 females and 60 males with a mean age of  $6.6 \pm 4.5$  yrs. Eighty-eight percent of them were salt wasting CAH. Older children and adolescents had significantly lower QOL scores ( $r=-0.151$ ,  $p=0.033$ ). Total QOL score correlated significantly with degree of virilization (Prader score) in females ( $r=-0.314$ ,  $p=0.041$ ), frequency of hospitalization ( $r=-0.272$ ,  $p=0.000$ ) and level of androstenedione ( $r=-0.274$ ,  $p=0.007$ ). Psychological domain was affected by age ( $r=-0.157$ ,  $p=0.026$ ) and timing of genitoplasty ( $r=-0.326$ ,  $p=0.001$ ) while social domain was affected by age ( $r=-0.277$ ,  $p<0.001$ ) and pubertal stage ( $r=-0.195$ ,  $p=0.006$ ). Females had lower scores at psychological domain ( $p<0.001$ ), whereas males showed lower scores at physical domain ( $p=0.003$ ). Salt losing CAH patients had lowest QOL scores at physical domain ( $p=0.003$ ). Patients on regular follow up scored higher at the environmental domain ( $p=0.037$ ) and those with good hormonal control had higher total QOL scores ( $p=0.032$ ).

**Conclusions:** HRQOL was relatively more affected in CAH patients with older age, poor hormonal control, more frequent hospital admissions and those who developed complications.

P1-111

#### MUTATION SPECTRUM OF ABCD1 IN 20 VIETNAMESE PATIENTS WITH X-LINKED ADRENOLEUKODYSTROPHY

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**Objectives:** X-linked adrenoleukodystrophy (X-ALD) is caused by a defect in the gene *ABCD1*, which maps to Xq28 and codes for a peroxisomal membrane protein that is a member of the ATP-binding cassette transporter superfamily. This disease characterized by progressive neurologic dysfunction, occasionally associated with adrenal insufficiency. We identified mutations of gene *ABCD1* in Vietnamese patients with X-ALD.

**Methods:** Genomic DNA from 20 Vietnamese patients from 18 unrelated families was extracted using standard procedures from the peripheral blood leukocytes. Mutation analysis of *ABCD1* was performed using Polymerase chain reaction (PCR) and DNA direct sequencing.

**Results:** We identified 17 different mutations of *ABCD1* in 20 patients including missense mutations (11/17), deletion (4/17), frameshift mutation (1/17) and splice site mutation (1/17). Of which, six novel mutations including c.1202G>T (p.Arg401Trp); c.1208T>A (p.Met403Lys); IVS8+28-551bp del; c.1668G>C (p.Q556H); c.292\_296delTCGGC (p.S98RfsX95);

and the extent of deletion included between IVS1+505 and IVS2+1501, containing whole the exon 2 (4243bp), plus insertion of 79bp from BAP31 and 8bp from unknown origin in this deleted region were identified in six unrelated patients. Eleven reported mutations including c.796G>A (p.Gly266Arg); c.1628C>T (p.Pro543Leu); c.1553G>A (p.Arg518Gln); c.1552 C>T (p.Arg518Trp); c.854G>C (p.R285P); c.1825G>A (p.E609K); c.1415\_1416delAG (p.Q472RfsX83) and c.46-53del insG, c.1553G>A (p.Arg518Gln), c.1946-1947insA (p.Asp649fsX733), c.1978C>T (p.Arg660Trp) were identified in 14 patients from 11 families.

**Conclusions:** Mutation analysis of *ABCD1* helped confirmation of diagnosis of X-ALD, genetic counselling and prenatal diagnosis.

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#### COULD WE BE OVER DIAGNOSING CENTRAL ADRENAL INSUFFICIENCY IN PRADER-WILLI SYNDROME?

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**Objectives:** To examine the function of the hypothalamic adrenal axis and presence of central adrenal insufficiency (CAI) in patients with Prader-Willi Syndrome (PWS), and to determine the correlation of the low dose ACTH stimulation test (LDAST) compared to the overnight metyrapone test (OMT) when used sequentially in the same patient.

**Methods:** Subjects with PWS ( $n=21$ ), age 3-53 yo, 10 male, 11 female were admitted to the hospital for overnight testing. Subjects did not have recent oral glucocorticoid use or known diagnosis of CAI. LDAST (1 mcg/m<sup>2</sup>, maximum 1 mcg) was performed followed by OMT. OMT was performed by administering a single dose of metyrapone (30 mg/kg, maximum 1 g) orally at 2400h. Serum was collected for cortisol, 11-deoxycortisol (11-DOC), and ACTH the following morning at 0800h. Peak cortisol results  $>15.5$  mcg/dL following LDAST and 0800 11-DOC results  $>7$  mcg/dL following OMT were classified as adrenal sufficiency. Peak cortisol result indicating adrenal sufficiency on LDAST was chosen based on institutional accepted normal values for a specific cortisol assay. OMT was used as the standard test for comparison.

**Results:** All patients (n=21) had 0800 11-DOC values >7 mcg/dL following OMT, indicating adrenal sufficiency. 6/21 (29%) failed LDAST based on peak cortisol < 15.5 mcg/dL. Using the traditionally accepted cut-off for stimulated cortisol of 18.1, 13/21 (62%) failed LDAST. There was no apparent relationship between those who passed and those who failed LDAST in age, gender, or body mass index. No patient displayed signs or symptoms of adrenal insufficiency.

**Conclusions:** Our results indicate poor agreement between LDAST and OMT results in patients with PWS. We found no evidence of CAI in our PWS population based on 0800 11-DOC values following OMT, yet 29-62% of our PWS population demonstrating a normal response to OMT failed LDAST. This data suggests that LDAST may have a high false positive rate in diagnosing CAI patients with PWS which may lead to over diagnosis.

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#### CLINICAL AND MOLECULAR CHARACTERIZATION OF PATIENTS WITH CONGENITAL LIPOID ADRENAL HYPERPLASIA IN SOUTHEAST ASIA

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**Objectives:** Mutations in Steroidogenic Acute Regulatory protein (*StAR*) cause congenital lipoid adrenal hyperplasia (lipoid CAH), characterized by absent steroidogenesis, potentially lethal salt loss, 46,XY sex reversal and massively enlarged adrenals engorged with cholesterol esters. Nonclassic lipoid CAH is a recently recognized disorder caused by *StAR* mutations that retain partial function. We aim to delineate the clinical, hormonal, and molecular characterization of *StAR* mutations in patients with lipoid CAH.

**Methods:** The entire coding regions of the *StAR* gene were assessed by polymerase chain reaction and sequencing analysis. Novel *StAR* missense mutations were re-created in expression vectors and *StAR* activity was measured as pregnenolone production in COS-7 cells. A minigene assay was used to determine the effects of the splicing mutation.

**Results:** There were 10 patients of lipoid CAH had mutations in the *StAR* gene with 5 novel mutations (p.P230L>WfsX, IVS6-1G>A, IVS3+(2-3)insT, p.W147R, p.Q264R). Eight patients had classic lipoid CAH presenting with adrenal crisis during early infancy (range of onset 3-11 months of age). Two siblings had nonclassic phenotypes with later onset adrenal insufficiency without disordered sex development. Adrenal enlargement by imaging was demonstrated in only 3 cases of classic lipoid CAH. The *in vitro* activities of W147R, and Q264R

were 3.9%, and 1.6% of wild-type activity. The IVS6-1G>A mutation caused intron retention in the *StAR* gene.

**Conclusions:** *StAR* mutations may not be rare in Southeast Asian population. There is a broad clinical spectrum of *StAR* mutations varying from early onset adrenal insufficiency to late onset of glucocorticoid deficiency with only mild defects in mineralocorticoid and sex steroid synthesis. Adrenal gland enlargement is not pathognomonic for lipoid CAH.

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#### SERUM FREE CORTISOL IS SUPERIOR TO TOTAL CORTISOL IN ASSESSING THE ADRENAL AXIS DURING GLUCAGON STIMULATION TEST IN CHILDREN AND ADOLESCENTS

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**Objectives:** Total cortisol (TC) response is routinely measured during glucagon stimulation test for growth hormone reserve in order to assess the adrenal axis. We recently published norms for serum free cortisol (sFC) response in children and adolescents during ACTH stimulation test. We extended this research to assess whether sFC is superior to TC in assessing the adrenal axis during glucagon test and could predict growth hormone (GH) response to glucagon stimulation.

**Methods:** Infants and children referred for evaluation of GH reserve underwent glucagon testing. Baseline and stimulated serum TC, sFC, GH and glucose levels were measured before and every 30 minutes for 180 minutes after IM administration of Glucagon (30 mcg per kg, max of 1 mg). Serum TC and GH were determined by chemiluminescence and sFC was measured by the same method following equilibrium dialysis. The cutoff value was set at >20 mcg/dl for TC and >0.9 mcg/dl for sFC.

**Results:** The study group consisted of 103 subjects (62 girls), median age 3.9 years (range, 0.5-14). The mean basal and peak TC levels were  $13.3 \pm 6.7$  mcg/dl and  $29.6 \pm 8.8$  mcg/dl, respectively. The mean basal and peak sFC levels were  $0.7 \pm 0.8$  mcg/dl and  $1.7 \pm 1.1$  mcg/dl, respectively. There was a positive correlation between TC and sFC levels at all time-points. Girls had higher TC levels than boys at all time-points ( $P=.05$ ), but there were no significant differences in sFC. There was a negative correlation between peak TC and age ( $r=-0.3$ ,  $P=.007$ ), but not between peak sFC and age. Of particular significance is the observation that 5 of the patients showing subnormal TC had a normal sFC response based on the previously published norms. We did not find a correlation between sFC and GH reserve.

**Conclusions:** sFC may spare the need for further evaluation of the adrenal axis in children undergoing glucagon stimulation test. The finding that TC is age and gender dependent while sFC is not may suggest that the sFC is superior to TC measurement in the pediatric population.

### PRESENTING CHARACTERISTICS OF CHILDREN WITH CONGENITAL ADRENAL HYPERPLASIA IN SRI LANKA : A GENDER BASED ANALYSIS

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**Objectives:** To describe and compare clinical and biochemical characteristics at initial presentation in male and female children with congenital adrenal hyperplasia (CAH) from Sri Lanka, in the absence of newborn screening.

**Methods:** This retrospective study was carried out in all consenting patients with CAH followed up at a tertiary care paediatric endocrinology clinic in Colombo, Sri Lanka in 2016. Data was collected on to a structured data collection sheet, from past clinical records. The characteristics of male and female patients were compared using Chi square for discrete variables and student t-test for continuous variables.

**Results:** Thirty nine participants aged between 1.5-17.5 years were included, of which 29 (74%) were salt wasters. Parental consanguinity was seen in 9 (23 %), while 6 (15 %) had a previously diagnosed sibling. A majority (77%) had hyper-pigmentation, while more than 50% had features of salt wasting (vomiting, dehydration) at presentation. All girls except one, had virilised genitalia. Hyponatremia (Na less than 125 mmol/l) was present in 12 (30%) and hyperkalaemia (K more than 5.5 mmol/l) in 27 (69%).

Majority was genetically female 30 (77%), and amongst one was being reared as a male due to severe virilisation. Males were more compromised at presentation, with higher numbers having dehydration (89 % of males vs 43% of females,  $p = 0.016$ ) and vomiting (89% of males vs 27% of females,  $p = 0.001$ ). Two (22%) males and 4 (13%) females presented in a hypotensive/ collapsed state. Mean serum Na at presentation was 120 mmol/l in males and 125 mmol/l in females.

**Conclusions:** Majority of children with CAH had evidence of salt wasting at presentation, with male children being more compromised. The discrepancy in distribution among the two genders suggests that male children with CAH may have succumbed to the illness at a young age, without proper diagnosis. Addition of CAH screening to the newborn screening program in Sri Lanka may help to detect those affected earlier, before salt wasting crisis occurs.

**Objectives:** Pharmacologic doses of glucocorticoids are commonly used for immunosuppression, leading to higher risk for infections, related in part to lymphopenia. Adult patients with endogenous hypercortisolemia have been reported to have an abnormal cellular immune system and high risk for infections. Similar data have not been described in the pediatric population with endogenous Cushing Syndrome (CS).

**Methods:** We identified 195 pediatric patients (mean age at diagnosis: 12.5 years, range: 2.7-18, 88 males) with endogenous CS due to various causes (Cushing Disease: 152, ACTH-independent CS: 38, Ectopic CS: 5). A group of 66 children (mean age: 12.5 years, range: 2.9-17.9, 29 males) with documented normal cortisol levels was defined as the control group. We collected WBC with differential, urine cortisol, serum cortisol and ACTH levels at the time of diagnosis and at the follow up visits. We noted the presence of infection (including common bacterial, viral, and fungal infections, and opportunistic infections) at the time of their presentation.

**Results:** The lymphocyte count of the patients with CS was significantly lower than that of controls ( $2.2 \pm 0.8$  vs  $2.6 \pm 0.8$  K/mcL,  $P=0.002$ ). In addition, the lymphocyte count was negatively associated with the parameters of Cushing's severity, including serum morning and midnight cortisol, morning ACTH (for the patients with Cushing Disease) and urinary free cortisol levels ( $P<0.01$ ). For the patients who were followed after cure ( $n=126$ ), the lymphocyte count improved significantly after resolution of hypercortisolemia from  $2.1 \pm 0.8$  to  $2.9 \pm 1.0$  K/mcL ( $P<0.001$ ). The percentage of patients who were lymphopenic decreased from 7% at diagnosis to 2.4% after cure (Table 1). Infections were identified in 34 patients (17.5%) at the time of diagnosis. The presence of infection correlated with the serum morning cortisol ( $P=0.005$ ), midnight cortisol ( $P=0.003$ ) and urinary free cortisol ( $P=0.006$ ) levels.

**Conclusions:** Children with endogenous CS have significant derangements of their lymphocyte count, which correlates with the severity of their disease and normalizes after the resolution of the hypercortisolemia. This has significant implications for the infection risk and the dysregulation of the immune system in children with iatrogenic CS.

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### LYMPHOPENIA AND INFECTION RISK IN PEDIATRIC CUSHING SYNDROME

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	Lymphocyte count (K/mcl) Mean +/- SD	Lymphopenia N (%)
<b>At diagnosis</b>		
Males <6yo (n=4)	2.9 (+/-0.4)	0 (0)
Males 6-12yo (n=35)	2.1 (+/-0.07)	1 (2.9)
Females 6-12yo (n=44)	2.3 (+/-0.8)	2 (4.5)
Males ≥ 12yo (n=49)	2.2 (+/- 0.8)	6 (12.2)
Females ≥ 12yo (n=62)	2.1 (+/-0.8)	5 (8)
<b>After cure</b>		
Males <6yo (n=2)	5.3 (+/-3)	0 (0)
Males 6-12yo (n=22)	2.8 (+/-1.3)	0 (0)
Females 6-12yo (n=32)	3.1 (+/-0.8)	0 (0)
Males ≥ 12yo (n=34)	5.6 (+/-0.9)	1 (2.9)
Females ≥ 12yo (n=36)	2.8 (+/-0.8)	2 (5.6)

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# SPECTRUM OF CONGENITAL ADRENAL HYPERPLASIA AT THE NORTH PEDIATRIC REFERRAL CENTRE OF VIETNAM

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**Objectives:** Our aim is to analyze spectrum of all congenital adrenal hyperplasia (CAH) patients from 1999-2016 at the National Children's Hospital (NCH), Hanoi, Vietnam - an 1200 bed tertiary referral centre servicing approximately 30 million people from northern provinces of Vietnam.

**Methods:** This is cases series study including clinical and biochemical characteristic analysis. Phenotype classification using criteria of Pang S. 1993 for cases with 21-hydroxylase deficiency (21-OHD). Virilisation severity was evaluated using Prader grading, puberty stages were evaluated using Tanner criteria. Bone age was obtained for children > 3 years and compared with Atlat of Greulich and Pyle. Serum electrolyte using automated Beckman Coulter AU2700/AU 680 system, serum 17-OHP levels before and after stimulation by ACTH were measured by ELISA using DRG kits, and Elx808 reader system. Urinary steroid profile was analysed by GC/MS. Rare forms of CAH were confirmed by mutation analysis.

**Results:** At the start of 1999 there were 90 children with CAH managed at NCH. By Dec 2016 this increased to 848 including 441 (52%) male patients and 407 (48%) female patients. Age at diagnosis was 3 hours to 31 years. Number of cases with 21-OHD, 11β-hydroxylase deficiency and 3β-hydroxysteroid dehydrogenase deficiency was 833 (98.2%); 12 (1.4%) and 3 (0.4%), respectively. 829 of 833 patients with 21-OHD were classical phenotype and 4 of 833 cases were non classical phenotype. Among cases with 21-OHD classical phenotype, 74% were salt wasting and 26% were simple virilisation. Total number of cases representing a more than nine fold increase over 16 years. Most children (85%) were diagnosed at less than 12 months of age (55% at less than 1 month of age); 74% of all children were younger than 10 years. Formal mortality figures were low (11 known deaths).

**Conclusions:** The caseload of CAH at NCH has increased since 1999 and additional capacity is needed for patients care.

Newborn screening would enable more accurate estimation of CAH incidence, reduce infant mortality and minimize trauma to affected infants and their families.

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# BILATERAL ADRENAL CALCIFICATIONS IN WOLMAN DISEASE

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## Background:

Wolman disease (WD) is a severe rare inherited disorder due to mutation in Lysosomal Acid Lipase gene, localized to 10q24-q25. To our knowledge, approximately only 50 patients were reported worldwide. We present a 2-month-old child with the disease and extensive adrenal calcifications.

**Methods: Case Report** A 2 months old girl who is an outcome of full-term uneventful pregnancy and delivery, presented with recurrent vomiting, jaundice and anemia. Examination showed distended tense abdomen, marked hepatosplenomegaly and ascites. Abdominal girth was 43 cm. She had a sister previously diagnosed as Hemophagocytic Lymphohistiocytosis (HLH) who died at 3 months of age. A provisional diagnosis of HLH was suggested and the patient treated accordingly for 2 days. Investigations showed pancytopenia, high ferritin, hyperbilirubinemia, elevated liver enzymes, and high triglycerides. The ascites compressed her lungs and therefore we obtained a chest X-ray showing striking yet classic bilateral adrenal calcifications. Based on clinical and radiological presentations, we considered WD as a working diagnosis. We, therefore, started Sebelipase alpha (Recombinant form of LAL). However, a confirmatory genetic diagnosis is still awaited.

**Results: Discussion** In WD, lipids accumulate in different tissues such as liver, spleen and adrenal glands. WD and HLH may share common features of deranged lipid profile and abnormal LFT. However, the classic bilateral adrenal calcification with clear demarcation of the glands is unique for WD. The underlying mechanism of adrenal calcification is not understood.

Since the patient may rapidly develop multi-organ failure, and/or may require invasive procedures such as liver biopsy, the adrenal reserve needs to be verified and a replacement started accordingly. In addition, stress doses may need to be considered during the critical course of the illness. An early use of the recently became available Enzyme replacement therapy (ERT) should be prioritized.

**Conclusions:** WD is very rare and may mimic the presentation of HLH. However, the combination of impaired liver function, hyperlipidemia, pancytopenia and classic adrenal calcifications may favor the diagnosis of WD and support an early start of ERT.



# **FAMILIAL GLUCOCORTICOID DEFICIENCY TYPE 2: A NEW MUTATION IN THE MRAP GENE P. K30DEL**

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**Objectives:** Familial glucocorticoid deficiency is an autosomal recessive disorder characterized by isolated glucocorticoid deficiency. Type 1 due to MC2R gene mutation and type 2 due to MRAP gene mutation.

## **Methods:** Case 1

The fifteen years old male who was admitted due to short stature have a history of term, 2000 gr, twin spouse and renal transplantation 1 month ago due to Chronic Renal Failure. Her parents were first degree cousin and a 21-day sister death before him. In physical examination bone age was 11 years, weight of him was 32,5 kg (<3p), his height was 139,1 cm (<3p), Boy SDS: -3,7sd, testis volume 10 ml. in his growth hormone stimulation tests peak response was 7.2 so growth hormone therapy initiated. Primary adrenal insufficiency was diagnosed when ACTH :1250 pg / ml and cortisol : 2.78 µg / dl due to the darkening of the skin pigmentation during the first year of treatment with growth hormone and prednisolone 5 mg / day. The tests for etiology were normal. Despite hydrocortisone treatment at 15 mg / m<sup>2</sup> / day, ACTH was 5560 pg / mL and cortisol was 2.34 µg / dL in the second month.

## **Case 2 :**

At the age of 5 years, TSH elevation was detected in the external center and the patient's medical history was inapplicable. Mother and father were first-degree cousins in the family history. Physical examination weight: 15,8 kg (10-25p), height: 104,9 cm (10-25p), bone age was 4 years and 6 months, testis volume 2 ml, penis size 8 cm. On follow-up, skin thickening was observed in ACTH: 1294 pg / ml, cortisol: 6, 1 µg / dl. The family story was re-questioned and the patient learned that the first case was uncle of him.

**Results:** In a genetic analysis of cases with familial glucocorticoid deficiency, a new mutation in the MRAP1 gene, p.K30del mutation, was detected.

**Conclusions:** MRAP (MC2 receptor accessory protein) is associated with its travel to the plasma membrane of the MC2 receptor. MC2 receptor function is impaired in MRAP gene mutations. Previously, MRAP mutations have been reported to account for 20% of all familial glucocorticoid deficiency cases. It is shared because of a new mutation identified in the MRAP gene.

# **SHORT STATURE AND HYPERGONADISM WITH RESOLUTION OF HYPERCORTISONISM AND HYPERTHYROIDISM IN SEVERE MCCUNE ALBRIGHT SYNDROME**

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**Objectives:** To demonstrate a case of severe McCune Albright syndrome with remission of hypercortisonism and hyperthyroidism while growth failure, hypergonadism, polyostosis fibrous dysplasia and pauciductal cholestasis remain at 9 y of age.

## **Methods:** Case report

**Results:** An African American male was diagnosed with McCune Albright syndrome at age 2 mo due to R201H mutation of GnAs1. He had multiple large cafe-au-laid spots, growth failure, hyperthyroidism, hypercortisonism, hypergonadism, polyostotic fibrous dysplasia, severe pauciductal cholestasis, nephrocalcinosis, hypertension, developmental delay, and bilateral hip rotations.

His initial serum cortisol was 38 mcg/dl and post-dexamethason cortisol was 28.4 mcg/dl. He was treated with metyrapone since at age 3 mo, peak dose 450 mg/m<sup>2</sup>/day during the first 4 y, but not increase thereafter. The dose was 57 mg, t.i.d at age 9 y. A 24-h urine free cortisol was 30.8 mcg/24h (1-30 for age 5-9 y) after withholding metyrapone for 5 days, and was 11.2 mcg/24 h after withholding for 10 days.

At age 1.7 mo, TSH

At age 5 y, testicles were 2.7x1.3 cm and penile length was 4.3 cm. At age 9 y 2 mo, testis were 3.7 x 1.7 cm. The bone age (BA) was 6 y 6 mo while chronological age (CA) was 3 y 8 mo. BA was 11 y 6 mo when CA was 7 y 8 m. Testosterone was 52 ng/dl (was 41 ng/dl at 2 y of age). GnRH stimulation test was prepubertal. Alpha-FP and hCG were normal. Because of his severe liver disease, ketoconazole was not used.

He has been very short since infancy. Ht Z = -4.2 at 2 y 8 mo. At 8 y 9 mo, ht z = -3.7. Wt 19.1 kg, z = -3.2. His peak GH was 10 ng/ml after stimulation at age 2 y 2mo, and was 30 ng/ml at age 7 y 8 mo.

**Conclusions:** Hypercortisonism and hyperthyroidism in severe McCune Albright syndrome may resolve years later.

Treatment with GnRH analog or aromatase inhibitor or tamoxifen for hypergonadism in this case is debatable due to severe fibrous dysplasia and uncertain effectiveness.

### A CASE OF MIRAGE SYNDROME WITH A NOVEL HETEROZYGOUS MUTATION IN THE SAMD9 GENE

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**Objectives:** MIRAGE (Myelodysplasia, Infection, Restriction of growth, Adrenal hypoplasia, Genital phenotypes, and Enteropathy) syndrome is a new form of syndromic adrenal hypoplasia caused by heterozygous mutations in the SAMD9 gene. This study described a case of MIRAGE syndrome in Korea.

**Methods:** A patient presented with intrauterine growth retardation (IUGR) and adrenal insufficiency was included. He was born at 31st weeks of gestation with a birth weight of 882 g (<3rd percentile). Diagnostic exome sequencing was performed using genomic DNA from peripheral blood leukocytes. Exome was captured using Trusight One Panel (Illumina) and sequenced on the NextSeq platform (Illumina). The mean depth of coverage was 114x and approximately 98% of targeted bases were read more than 10x. Reads were aligned to the hg19 human reference genome.

**Results:** The patient's birth length and head circumference were 35 cm (<3rd percentile) and 24 cm (<3rd percentile), respectively. There was no family history of adrenal insufficiency. He had highly pigmented skin, bilateral cryptorchidism, and a micropenis. At three days of age, acute adrenal insufficiency was evident by hypotension, hyponatremia, hyperkalemia. His plasma ACTH level was 4,670 pg/mL with 217 ng/mL/h of plasma renin activity. An abdominal ultrasonogram did not visualize any adrenal structure, and both testes were found in his abdominal cavity. Replacement of hydrocortisone, fludrocortisone, and sodium were initiated. However, he was died of recurrent infection and septic shock at the age of 4 months. Diagnostic exome sequencing identified a novel heterozygous variant of c.2944C>T (p.R982C) in exon 3 in the SAMD9 gene. This variant was not found in normative databases including 1000genomes browser, NHLBI ESP Exome Variant Server, and genome Aggregation Database, and predicted to be damaging by *in silico* prediction programs including PolyPhen-2, Sorting Intolerant From Tolerant, and MutationTaster. The variant was validated by Sanger sequencing using custom-designed primers.

**Conclusions:** We describe a case of MIRAGE syndrome presented with severe adrenal insufficiency, IUGR) and recurrent infection.

### ALDOSTERONE SYNTHASE DEFICIENCY : A NEW MUTATION

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**Objectives:** Aldosterone synthase deficiency is a rare disease with autosomal recessive inheritance which is confronted with findings of growth retardation, hypotension, hyponatremia, hyperkalemia in infant. The aldosterone synthase is a cytochrome P450 enzyme which located in the inner mitochondrial membrane of cells in zona glomerulosa, and catalyses the last steps of aldosterone synthase pathway (11 beta hydroxylation, 18-hydroxylation, 18-oxidation).

**Methods:** A 1-month-old boy of cousin marriage was examined for failure to thrive and poor weight gain. In physical examination his weight was 4200 gr (90-97p), height was 50 cm (25-50 p), a pulse rate of 100 / min, blood pressure: 90 / pulse, thyroid stage 0, testis volumes 2 ml / 2 ml , no scrotal hyperpigmentation was detected. Laboratory findings were hyponatremia, hyperkalemia, high plasma renin and low aldosterone levels. Serum analysis by Liquid chromatography–mass spectrometry(LC-MS) showed that synthesis of corticosterone, 11 deoxycorticosterone was elevated. The patient was therefore suspected to have aldosterone synthase deficiency.

**Results:** Genetic analysis revealed a c1015- 1029del15bp homozygous mutation in the CYP11B2 gene. Fludrocortisone and oral salt treatment was initiated.

**Conclusions:** Aldosterone synthase deficiency is a rare disease in childhood. A new mutation was detected in our patient so is shared.

### CYP11A1 MUTATIONS RESULT VARIOUS CLINICAL PHENOTYPES

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**Objectives:** Cytochrome P450 side-chain cleavage enzyme (CYP11A1) is the first enzyme and catalyzes the rate-limiting step of steroidogenesis. CYP11A1 deficiency is associated with adrenal insufficiency (AI), and commonly a disorder of sex development (DSD) in 46, XY individuals. Our objectives was to define the clinical presentation of our patients with CYP11A1 mutations, one of whom had a novel CYP11A1 mutation.

**Methods:** Four patients were presented. Case 2 has been reared as a girl and she has a novel *CYP11A1* mutataion. Case 3 and 4 are siblings. Clinical findings are given in Table.

**Results:**

	Case1	Case2
Age at diagnosis, year	1.24	0.08
Karyotype	XX	XY, t(4;9)
Birth weight, gr/gestational weeks	3600/39	1750/33
Parents	1.cousin	1.cousin
Presentation	Adrenal Crisis	Adrenal
Height, cm (SD)	72 (-1.83)	44(-6.05)
Weight, kg (SD)	8000 (-2.65)	1675 (-4.
External genitalia	Labial synechiae	Normal f
Basal cortisol, mcg/dL	<1	8.15
Stimulated cortisol, mcg/dL	<1	8.03
ACTH, pg/mL	259	>1250
Progesterone, ng/mL	1.4	0.03
DHEAS, mcg/dL	4.2	16.41
17-OH Progesterone,ng/mL	0.7	0.56
1.4 Andrestenedion, ng/mL	0.18	1.2
Testosterone, ng/mL	0.3	0.02
Aldosterone, ng/mL	<1	33
Renin, pg/mL; PRA ng/mL/hr	>500	>520
<i>CYP11A1</i> mutation	p.R451W	p.W152X

**Conclusions:** These cases demonstrate That *CYP11A1* deficiency can be seen in newborn period or in early childhood as a classical or nonclassical forms. Normal genital appearance can be found in 46, XY patients in nonclassical form and this does not exclude life-threatening AI risk.

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**HYPERTHYROTROPINEMIA : A PRESENTATION OF SECONDARY ADRENAL INSUFFICIENCY**

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**Objectives:** To present a case of hyperthyrotropinemia in the setting of newly diagnosed secondary adrenal insufficiency (AI) that resolved with glucocorticoid replacement therapy.

**Methods:** Case Report

**Results:** A 10- year and 7- month old Caucasian male presented with a history of TSH elevations, 13.1 and 9.8 (0.32-5mIU/mL), one week apart. There was a longstanding vague history of tiredness unassociated with other symptoms of thyroid dysfunction. Of significance, he had three episodes of culture negative shock each requiring Intensive care management with pressors. At the time of the last episode of septic shock (five years prior); serum cortisol was 27.5 mcg/dL at 4:30 am (hydrocortisone was not administered prior to this lab draw). To evaluate fatigue, testing indicated TSH 11.47 (0.6-4.5mIU/mL), free T4 0.9 (0.7-2.1 mg/dL) with negative anti- thyroid peroxidase and anti- thyroglobulin antibodies. Random cortisol level at 11 am <0.9 mcg/dL and ACTH 16 (0-50 pg/mL), with normal sodium and potassium levels. Peak cortisol level after sequential low (1 mcg) and high (250 mcgs) dose cosyntropin stimulation tests was 1.7

mcg/dL and 2.7 mcg/dL, respectively. 21-hydroxylase antibodies, renin, aldosterone, LH, FSH as well as pituitary dual MRI were all normal. Immunological work up to exclude an immune-deficient state as a contributor to the septic shock episodes was unremarkable. Hydrocortisone therapy was initiated, 10 mg/m<sup>2</sup>/day.Two and four weeks later, the XY, t(4;9)TSH normalized with level of 4.22 and 3.25 respectively. There was marked increase in baseline energy levels, physical activity and exercise tolerance.

**Conclusions:** As in primary AI, hyperthyrotropinemia may exist at presentation in ACTH deficiency. This should be suspected when a history of poor exercise tolerance, cardiovascular instability suggested by episodes of shock, exists. As in primary AI, TSH normalization will occur with glucocorticoid replacement hence, practitioners should delay treating initial hyperthyrotropinemia.

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**UNUSUAL CAUSE OF CUSHING SYNDROME**

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**Objectives:** A primary hepatic tumor / adrenal rest tumor producing hypercortisolism has not been previously reported in the pediatric age group. We report a novel case of paediatric Cushing syndrome due to adrenal rest cells in the liver.

**Methods:** Retrospective case report and review of the literature

**Results:** Cushing syndrome comprises symptoms secondary to high levels of circulating serum cortisol. It is a rare entity in pediatric age group. The most common cause of Cushing syndrome is iatrogenic, secondary to exogenous steroid use. However endogenous Cushing syndrome secondary to adrenal tumours or an ectopic ACTH producing tumour is uncommon. The usual diagnostic features of childhood hypercortisolism include weight gain, growth retardation, fatigue, hypertension, easy bruisability and hirsutism. We report on an extremely interesting case of a 13-year old boy who was first referred for a hepatocellular carcinoma but found to have endogenous Cushing syndrome possibly secondary to an adrenal rest tumour of the liver. We reviewed the literature on hypercortisolism due to ectopic adrenals and adrest rest tumours.

**Conclusions:** This is a novel case which highlights a rare cause of paediatric Cushing syndrome masquerading as a hepatocellular carcinoma.

Medical therapy for Cushing syndrome in the pediatric age group has not been widely used, but it has a role in children with surgically inoperable Cushing syndrome who present with symptoms of hypertension and depression.

**TWO SIBLINGS WITH FAMILIAL GLUCOCORTICOID DEFICIENCY: A CASE SERIES**

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**Objectives:** to describe a case series of two siblings with familial glucocorticoid deficiency (FGD)

**Methods:** case series

**Results:** Case 1: 3-month-old boy presented with septic shock. Exam was remarkable for significant hyperpigmentation. Lab evaluation revealed low cortisol and markedly elevated ACTH however normal serum electrolytes, aldosterone and renin activity. At 15 months of age, the diagnosis of FGD was confirmed by homozygous mutation for a 409C>T change (p Arg137Trp) in MC2R gene. He was treated with hydrocortisone (HC) since initial presentation. He is now 10 and doing well.

Case 2: Patient is case 1's sister and 6 years older. Since birth, increased pigmentation was noted when compared to other members of the family. At one year of age, she was admitted to a hospital (out of country) for pneumonia and shock. She was discharged with prednisone 5mg daily with a diagnosis of "adrenal hypoplasia" (record unavailable). At 2.5 years of age when she was first referred to our endocrine clinic, she had continued to be on prednisone for adrenal insufficiency. She was switched to HC and never required mineralocorticoid replacement as there was no evidence of mineralocorticoid deficiency. The diagnosis of FGD was not uncovered until she was 7 after FGD was confirmed in her baby brother (case 1). Although she did not have genetic testing, we assumed that she has the same mutation as parents are both from a relatively small town with a population of approximately 2000 people. She is now 16 and also doing well.

**Conclusions:** FGD is a rare autosomal recessive disorder characterized by primary hypocortisolism and normal mineralocorticoid production. To date FGD has been associated with mutations in the following genes: MC2R, MRAP, STAR, MCM4, and NNT. This case series serves as a reminder to have a high index of suspicion for FGD as a rare cause of primary AI especially when lack of evidence of mineralocorticoid deficiency. Prompt initiation of steroids along with a thorough diagnostic evaluation is important to avoid unnecessary lifelong mineralocorticoid replacement and recurrent illness secondary to life threatening adrenal insufficiency in patients with FGD.

P1-127

**VIRILIZING ADRENOCORTICAL CARCINOMA IN A TWO YEAR OLD FEMALE**

*Anamaria M Manea, MD; Stephen H Lafranchi, MD, Oregon Health & Science University, Portland, OR, United States*

**Objectives:** We present a case of virilizing adrenocortical carcinoma (ACC) in a 2 year old female. Pediatric ACC is extremely rare and not well characterized. The incidence is

0.2-0.3/million among patients <20 years of age. Virilization is the most common presentation in younger children.

**Methods:** 2 year old female was admitted to pediatric oncology service for an abdominal mass suspicious for Wilms' tumor. Abdominal distension has progressed for the past year, but child was never taken by her parents for an evaluation, until she was placed in foster care. A primary care provider found a diffusely enlarged abdomen, UTI, and an abdominal mass on ultrasound (19.8x14.8x12.2cm). She developed pubic hair and adult body odor at 12 months of age. ROS was positive for profuse sweating, increased thirst, occasional abdominal discomfort. On exam weight is 20 kg (>99<sup>th</sup>%), height is >97<sup>th</sup>%. Blood pressure was elevated (131/90, >99<sup>th</sup>%), and antihypertensives were started after admission. She had Tanner stage 3 pubic hair and stage 1 breasts, clitoromegaly (length 1.5cm, width 0.75cm), hirsutism, no Cushingoid features.

**Results:** Computer tomography showed a dominant heterogeneous encapsulated mass at the left superior kidney pole (15.5x11x16.5cm), 2 possible metastasis. Echocardiography showed left ventricular hypertrophy secondary to HTN. Laboratory results were compatible with a testosterone producing adrenal tumor (see table), and tumor biopsy disclosed the adrenocortical carcinoma. GeneTrails® Solid Tumor Panel showed a mutation of potential clinical significance (KDR p.G873E), not previously described in ACC. Considering the tumor extension surgery was postponed. Combination chemotherapy with Mitotane was started per protocol ARAR0332. Since Mitotane produces adrenal necrosis, hydrocortisone and fludrocortisone were initiated. Child tolerated 3 chemotherapy cycles, the tumor size decreased (13.8x10x14.6cm), biopsy of the presumable pulmonary metastasis were negative. Child is scheduled for surgical tumor excision.

**Conclusions:** As our patient illustrates, pediatric ACC has a female preponderance, commonly presenting <4 years of age, with survival rates 50-80% in this age group. Early diagnosis and treatment of ACC are essential. Complete tumor resection is required for cure.

Laboratory Test	Result	Reference Range
Total Testosterone	178	<=19 ng/dL
Free Testosterone	27.2	0.0 - 0.6 pg/mL
SHBG	41	60 - 190 nmol/L
Androstendione	2510	<=15.9 ng/dL
DHEA	2250	<=67 ng/dL
17-OH-Progesterone	268	<=256 ng/dL
DHEA-S	3064	<57 ug/dL
Cortisol (10 AM)	23.8	-
Aldosterone	3.5	7.0 - 93.0 ng/dL
Plasma Renin	7.8	1.71 - 11.00 ng/mL/hr

**PSEUDOHYPOALDOSTERONISM TYPE 1: A CHALLENGING DIAGNOSIS**

*Dr Shaila Bhattacharyya Shamanur, MD DCH DM, Manipal Hospitals, Bangalore, India; Kirti V Prabhu, DNB Pediatrics, Manipal Hospital , Bangalore, Bangalore, India*

**Objectives:** To understand the presentation of Primary Pseudohypoaldosteronism type 1(PHA1) and differentiate it from Congenital Adrenal Hyperplasia (CAH)

**Methods:** Case Report: 5 day old female baby,first by birth order born of 2<sup>nd</sup> degree consanguineous marriage,brought with not feeding well and lethargy for 1 day.The baby was born full term normal delivery with birth weight of 2.5 kg(5th percentile) and normal APGAR.There were no perinatal problems and family history unremarkable.Baby was exclusively breast feed and had a weight loss of 17% from birth.Pulse was 89/min,respiratory rate 68/min,mean arterial blood pressure 52 mmHg,hypothermia with cold peripheries,prolonged capillary refill with acidotic breathing and distress.Tone was poor,anterior fontanelle sunken and skin turgor decreased.She had normal external female genitalia,no hyperpigmentation,no signs of virilisation.Investigations showed hyponatremia(118),hyperkalemia(8) and metabolic acidosis(pH 7.22,bicarbonate 7).Sepsis work up was normal.BUN(49.50) and creatinine(0.7) were elevated.Metabolic work up and TMS/GCMS was normal.A provisional diagnosis of adrenal insufficiency was considered and relevant hormonal assays were sent which revealed a normal 17-hydroxyprogesterone (1.67ng/ml), thyroid (7.20) and cortisol (1721 nmol/L) level.Renal ultrasonography was normal.Baby was treated with calcium gluconate,soda bicarbonate,glucose insulin infusion,potassium binding resins,3% saline but continued to have recurrent persistent hyperkalemia and hyponatremia,hence suspected to have PHA.Repeat 17-OHP and Cortisol were normal with increased Aldosterone levels(1544pg/ml) favouring PHA.Treatment was continued with high oral sodium supplements,K<sup>+</sup> binding resins and started on oral Fludrocortisone

**Results:** Recurrent hyponatremia and hyperkalemia with metabolic acidosis with normal 17-OHP & Cortisol and elevated Aldosterone suggest PHA. The genetic testing revealed a homozygous insertion of 2 nucleotides at 744 and 745 positions(c.744\_745insTG;p. Arg249\*) in the Exon 3 of the SCNN1A gene which confirmed diagnosis

**Conclusions:** Hyperkalemia, hyponatremia and weight loss should be evaluated for adrenocortical function. It is important to differentiate PHA1 from CAH as the former does not respond to corticosteroids.

PLEASE SEE TABLE IN NEXT COLUMN

The initial laboratory investigations were as follows:

	Patient's value	Normal range
Hb	18.9 g/dl	11.1 – 14.1
TLC	17500 /cu.mm	5000 -15000
N	76%	
L	14%	
Platelet	80,000	
Blood culture	Sterile	70 – 150
CRP	WNL	0-10mg/dL
pH	7.22	7.380 – 7.440
Bicarbonate	7.0 mmol/l	21.0 – 31.0
Base deficit	-17.4 mmol/l	-2.4 -2.3
Potassium	8 mmol/l	4.1 – 5.3
Sodium	118 mmol/l	134 – 145
Magnesium	2.0 mg/dl	1.7 - 2.2
RBS	78 mg/dl	
BUN	49.50 mg/dl	4 -12
Creatinine	0.7 mg/dl	0.2 – 0.5
Ammonia	173 mcg/dl	27 – 102
Lactate	20 mg/dl	4.5 – 19.8
17 –OHP	1.67 ng/ml	0.1 - 9.4
Cortisol random	1721 nmol/L	
Cortisol 8 am	189 nmol/L	78 - 639
TSH	7.200 mIU/ml	1.7 – 9.1
TMS	Normal	

P1-129

**ALDOSTERONE SYNTHASE DEFICIENCY IN TWO UNRELATED LEBANESE CHILDREN**

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**Objectives:** To report two unrelated Lebanese children with aldosterone synthase deficiency, one of whom has a novel mutation in *CYP11B2*.

**Methods:** Patient 1 was born to first cousin parents, weighing 3.680 kg and was referred at 9 days weighing 3.230 kg, looking wasted and dehydrated. The external genitalia were normal. Serum sodium was 128 mEq/L and potassium 8.9 mEq/L. Urine sodium was 91 mEq/L. Serum cortisol was 513.9 nmol/L, DHEAS 11.3 µmol/L and testosterone 3.9 nmol/L. 21 hydroxylase deficiency was suspected. Treatment was started with hydrocortisone (20 mg/m<sup>2</sup>.day), fludrocortisone (0.05, then 0.1 mg/day) and NaCl (4 mEq/kg.day). Upon receipt of the normal serum androstenedione (8.1 nmol/L) and 17 OH progesterone (7.2 nmol/L), the diagnosis was revised to primary adrenal insufficiency, until the results of exome sequencing were obtained. Patient 2 is a girl born to unrelated Lebanese parents. She was born at term, weighing

3.100 kg, and had normal female external genitalia. She was initially breast fed, but failed to thrive, prompting a switch to exclusive formula feeding at one month of age. At three months, she was admitted weighing 3.400 kg and looked malnourished and slightly dehydrated. Serum sodium was 122 mEq/L, potassium 6.6 mEq/L. Urine sodium was 36 mEq/L. Serum 17 OH progesterone was 2.2 nmol/L, cortisol 392 nmol/L and renin > 30.000 mU/L. A diagnosis of aldosterone synthase deficiency was made. Under treatment with fludrocortisone 0.05 mg bid, plasma renin normalized.

**Results:** Exome sequencing of patient 1 revealed a novel homozygous mutation in *CYP11B2* (Asn201Asp, Polyphen score 0.589, possibly damaging). The functional effects of this mutation is being tested *in vitro*. This established the diagnosis of aldosterone synthase deficiency and allowed hydrocortisone to be gradually discontinued. At 2 years of age, low dose ACTH stimulation evoked a rise in serum cortisol from 357 to 473 nmol/L. In patient 2, molecular confirmation of the diagnosis is pending.

**Conclusions:** a) Causes other than 21 hydroxylase deficiency should be kept in mind in salt wasting newborns; b) Exome sequencing is a powerful technique for establishing the correct diagnosis in atypical presentations and led to simplifying treatment in patient 1.

P1-130

#### AN AUDIT OF ACUTE ILLNESS AND ITS MANAGEMENT IN CAH: VARIATIONS BETWEEN HOSPITALS

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**Objectives:** This study assessed the incidence of acute adrenal insufficiency (AI), adrenal crisis (AC), and the utilisation of stress management strategies in patients with Congenital adrenal hyperplasia (CAH) who were treated at the three referral paediatric hospitals in NSW, Australia between 2000 and 2015.

**Methods:** The records of all hospital attendances (admission or emergency only) for children with a diagnosis of CAH who had at least one admission to a referral hospital between 2000 and 2015 were audited. All admissions for each patient over the time period of the study were examined for the underlying diagnosis, use of stress dosing (including IM hydrocortisone), precipitating illnesses and outcomes. Chi square tests were used to assess the significance of categorical variables and t tests were used to assess

differences in the distribution of continuous variables between groups.

**Results:** There were 588 records of hospital attendance for children with CAH, with 409 (69.9%) attendances for an acute medical condition or injury. Of these, 344 attendances were for children who were receiving glucocorticoid therapy. The median age was 3.0 (IQR: 1-8) years and 189 (54.9%) were for males. A principal diagnosis of CAH or an AC was identified in 77 attendances (22.4%) and there were 29 ACs recorded (8.4%). Fifty-one (14.8%) of the attendances had a principal diagnosis of gastroenteritis and another 85 (24.7%) had a principal diagnosis of infection. Stress dosing prior to presentation was documented in 207 (60.2%) of the treatment episodes. IM hydrocortisone use was documented in 72 (20.9%). Use of stress dosing (oral or IM) and IM hydrocortisone differed significantly by hospital (both  $p < 0.01$ ). Documented stress dosing ranged from 42.4% to 70.9% and IM hydrocortisone from 8.3% to 24.0% between the hospitals. No in-hospital deaths were recorded.

**Conclusions:** Among CAH patients on replacement therapy with an acute health condition presenting to hospital, a diagnosis of AC was recorded in 8.4%. Stress dosing was documented in 60% of patients overall but this varied significantly by hospital, as did the use of IM hydrocortisone. Variations in the use of stress dosing among patients treated in specialist centres are important and merit further investigation.

P1-131

#### INCIDENCE AND RATE OF ADRENAL INSUFFICIENCY AND STRESS DOSING IN A LARGE COHORT WITH CONGENITAL ADRENAL HYPERPLASIA

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**Objectives:** Patients with congenital adrenal hyperplasia (CAH) are at risk for adrenal crisis which may lead to increased hospitalization rate and excess mortality. As a preventative measure, education regarding stress dosing is routinely enforced at each visit for our CAH patients. In this study, we sought to characterize the rates and causes of stress dosing and related consequences in a cohort of patients with CAH.

**Methods:** Retrospective longitudinal study of a cohort of CAH pediatric patients (followed every 6 months) and adults (followed annually) over 10 years at the National Institutes of Health (NIH) Clinical Center.

**Results:** The cohort consisted of 156 patients, 60% male. Patients were followed for an average of 10 years. Pediatric patients had the highest rate of illness episodes and stress dosing in the 0-4 year old age group as compared to 4-18 year



old age group ( $2.5 \pm 3.0$  vs.  $1.5 \pm 2.3$  illness episodes/year,  $p < 0.0001$ ;  $5.0 \pm 10.2$  vs.  $2.2 \pm 3.8$  stress dose days/year,  $p < 0.0001$ ). Among adults, an increase in stress dosing and illness episodes was seen in patients age 55 or older ( $1.9 \pm 2.3$  vs.  $0.7 \pm 1.7$  illness episodes/year,  $p = 0.01$ ;  $2.6 \pm 3.5$  vs.  $0.7 \pm 1.9$  stress dose days/year,  $p = 0.006$ ). For pediatric patients only, females reported higher rates of illnesses and stress dosing than males ( $1.9 \pm 2.9$  vs.  $1.4 \pm 2$  days/year,  $p < 0.0001$ ). The main factors requiring stress dosing in both adult and pediatric patients were gastro-intestinal, upper respiratory and febrile illnesses. Thirteen patients had documented episodes of hypoglycemia (age range: 1.1 to 5.2 years) including 2 with hypoglycemic seizures, usually precipitated by fever and decreased oral intake. For the pediatric group only, age was negatively correlated with rate of yearly hospitalizations and ER visits ( $p < 0.0001$ ).

**Conclusions:** In this cohort of patients with CAH receiving repeated adrenal insufficiency education, stress dosing was mostly according to our teaching protocol, but hospitalizations and hypoglycemic events still occurred. Special attention should be given to the youngest and eldest age groups in this population, who may be more susceptible to illnesses. Further preventative measures should be undertaken in an attempt to minimize morbidity and mortality in patients with adrenal insufficiency.

P1-132

#### **AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE 1: A CASE REPORT**

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**Objectives:** APS type 1 also known as APCED: Autoimmune Polyendocrinopathy – Candidiasis – Ectodermal dystrophy is an autosomal recessive disorder with mutations in a particular autoimmune regulator gene (AIRE gene) on chromosome 21q22.3 and presents with a classical Whitaker's triad of Chronic mucocutaneous candidiasis, Hypoparathyroidism and Addison's disease.

##### **Methods: Case Report:**

4y8month old, male presented to pediatric casualty with complaints of seizures, fever, neck stiffness. He had a past history of an episode of tetanic spasms 1month prior to this. Se Calcium remained low normal despite Calcium supplements. Work up revealed low se. calcium, ionized Ca, low PTH, high phosphorus and a normal 25(OH) Vitamin D3 level. Diagnosis of Hypoparathyroidism was made. Initially stabilised in hospital with i.v. Ca gluconate, i.v. MgSO4 & Rocaltrol. He was discharged on calcium supplements & Calcitriol and was advised a low phosphorus diet. On follow up he showed normal growth & was maintaining normal values of Calcium, ionic calcium, phosphorus, PTH & Vit d. Dose of rocaltrol & calcium were being titrated. At 7yr of age, on follow up visit, oral candidiasis mostly at angles of mouth and on tongue, dental enamel defects and blackish discolouration of the nails were noticed. Possibility of

Autoimmune polyglandular endocrinopathy type 1 was considered and sample was sent for AIRE gene study.

**Results:** Gene sequencing revealed two heterozygous mutations in the AIRE gene c.1A>G in exon1 and c.274C>T in exon2, confirming the diagnosis of Autoimmune polyendocrinopathy type1. Carrier testing in parents and checking for mutation in sibling was done.

Sibling tested positive for the same mutation. He was a 1y7m old male with past history of repeated episodes of oral candidiasis treated with oral fluconazole. Biochemical parameters were within normal range except for Vit D deficiency (12ng/ml). The child is having no complaints on follow up.

**Conclusions:** Genetic testing forms an integral part of diagnosis and management of APS. Mutation may co-exist in other family members thereby necessitating the screening of family members to enable timely diagnosis. Annual testing recommended to look for evolving Autoimmune endocrine and non-endocrine organ involvement.

P1-133

#### **SEVERE ADRENAL INSUFFICIENCY AND REVERSIBLE DILATED CARDIOMYOPATHY IN A NEWBORN DUE TO STAR PROMOTOR DELETION**

*Anil Piya, MD, Memorial Health University Medical Center/Mercer University School of Medicine, Savannah, GA, United States; Himangshu S Bose, PhD, Mercer University School of Medicine, Savannah, GA, United States*

**Objectives:** The steroid synthesis starts with cholesterol, the only substrate to initiate the synthesis of steroid prednenolone. Cholesterol cannot be transported into the mitochondria by itself. Steroidogenic acute regulatory protein(StAR), which acts at the outer mitochondrial membrane that helps in the transport of cholesterol from the outer to inner mitochondrial membrane. Mutations in the StAR protein result in most fatal form of congenital adrenal hyperplasia called lipoid congenital adrenal hyperplasia(CAH). StAR protein consists of seven exons and distal promotor 35 bp upstream of the start codon. Biochemical analysis in nonsteroidogenic COS-1 cells showed that the first two exons are not essential to initiate pregnenolone synthesis. Our patient presented with ambiguous genitalia, severe adrenal crisis and dilated cardiomyopathy within two weeks after birth. Laboratory analysis revealed diminished steroidogenesis in all the pathways and elevated ACTH level. Echocardiogram revealed dilated cardiomyopathy and 35% ejection fraction.

**Methods:** Sequence analysis of the StAR. Mitochondrial protein import analysis.

**Results:** Sequence analysis of the StAR, including the exon intron boundaries, showed complete deletion of exon 1 as well as more than 50 nucleotides upstream of StAR promotor. Mitochondrial protein import analysis of the mutant StAR protein lacking exon 1 showed the absence of import and no signal sequence cleavage following import.



**Conclusions:** Cardiomyopathy resolved dramatically after glucocorticoid and mineralocorticoid therapy. Thus, cardiomyopathy and impending heart failure can be reversed by early diagnosis and treatment of CAH. Moreover, full-length StAR gene is essential to initiate pregnenolone synthesis in human.

P1-134

**STRESS-INDUCED CUSHING (SIC) SYNDROME: PROPOSAL TO RENAME PSEUDO-CUSHING SYNDROME EXEMPLIFIED BY PRESENTATION OF A PATIENT WITH PEDIATRIC GLYCOGEN STORAGE DISEASE**

Margaret A Stefater, MD/PhD; Nina S Ma, MD; Joseph I Wolfsdorf, MD, Boston Children's Hospital, Boston, MA, United States; Joseph A Majzoub, MD, Harvard Medical School, Boston, MA, United States

**Objectives:** Cushing syndrome (CS) is one of the most challenging endocrine disorders to diagnose, particularly in children, and it is difficult to distinguish classical CS from non-classical cases that share similar clinical manifestations such as growth failure, obesity, and cushingoid features. The presence of increased cortisol secretion without classical causes such as neoplastic pituitary or adrenal disease is typically referred to as pseudo-CS. However, the term pseudo-CS may be misleading as it implies that abnormally high cortisol secretion does not have pathological consequences.

**Methods:** We present an infant with a physical exam and laboratory evaluation consistent with CS.

**Results:** The patient had moon facies, growth failure and obesity (Figure), and laboratory evaluation consistent with CS: an elevated midnight cortisol and lack of suppression to low dose dexamethasone (Table). During the evaluation, he was found to have liver disease and hypoglycemia; genetic testing revealed a diagnosis of glycogen storage disease type IXa. The child's cushingoid appearance, poor linear growth, obesity and dexamethasone suppression test improved (Figure, Table) after instituting treatment to prevent recurrent hypoglycemia.

**Conclusions:** We suspect this child's CS-like presentation was caused by hypothalamic-pituitary-adrenal activation induced by chronic hypoglycemia, and we suggest that excessive cortisol secretion may be a response to physiologic stress such as the recurrent hypoglycemia observed in this child. Further, the elevated cortisol in pseudo-CS may cause poor growth and excessive weight gain. This case highlights that pseudo-CS can have serious adverse effects, and emphasizes that growth in children is a particularly sensitive assay for glucocorticoid exposure. We speculate that other types of chronic stress may also lead to CS-like features, and that relief of the underlying stressor may ameliorate phenotypic symptoms such as poor growth and obesity. Consequently, we propose that pseudo-CS be renamed stress-induced Cushing (SIC) syndrome, to emphasize that elevated cortisol secretion in the diseases associated with SIC can be

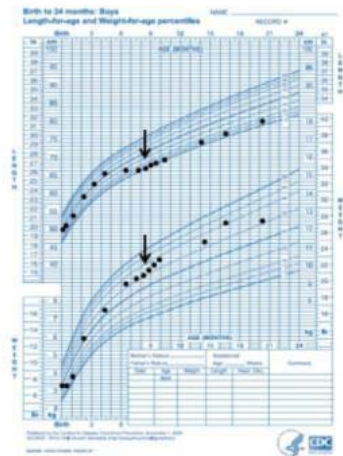
detrimental, and that SIC is a subtype of CS and not a benign entity to be ruled out.

Table. Laboratory Data.

Diurnal assessment of adrenal function			
Measurement	Day 1	Day 2	Normal Range
Morning cortisol	20.4 mcg/dL	18.4 mcg/dL	5-25 mcg/dL
Morning ACTH	7 pg/mL	10 pg/mL	≤46 pg/mL
Morning DHEA-S	2.2 mcg/dL		5-20 mcg/dL
Midnight cortisol	10.4 mcg/dL	7.0 mcg/dL	5-25 mcg/dL
Midnight ACTH	9 pg/mL	6 pg/mL	≤46 pg/mL
Midnight DHEA-S	0.9 mcg/dL		5-20 mcg/dL
Low-dose dexamethasone suppression test			
Measurement	Test 1	Test 2*	Normal Range
Morning cortisol	9.8 mcg/dL	1.8 mcg/dL	5-25 mcg/dL
ACTH		6 mcg/dL	<46 pg/mL
Dexamethasone level		89.3 mcg/dL	NA
DHEA-S	<15 mcg/dL		<15 to 120 mcg/dL
24-hr urine			
Measurement	Collection 1	Collection 2	Normal Range
24-hour UFC	5.7 mcg	3.9 mcg	3-9 mcg
24-hour urine creatinine	76 mg (7.75 mg/kg)	33 mg (3.36 mg/kg)	NA**
Urine volume	475 ml	550 ml	NA

Low-dose (0.015 mg/kg) dexamethasone suppression test 2 performed after euglycemia was achieved. \*Expected urine creatinine excretion per 24 hours in children is ~10 mg/kg/day

Figure. WHO Growth chart. Arrow indicates approximate timing of diagnosis and initiation of dietary therapy.



P1-135

**CHALLENGES IN CHOOSING SOCIAL SEX IN THE LATE DIAGNOSIS OF CONGENITAL ADRENAL HYPERPLASIA**

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**Objectives:** To identify issues related to sexual definition and reassignment in patients with congenital adrenal hyperplasia (CAH).

**Methods:** Retrospective review of medical records.

**Results:** RKMI, 4 years and 8 months, hispanic, from Marília-SP, born with bilateral cryptorchia. The patient had a 5.5 cm falus with no palpable gonads, and was being raised as male since then. Ultrasound of abdomen and inguinal canal did not show presence of gonads, only Mullerian derivatives. Adrenal

glands with no alterations. Baseline total testosterone was 290 ng/dL. *Dehydroepiandrosterone sulfate (DHEA-S)* 2321 ng/ml. *17 $\alpha$ -Hydroxyprogesterone (17 $\alpha$ -OHP)* 393 ng/ml. Plasma renin 1215.5 pg/ml. Karyotype 46, XX. Diagnosis of congenital salt-wasting adrenal hyperplasia after test results was signed. In a meeting with a multiprofessional team and the parents of the child, the team decided jointly by the surgical exeresis of Mullerian remains and maintaining male social sex. Promptly initiated treatment for CAH with glucocorticoids and mineralocorticoids. At age 10 the patient opted for surgical testicular prosthesis bilaterally. Patient develops progressive increase of *gonadotropins* (LH and FSH) when, at age eleven (bone age of thirteen), was chosen to introduce testosterone monthly for the development of secondary male sexual characters with consequent penile enlargement. Patient maintains option in the masculine social sex with the passing of his adolescence, and in the 20 years old was performed another surgery for placement of penial expanders. Currently patient has sexual relations with erections and ejaculations present. He is still satisfied with his sexual performance, but with a final height of 148.5 cm.

**Conclusions:** The precise diagnosis in cases of HAC is important to avoid situations of risk to the patient's life as in cases of salt-losing form, however, the definition of social sex is a fundamental part of the treatment as well, and causes great impact on the family. It is essential to understand that the definition of social sex rests with the multiprofessional team and family, taking into accounts the convictions and interests, cultural and emotional aspects of the family.

**POSTER SESSION 1**  
**Thursday, September 14, 2017, 5:45-6:45pm**  
**P1 - Bone and mineral metabolism**  
**P1-200 – P1-234**

P1-200

**BONE MICROSTRUCTURE DETERMINED BY HIGH-RESOLUTION PERIPHERAL QUANTITATIVE COMPUTED TOMOGRAPHY (HR-PQCT) IN PRE-PUBERTAL GROWTH HORMONE DEFICIENT MALES**  
*Tamar G Baer, MD; Sanchita Agarwal, MS/MA; Fernando Rosete, RT; Sharon E Oberfield, MD; Kyle Nishiyama, PhD; Patricia Vuguin, MD, Columbia University Medical Center, New York, NY, United States*

**Objectives:** Growth Hormone affects bone density, though there are limited studies in prepubertal children assessing the impact of growth hormone deficiency (GHD) on bone microstructure. Our objective is to characterize bone microarchitecture by high resolution peripheral quantitative computed tomography (HR-pQCT), a novel imaging modality, in prepubertal boys with GHD, prior to therapeutic intervention.

**Methods:** To date, scanning by HR-pQCT with isotropic voxel size of 61 $\mu$ m was performed at the distal radius (7%) and tibia

(4.5%) in 15 prepubertal boys, age 5-10 years, n=12 controls (height Z score -0.3 $\pm$ 0.31) and n=3 GHD (height Z score -2.52 $\pm$ 0.59) (Table 1). Volumetric bone mineral density (vBMD), microstructure, and geometry were evaluated (Table 2). Statistical analysis was done using descriptive measures of mean and standard error, and correlation analysis was applied to control data.

**Results:** Correlation analysis in control subjects showed that older age was associated with decreased trabecular vBMD (Tb.vBMD) (p=0.05) and with increased cortical vBMD (Ct.vBMD) (p <0.05). Higher BMI%ile was associated with decreased trabecular inhomogeneity (Tb.1/N.SD) (p<0.01) and decreased trabecular separation (Tb.Sp) (p=0.06). Preliminary results comparing GHD to controls:

**Bone Mineral Density:** At the radius, cortical vBMD (Ct.vBMD) was 9% higher in GHD compared to controls.

**Bone Microstructure:** At the radius, trabecular bone volume fraction (BV/TV) was 16.2% lower while trabecular separation (Tb.Sp) was 11% larger in GHD compared to controls. At the tibia, the cortical bone was 66.6% less porous (Ct.Po) and 15% thinner (Ct.Th) in GHD compared to controls.

**Bone Geometry:** At the radius, total area (Tt. Ar) was 25.5% smaller in GHD compared to controls. At the tibia, total area was 6.9% smaller in GHD compared to controls.

**Conclusions:** The preliminary findings of our ongoing study demonstrate that age and BMI related differences in vBMD and microarchitecture within controls may vary by bone compartments. Differences in vBMD, microarchitecture, and geometry in GHD boys possibly suggest an important role of growth hormone in prepubertal bone health, though significance was not calculated due to disparity in group size at this early point in recruitment.

Table 1: Demographic characteristics of all subjects at study visit (mean  $\pm$  standard error)

	Controls (n=12)	GHD (n=3)
Ethnicity	6 Hispanic, 2 Asian, 1 African, 3 Caucasian	1 African American, 2 Hispanic
Height Z score	-0.3 $\pm$ 0.31	-2.52 $\pm$ 0.59
Height %ile	37.3 $\pm$ 9	2.1 $\pm$ 1.6
BMI	16.9 $\pm$ 0.4	15.4 $\pm$ 0.6
BMI %ile	65 $\pm$ 6	37 $\pm$ 12
Age (yrs)	7.8 $\pm$ 0.3	8.3 $\pm$ 0.8

P1-201

**TRANSDERMAL 17- $\beta$  ESTRADIOL INCREASES BONE DENSITY AT THE LUMBAR SPINE AND FEMORAL NECK IN OLIGO-AMENORRHEIC ATHLETES**  
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Boston, MA, United States; Alexander Toth, BS/BA, Massachusetts General Hospital, Boston, MA, United States; Hang Lee, PhD; Anne Klibanski, MD; Madhusmita Misra, MD, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

**Objectives:** Normal-weight oligo-amenorrheic athletes are at risk for low bone mineral density (BMD) at sites of predominantly trabecular bone. However, data are lacking regarding the impact of estrogen administration on BMD in this population. Our objective was to determine the impact of estrogen administration via a transdermal versus oral route on BMD in normal-weight oligo-amenorrheic athletes engaged in weight-bearing activity of the lower extremities.

**Methods:** 121 oligo-amenorrheic athletes 14-25 years old were randomized to receive either (i) the 100 mcg 17-β estradiol transdermal patch applied continuously with cyclic oral micronized progesterone (200 mg for 12 days of each month) (PATCH group), or (ii) the 30 mcg ethinyl estradiol oral pill with 0.15 mg desogestrel daily with a week of placebo pills every month (PILL group), or (iii) no estrogen/progesterone (NONE). All participants received calcium and vitamin D supplementation. BMD was assessed at the lumbar spine, femoral neck and whole body using dual energy x-ray absorptiometry at baseline, 6 and 12 months. An intention to treat population based analysis set included all randomized study participants in the longitudinal linear mixed effects model to determine whether the transdermal patch performed better than the oral pill or no estrogen in improving BMD. We adjusted for age, height, race and ethnicity in all analyses.

**Results:** The randomization groups did not differ significantly for age, BMI or BMD Z-scores at baseline. Mean age was 19.9±2.6 years, and BMI 20.7±2.3 kg/m<sup>2</sup>. Compared with the other two groups by means of linear contrasts of the time x treatment interaction, the PATCH group demonstrated significant increases over the study duration in lumbar spine and femoral neck mean BMD Z-scores compared to the PILL (p=0.0161 and p=0.0287 respectively) and NONE (p=0.0139 and p=0.0244 respectively) groups after controlling for covariates. Groups did not differ for changes in total hip and whole body BMD Z-scores over the study duration.

**Conclusions:** These data demonstrate the efficacy of transdermal 17-β estradiol in increasing BMD measures at predominantly trabecular sites in adolescent and young adult oligo-amenorrheic athletes.

P1-202

**LOW BONE MASS GAIN FROM ADOLESCENCE TO EMERGING ADULTHOOD IS ASSOCIATED WITH OBESITY, INSULIN RESISTANCE AND CARDIOMETABOLIC PROFILE AT AGE 16**  
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**Objectives:** Despite that obesity has been associated with lower fracture risk, evidence show that peripheral fat may also have a deleterious effect on bone mass (BM). Increased peripheral and bone marrow fat and insulin resistance (IR) alter osteoblast differentiation and function and increase osteoclastic activity. We studied BM gain from adolescence to emerging adulthood and its association with anthropometric and cardiometabolic (CM) profile at 16y.

**Methods:** Observational, prospective study in n=325 22 year-olds (51% males) from an infancy cohort. BMI, waist circumference (WC), arterial blood pressure (BP), bone mineral density (BMD=gr/m<sup>2</sup>) by DXA, triglycerides (TG), HDL, glucose, and insulin were measured at 16y and 22y. BMIz, HOMA-IR, SPISE Index (SI=600 × HDL<sup>0.185</sup>/(TG<sup>0.2</sup> × BMI<sup>1.338</sup>)) and TG/HDL were estimated. HOMA-IR values ≥2.6 were considered IR. BM gain was estimated as the percentage difference between BMD at 22y and 16y. To assess quality of gain, BM gain distribution was divided into tertiles: low (? ≤3.4%), intermediate (? 3.5%-9.1%) and high (? ≥9.2%). Regression models examined the associations of anthropometric and CM biomarkers in adolescence with the risk for low BM gain controlling for sex, physical activity, diet and obesity at 5y and 10y.

**Results:** There was a significant association (P<0.01) of BM gain with anthropometric and CM biomarkers at 16y. Participants with low BM gain had significantly higher values of BMIz, WC, TG, insulin and HOMA-IR and lower valued of SPISE compared to participants in the middle and highest BM gain tertile. Participants with low BM gain showed a significantly higher prevalence of obesity (21.4%) abdominal obesity (49.1%) and IR (22.5%) compared to participants with highest BM gain (8.3%, 23.2% and 9.3% respectively). As BMIz, WC, BP, TG, TG/HDL, insulin and HOMA increased, the odds of having BM gain in the lowest tertile increased. Conversely, as SPISE increased, the risk of low BM gain decreased.

**Conclusions:** BM gain from adolescence to early adulthood was associated with better 16y nutritional status, insulin sensitivity and CM profile. Increased BMIz, WC, BP, TG, insulin and HOMA and lower SPISE were associated with lower BM gain. **Funding:** NHLBI-HL088530, CONICYT-PAI7914003.

TABLE 1 Anthropometric and cardiometabolic profile in adolescence by categories of bone mass gain.

	Low BM gain Tertile (≤3.4%) (1)		Middle BM gain tertile (3.5-9.1%) (2)		High BM gain tertile (≥9.2%) (3)	
	Mean	SD	Mean	SD	Mean	SD
Age (y)	16.8	0.3	16.8	0.3	16.8	0.3
BMI	0.89 <sup>***</sup>	1.2	0.47	1.1	0.33	1.1
Waist circumference (cm)	84.0 <sup>***</sup>	13.7	79.7	9.9	78.8	9.5
Systolic BP (mm Hg)	111.7	11.8	110.7	10.7	112.6	9.2
Diastolic BP (mm Hg)	69.2	7.7	69.1	7.1	69.6	6.7
Glycaemia (mg/dl)	86.0	10.6	88.3	9.2	88.6	8.5
Insulin (μU/dl)	9.4 <sup>**</sup>	7.4	7.8	5.6	7.0	3.7
HOMA-IR	2.1 <sup>*</sup>	1.8	1.7	1.3	1.5	0.8
SPISE Index	7.0 <sup>***</sup>	2.1	7.8	2.1	8.0	1.9
Triglycerides (mg/dl)	95.8 <sup>*</sup>	64.6	82.2	42.2	79.9	38.5
HDL (mg/dl)	37.6	10.6	37.8	10.3	37.3	9.4

Statistical significance (ANOVA with Bonferroni adjustment): \*P<0.05, \*\*P<0.01, \*\*\*P<0.001

# NATIONAL VITAMIN D INTOXICATION OUTBREAK AMONG INFANTS DUE TO A MANUFACTURING ERROR OF VITAMIN D3 DROPLETS: CHALLENGES FOR MANAGEMENT

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**Objectives:** Danish Health Authorities (DHA) recommends vitamin D supplementation for children <2y with 10 µg (400 IU)/day. This dose is considered safe and less than recommended in a recent global guideline, why vitamin D intoxication should not be expected.

**Methods:** Patient evaluation, national warnings, national surveys.

**Results:** An infant presented with hypercalcemia and unmeasurable high s-25OHD levels despite vitamin D3 supplementation strictly as recommended. Suspicion was raised on the vitamin D3 droplet product used. Laboratory analysis showed that the specific vitamin D3 product contained 150 µg/droplet instead of the intended 2 µg/droplet. Infants dosed as recommended therefore received 750 µg (30,000 IU) daily. The product was immediately withdrawn after actions from The Danish Poison Information Center and Danish Health Authorities (DHA). A total of 340 bottles were already sold from March 2016. Nine days after withdrawal of the product the DHA had identified 150 children <2 years at risk of intoxication. Of those, 87 children had already been diagnosed with s-25OHD >150 nmol/L. Serum ionized calcium >1.35 mmol/L was detected in 76 infants, and 18 infants had severe hypercalcemia with ionized calcium of >1.49 mmol/L. A few patients had severe symptoms and extremely high concentrations of s-25OHD and calcitriol. We developed an urgent national tracing, diagnosis and treatment algorithm for vitamin D intoxication. Warnings and public emergency announcements were issued from the DHA and a strategy for keeping the media attention to the matter was made to ensure identification and management of all exposed infants. Treatment of this exceptional vitamin D intoxication outbreak included the - in infants - unprecedented use of calcitonin in the acute phase and repeat biphosponate infusion over months on top of standard treatment. Despite, severe nephrocalcinosis was seen.

**Conclusions:** Delay in clinical diagnosis and errors in distribution of important information regarding triage and treatment were numerous. The outbreak gave occasion to an acutely made national management guideline on vitamin D3

intoxication in infants. The intoxication outbreak illustrates the legislation challenges by categorization of potentially toxic substances as food supplements instead of registered pharmaceuticals.

# BONE DENSITOMETRIC PARAMETERS AND BODY COMPOSITION IN PRETERM AND TERM INFANTS AT FORTY WEEKS OF GESTATIONAL AGE

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**Objectives:** Limited data are available on body composition of preterm and term infants. The aim of this study was to assess bone, fat (FM) and free fat (FFM) mass in preterm and term infants at 40<sup>th</sup> wks of gestational age (GA).

**Methods:** We analyzed 62 infants, n=54 preterm (23 M, 31F) born at the mean GA of 31.0±2.5 wks and n=8 born at term (4M, 4F) at a mean GA of 39.7±1.0 wks. A dual energy x-ray absorptiometry (DXA, LUNAR Prodigy, Infant software) was obtained at the mean GA of 40.9 ± 1.7 in both groups for bone mineral content (BMC, g), mineral density (BMD, gr/cm<sup>2</sup>), FM (gr,%) and FFM (gr). We considered the total body less head (TBLH) for body composition and the trunk (based on a designed ROI) for spine data.

**Results:** Preterm were significantly lighter (1545.7±484.4 vs. 3465±260.1 gr, p<0.0001) and shorter than born at term infants (41.4±5.1 vs 50.7±1.7 cm, p<0.0001) at the time of birth, but comparable for weight and length at 40.9 weeks of GA; they displayed more FM (20.5±5.1% vs. 16.7±6.3%, p 0.04) and similar FFM than those born at term. A significantly lower BMD(0.196±0.043 vs. 0.275±0.011 gr/cm<sup>2</sup>, p<0.0001), BMC(25.0±5.7 vs. 48.2±6.8 gr, p<0.0001) at the TBLH and lower BMD (0.183±0.042 vs. 0.252±0.020, p<0.0001), BMC (13.0±3.7 vs. 26.1±4.4, p<0.0001) at the spine was found in preterm compared to born at term neonates. All bone parameters were related to birth weight (r's range=0.09-0.25, all p's <0.07) and GA (r's range=0.16-0.49, all p's <0.004) in preterm infants. However, multiple regression analysis showed that in preterm infants FFM was a direct predictor (β 4.339e-5, p 0.0035) and %FM an indirect predictor (β -0.002, p 0.0069) of TBLH BMD (adj.R<sup>2</sup> =0.601, p <0.0001), after adjustment for GA and birth weight; also after correction for length (β 0.008, p 0.0075), the model confirmed %FM as a strong indirect predictor (β -0.003, p 0.0002) of TBLH BMD (p<0.0001, adj. R<sup>2</sup> 0,649).

**Conclusions:** Our data demonstrate that preterm infants exhibit early recovery in weight and length, but deficient in bone mass compared to full-term infants; already at the corrected term age FFM seems to be more important than

birth weight or prematurity for bone mass development, while fat mass might have a negative impact.

P1-205

**TRABECULAR BONE SCORE (TBS) OF CHILDREN AND ADOLESCENTS 4 TO 19 YEARS OLD IN MEXICO CITY**

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**Objectives:** Trabecular Bone Score (TBS) is a texture-based tool analyzing DXA images in order to assess bone microarchitecture in the lumbar region. In pediatric population, definition of normative values has remained elusive due to the disparities of results in normal population, probably linked to uncontrolled factors which impact bone microarchitecture and the nonlinear behavior of bone growth.

Our objective was to evaluate TBS in healthy Mexican children and adolescents using chronological age or bone age (BA) taking into account skeletal maturation and puberty onset as confounding variables.

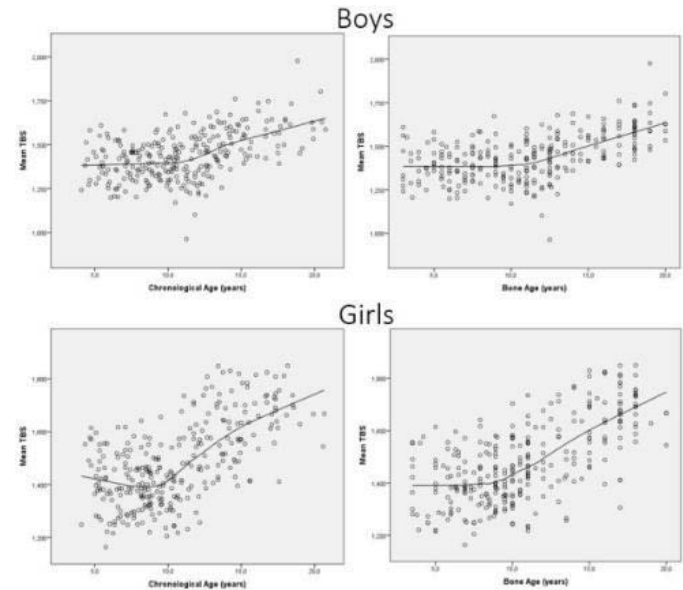
**Methods:** DXA acquisitions from 269 boys and 296 girls aged 5 to 20 years were included. Bone age was evaluated according to Greulich and Pyle method. Pseudo volumetric BMD (3D BMD) was calculated based on cylindrical model proposed by Kroeger et al. (Bone Mineral, 1992). TBS assessment was evaluated using a custom version of TBS (Med-Imaps SASU, France) that includes a soft tissue correction for pediatric subjects.

Loess method for local regression was used to show the means of the population on different ages using SPSS v23. The LMS statistical method proposed by Cole and Green (Stat Med, 1992) was used to construct aBMD, vBMD and TBS age-related curves using LMSchartmaker 2.0.

**Results:** When chronological age was used, girls' curve showed decreasing phase delineating a "U" shape similar to previous reports. However, when evaluated with bone age, both graphs show constant TBS until 9 years in girls and 12 years in boys, both in accordance to the age of puberty, the onset of which is different between genres, a well-known phenomenon.

**Conclusions:** Bone age, better related to puberty onset than chronological age, may be more useful to interpret TBS and may allow to have normative data for children. This preliminary data need to be reproduced by other groups in healthy children and adolescents as well as in groups with different pathologies affecting this population.

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P1-206

**PRIMARY OVARIAN INSUFFICIENCY IN ADOLESCENTS AND YOUNG ADULTS**

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**Objectives:** Primary ovarian insufficiency (POI) affects up to 1/1000 women under age 30, and in most cases, the cause is idiopathic (or unexplained). We sought to identify clinical features of POI in adolescents and young women and gather information on the initial presentation, evaluation, and treatment plan.

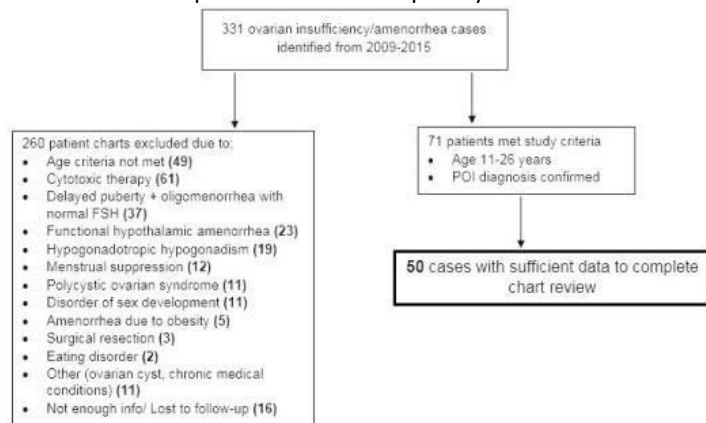
**Methods:** IRB-approved retrospective chart review of female patients ages 11-26 with initial presentation of POI at pediatric tertiary care center, 1/1/2009 to 12/31/15. Patients were included if they had confirmed diagnosis of POI that was not secondary to cytotoxic agents. Patients either met strict criteria for POI (two serum FSH >40 IU/mL), modified criteria (one FSH >40), or had outside diagnosis. Data collected included referral reason, symptoms, laboratory & imaging results, bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA), receipt of estrogen therapy, and data from follow-up visits. Descriptive statistics were generated.

**Results:** 331 charts were reviewed, 71 had confirmed diagnosis of POI, and 50 had sufficient data for inclusion (Figure 1). Among the 50, 21 (42%) had Turner syndrome, 18 (36%) remained idiopathic, and 11 (22%) had another condition (e.g., autoimmune polyglandular syndrome, galactosemia, chromosomal disorder). During evaluation, 36 patients (72%) were karyotyped; in 14 (28%), 21-hydroxylase antibodies were measured; 32 (64%) underwent DXA of lumbar spine (LS). On initial LS DXA, 10 of 32 (31%) had low BMD (Z-score ≤ -2.0) and 9 of 32 (28%) had slightly low BMD (-1.0 to -1.9). All 19 patients with borderline/low BMD started estrogen within 2 years of presentation, with 17 of 19 started within 6 months. 8 of 50 patients (16%) had history of fracture. Of these, at presentation, 4 (50%) had low BMD, and



2 (25%) were slightly low. In follow-up, only 2 patients (4%) saw a psychologist or social worker for emotional support.

**Conclusions:** POI is a model of pure hypogonadism and estrogen deficiency with many cases due to idiopathic causes. On initial presentation, many young patients have a low BMD and few are seen for psychological counseling and support. Due to the infertility aspect, the diagnosis causes emotional distress. Management of psychological well-being should be included as a component of multidisciplinary care.



P1-207

## CALCIUM-PHOSPHORUS METABOLISM AND BONE MINERAL DENSITY OF PEDIATRIC CELIAC DISEASE.

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**Objectives:** To analyze bone mineral density (BMD) and calcium-phosphorus metabolism of pediatric celiac disease patients at the moment of diagnosis.

**Methods:** A cross-sectional study was performed in the Pediatric Nutrition Unit of a tertiary hospital. We reviewed data regarding presenting symptoms, age of diagnosis and anthropometric measures.

Bone alkaline phosphatase, N-terminal Propeptide Type I (PINP),  $\beta$ -CrossLaps, PTH and 25-hydroxyvitamin D were measured.

BMD of total body, lumbar spine and femur (trochanter and neck) was measured in celiac patient older than 2 years of age, using dual-energy x-ray absorptiometry (DXA). DXA were performed using a total-body scanner (LUNARenCORE®).

**Results:** Seventy five celiac children (49 females) with median age of  $5.5 \pm 3.7$  years (range 0.91-14 years) were studied during the first 3 months after the diagnosis.

Sixty-two children (82.6%) were found to have vitamin D levels  $\leq 30\text{ng/mL}$  and twenty three children (30%) had levels  $\leq 20\text{ng/mL}$ . All patients had normal level of PTH.

A significant negative correlation between PINP levels and total body BMD ( $r = -0.425$ ,  $p 0.03$ ) and trochanter BMD ( $r = -0.368$ ,  $p 0.012$ ) were demonstrated.

DXA measurements were analyzed of 61 children older than 2 years. Seven children (11.5%) had a low BMD for chronological age at the level of lumbar spine (Z-scores  $\leq -2.0$ ).

Patients that presented malabsorption symptoms (diarrhea, growth failure and/or iron deficiency) had significantly lower values of lumbar spine, trochanter and total body BMD than patients who did not have these symptoms ( $p 0.017$ ,  $p 0.015$  and  $p 0.015$ , respectively).

**Conclusions:** A high percentage of celiac patients at the moment of diagnosis have hypovitaminosis D, without hyperparathyroidism.

Low BMD (Z-scores  $\leq -2.0$ ) affects up to 11% of celiac patients older than 2 years old.

Celiac children that present symptoms of malabsorption are more likely to have low lumbar spine, femoral and total body BMD.

Low BMD is associated with a high rate of bone remodeling (high PINP). In adult studies it was shown that these are independent predictors of relative risk of fractures. Therefore, in children, it could be a risk factor of accelerated loss of BMD.

P1-208

## VITAMIN D DEFICIENCY IS PREVALENT IN SHORT STATURE CHILDREN WITH UNDERLYING ILLNESS

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**Background:** Vitamin D (VitD) is essential for calcium phosphate homeostasis and bone health. In recent years, numerous clinical research papers have shown that VitD deficiency is becoming a global issue.

**Objective and hypotheses:** The aim of this study is to realize an adequate screening of VitD deficiency by reviewing cases in detail.

**Methods:** Medical records from 7 children diagnosed with VitD deficiency within one year were reviewed. Serum 25(OH) VitD less than  $20\text{ng/dL}$  ( $50\text{nmol/L}$ ) is considered to be VitD deficient, according to the guideline of the Japanese Society for Pediatric Endocrinology.

**Results:** The mean age of diagnosis was  $18 \pm 4.1$  months (1-31 months). The mean and standard deviation of Ca, iP, ALP and 25(OH)VitD were  $10.3 \pm 0.3\text{mg/dL}$ ,  $5.2 \pm 0.2\text{mg/dL}$ ,  $1334 \pm 242\text{IU/L}$  and  $13.4 \pm 2.3\text{ng/dL}$ , respectively. Six of the patients had growth retardation at diagnosis (height below -2 SD below mean) and had imaging findings of rickets by X-ray. All patients have underlying illness and the detail breakdown is the following: 1, egg allergy; 2, low birth weight infant; 2, systemic bone disease; 1, Bartter syndrome; 1, cutis marmorata telangiectatica congenital.

**Conclusions:** Careful checkup for VitD deficiency is needed for short stature children with any underlying illness, such as low birth weight infant, systemic bone disease, food allergy and so on. However, treatment should be deliberated to avoid overtreatment to avoid overtreatment.

# PUTATIVE EXTRA-GONADAL EFFECTS OF HCG STIMULATION TEST ON CALCIUM HOMEOSTASIS

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**Objectives:** Sex steroids and gonadotropins have been suggested to influence calcium homeostasis. hCG stimulation tests are used in boys and men to evaluate the presence or absence of functional Leydig cells. We aimed to investigate the possible link between calcium homeostasis and reproductive hormones in normal and hemicastrated men undergoing hCG stimulation test.

**Methods:** 300 healthy young men were included and delivered semen samples, and blood samples were drawn. Men with previous testicular cancer (treated with unilateral orchiectomy, n=49) were included. Blood samples were analyzed for 25-hydroxyvitamin D, PTH, albumin, calcium, LH, FSH, SHBG, testosterone and estradiol in sera from the 300 men, and in samples before (t=0) and after (t=72 hrs) an hCG injection (Pregnyl, 5000 IU).

**Results:** Serum calcium (albumin corrected) levels were inversely associated with SHBG ( $\beta$ -10.4 p=0.051) and testosterone/estradiol ( $\beta$ -0.054 p=0.025) levels in normal men. Serum calcium (albumin corrected) levels were inversely associated with circulating inhibin B ( $\beta$ -123 p=0.035), inhibin B/FSH ( $\beta$ -20 p=0.008), and positively associated with free testosterone ( $\beta$ 204 p=0.039), free androgen index ( $\beta$ 33 p=0.0002) and testosterone/LH ( $\beta$ .7 p=0.029) at baseline in the 49 hemicastrated men. Eighteen of forty-nine men experienced an average increase in calcium of 6.5% 72 hours after hCG injection, while 30 men had an average decrease of 7%. Men with a decrease in calcium had higher baseline estradiol (74 pmol/L vs 47 pmol/L p=0.006). Importantly, five men had a dramatic decrease of 17-44% in serum calcium (albumin corrected), they all developed transient hypocalcemia, had a lower increase in total and free testosterone after hCG injection (5.4 nmol/L p=0.053 and 154 pmol/L p=0.055 lower), and their BMI was higher (32.6kg/m<sup>2</sup> [29.1-36.1] vs 25.9 kg/m<sup>2</sup>[24.6-27.2] p=0.0012) compared to men who did not develop hypocalcemia.

**Conclusions:** We show here that sex steroids and calcium homeostasis are associated in young 19 year old men. A subset of patients who developed hCG-induced hypocalcemia were characterized by diminished Leydig cell function and higher BMI. Further studies on the potential acute effects of hCG on calcium metabolism are needed to clarify the possible mechanism of action and reproducibility in a prospective cohort.

# DETECTION OF SOMATIC ACTIVATING GNAS MUTATIONS IN PERIPHERAL BLOOD LEUCOCYTES BY NEXT GENERATION SEQUENCING IN ISOLATED MONOSTOTIC FIBROUS DYSPLASIA AND IN ISOLATED AUTONOMOUS OVARIAN CYST

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**Objectives:** McCune-Albright syndrome (MAS) caused by somatic activating *GNAS* mutations is characterized clinically by the classic triad of fibrous dysplasia, café-au-lait skin spots, and GnRH-independent precocious puberty due to autonomous ovarian cyst (AOC). Monostotic fibrous dysplasia (MFD) and AOC can also occur in isolation. We reported that next generation sequencing (NGS) detected somatic activating *GNAS* mutations sensitively from peripheral blood leucocytes (PBL) samples in MAS (PLoS One 2013; 8: e60525). On the other hand, there are no reports on detection of somatic activating *GNAS* mutations in PBL samples by NGS in isolated MFD or in isolated AOC. In a previous report, somatic activating *GNAS* mutations were found in 21 (52.5%) of 40 bone samples from patients with isolated MFD by direct sequencing (Hum Pathol 2012; 43: 1234) and in 13 (33.3%) of 39 ovarian samples from patients with isolated AOC by nested PCR and restriction enzyme digestion (J Clin Endocrinol Metab 2004; 89: 2107).

The objective of this study was to determine detection probabilities of somatic activating *GNAS* mutations in PBL samples by NGS in patients with isolated MFD and in patients with isolated AOC.

**Methods:** The study included 8 patients with isolated MFD and 8 patients with isolated AOC. We performed both NGS and combinatory method of peptide nucleic acids probe with NGS (PNA-NGS) using PBL samples from all patients.

**Results:** Detection probabilities of somatic activating *GNAS* mutations in patients with isolated MFD were 12.5% by NGS and 62.5% by PNA-NGS (Table.1). Those in patients with isolated AOC were 12.5% by NGS and 62.5% by PNA-NGS. The distribution of NGS measured mutation abundance in isolated MFD and isolated AOC were statistically significantly lower than that in MAS in our previous study (P=0.01, Wilcoxon rank sum test).

**Conclusions:** The combinatory method of PNA-NGS can detect somatic activating *GNAS* mutations sensitively from PBL samples in patients with isolated MFD and in patients with isolated AOC. Our data indicate that ratio of mutant to



wildtype alleles in PBL are lower in isolated MFD and isolated AOC than in MAS.

Table 1. Characteristics of Participants.

Case	Age (years)	Sex	Mutation detection method		
			NGS	PNA-NGS	Mutation abundance
MFD-1	10.8	M	Negative	Negative	<0.03
MFD-2	14 .0	F	Negative	Negative	<0.03
MFD-3	17.2	M	Negative	R201C	<0.03
MFD-4	23.5	F	Negative	R201H	<0.03
MFD-5	32.8	M	Negative	R201H	<0.03
MFD-6	39.5	M	Negative	R201C	<0.03
MFD-7	39.5	F	R201H	R201H	5.20
MFD-8	67.3	F	Negative	Negative	<0.03
AOC-1	0.3	F	Negative	Negative	<0.03
AOC-2	1.0	F	Negative	R201H	<0.03
AOC-3	1.4	F	R201H	R201H	2.71
AOC-4	1.5	F	Negative	R201H	<0.03
AOC-5	3.0	F	Negative	R201C	<0.03
AOC-6	3.3	F	Negative	R201C	<0.03
AOC-7	4.8	F	Negative	Negative	<0.03
AOC-8	5.3	F	Negative	Negative	<0.03

P1-211

TARGETED NEXT GENERATION SEQUENCING IN GENETIC DIAGNOSTICS OF OSTEOGENESIS IMPERFECTA

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**Objectives:** Osteogenesis imperfecta (OI) is a hereditary disease characterized by increased bone fragility and additional non skeletal findings. In most affected individuals OI is caused by dominant mutations in COL1A1 or COL1A2. Recessive forms of OI are caused by mutations in other genes affecting collagen synthesis. Molecular genetic testing can increase the sensitivity of clinical diagnosis. The exact diagnosis is relevant since it might have an impact on the treatment and is also important for family planning and genetic counselling. The aim of our study was to assess the utilisation of targeted next generation sequencing (NGS) for a select group of genes in diagnostic settings for OI.

**Methods:** The study population comprised 15 individuals with OI phenotype (3 males, 12 females) aged between 1 month and 18 years who were evaluated at the tertiary paediatric outpatient clinic. Fourteen patients had clinically mild OI and one patient had clinically severe OI. NGS had been performed as the initial diagnostic methodology in all patients. We performed targeted NGS with TruSightOne Sequencing Panel on the MiSeq platform (Illumina, USA) followed by interpretation of variants in the OI associated genes (ALPL, BMP1, COL1A1, COL1A2, CRTAP, FKBP10, IFITM5, LEPRE1, LRP5, PLOD2, PP1B, SERPINF1, SERPINH1, SP7) and subsequent Sanger sequencing confirmation.

**Results:** We detected ten different mutations in genes COL1A1 and COL1A2 in ten patients (66% success rate). Pathogenic mutation COL1A2, NM\_000089.3:c.1704\_1705insAAA (p.Gly568\_Lys569ins Lys)

found in patient with a severe OI phenotype was not previously reported. Among patients with mild OI two novel pathogenic variants, namely COL1A1, NM\_000088.3:c.1853delC (p.Ala618ValfsTer148) and COL1A1, NM\_000088.3:c.740C>T (p.Pro247Leu) were identified.

**Conclusions:** Presented subject group had mutations in genes commonly associated with OI. However each subject had his own private mutation. NGS enabled fast and precise molecular diagnosis by identifying causal mutations in several genes related to OI simultaneously.

P1-212

A NOVEL MUTATION IN FIBROBLAST GROWTH FACTOR 23 IDENTIFIED IN A PATIENT WITH HYPOPHOSPHATEMIC RICKETS PREVENTS PROTEOLYTIC CLEAVAGE.

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**Objectives:** Background: Fibroblast growth factor 23 (FGF23) plays a key role in regulation of phosphorus metabolism. Biologically active intact FGF23 is cleaved between Arg179 and Ser180, and this processing inactivates its function. The subtilisin-like proprotein convertase (SPC) proteolytic processes recognize Arg176 to Arg179 cleavage site (RXXR motif). Mutations of FGF23 at Arg176 and Arg179, the key residues for the cleavage, have been known to cause autosomal dominant hypophosphatemic rickets (ADHR). However, no mutation other than these residues has been reported.

Case: A 13-year-old boy visited our institution complaining of bilateral knee joint pain. His height was normal and there was no physical finding. Radiography of his bone revealed rickets, and blood examination showed a high level of ALP, low level of phosphorus (1.9 mg/dL), normal levels of calcium, and intact PTH, and undetectable level of FGF23. He also presented iron-deficient anemia.

**Methods:** We performed genetic analysis of FGF23, PHEX, DMP1, and SLC34A3 genes with informed consent and the approval of the Ethics Committee. For revealing the effect of a novel mutation of FGF23, we conducted Western blotting of overexpressed proteins, comparing with wild-type and other mutations located at the cleavage site (R176Q, R179Q) and our case (S180I). FGF23 cDNA expression plasmid were transiently transfected into UMR106 cells and the protein extracts from the extracellular fluid were analyzed by Western blotting using an antibody that recognizes the C-terminal regions of FGF23.

**Results:** The genetic analysis revealed a novel heterozygous missense mutation Ser180Ile in FGF23. No pathogenic mutation in PHEX, DMP1, SLC34A3 was found. Western blot analysis revealed that, whereas wild-type FGF23 protein showed two bands of the full-length protein (32kDa) and the

processed (12kDa), S180I showed only one band of 32kDa, which was the same pattern to the both of R176Q and R179Q.

**Conclusions:** We report a novel *FGF23* mutation, S180I detected in a hypophosphatemic rickets patient with iron-deficient anemia. S180I showed prevention of proteolytic cleavage *in vitro*. This is the first study to demonstrate that the mutation of *FGF23* other than SPC cleavage site leads to protease resistance.

P1-213

#### THE MECHANISM OF CNES UPSTREAM AND DOWNSREAM OF SHOX REGULATING SHOX

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##### Objectives:

To establish U2OS cell line with conserved noncoding DNA elements (CNEs) knocked out is to study the activity of CNE9 and CNE10 of short stature homeobox-containing gene (SHOX) by the functional deletion strategy ; To study the relationship of CNEs of SHOX gene and SHOXpromoter2(SHOXp2),and analyze the regulatory mechanisms of CNES.

##### Methods:

1. We established U2OS cell line with CNE9 and CNE10 knocked out by the usage of CRISPR/Cas9 technique; Sanger sequencing verified positive cell lines; Western-blot tested the protein expression of SHOX gene.
2. To construct the recombinant vector in the PsiCHECK-2 vector with SHOXp2 ; The various CNEs were cloned into the recombinant vector. Recombinant vectors and the control group were transfected into HEK293T cells , the relative activity of fluorescence was measured.

##### Results:

1. Sanger sequencing verified positive cell lines, and U2OS cell line with CNE9 and CNE10 knocked out were acquired.
2. The protein expression decreased and had a significant difference among U2OS cell line with CNE9 and CNE10 knocked out (  $P<0.01$ ).
3. PsiCHECK-2-SHOXp2 vector was successfully constructed, and the recombinant vector containing CNE-5, CNE-3, CNE-2, CNE9, CNE10, CNE11 were constructed respectively.
4. Compared with Rluc/Fluc of the control group, the activity of the recombinant vector containing CNE-3, CNE-2 rose( $P<0.01$ ), and the activity of CNE 9, CNE 10, CNE 11 reduced ( $P<0.01$ ). It had a significant difference between Each of the CNE-3, CNE-2, CNE 9, CNE 10, CNE 11 and the control group. The CNE-5 was no variation( $P>0.05$ ) .

##### Conclusions:

1. We established U2OS cell line with CNE9 and CNE10 knocked out .The expression quantity of SHOX protein of control group is higher than that cell line with CNE9 and CNE10 knocked out. It proved that CNE9,CNE10 strengthened the transcription and translation of SHOX gene, CNE9 and CNE10 had enhanced activity and that provided a

cell model for study of the regulatory mechanism of CNEs and SHOX gene.

2.It was verified that CNE-3, CNE-2 enhancing the activity of SHOXp2 may control the expression of SHOX and CNE9,CNE10 inhibiting the activity SHOXp2 may inhibit the transcription and translation of SHOX gene;In short, CNEs of SHOX gene may regulate the expression of SHOX gene by using a different promoter.

P1-214

#### PARTHYROID ADENOMA IN TURNER SYNDROME: THE IMPORTANCE OF AN EARLY DIAGNOSIS

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**Objectives:** Primary hyperparathyroidism is a rare condition caused by the overactivity of the parathyroid gland, which can lead to severe deleterious effects due to untreated hypercalcemia (muscle weakness, fatigue, volume depletion, neuropsychiatric symptoms, osteopenia, osteitis fibrosa cystica and the formation of renal stones). The most common cause of primary hyperparathyroidism is a single gland adenoma in postmenopausal women.

Turner Syndrome (TS) is a chromosomal abnormality that occurs in 1/2500 live born females and it is associated with multiple comorbidities such as osteoporosis, obesity, hypothyroidism and hypertension. Only a few cases of primary hyperparathyroidism have been described in association with TS, and most of them occurred in adult women

**Methods:** We report a case of primary hyperparathyroidism in a teenager with TS, diagnosed during her routine follow up.

**Results:** A 15-year old girl with TS and chronic lymphocytic thyroiditis was found to have mild hypercalcemia (10.9 mg/dl) and a hypoeogenic nodular thyroid lesion during a routine outpatient review.

Hypercalcemia was confirmed on a repeated blood test (10.1 mg/dl) that also showed elevated levels of parathyroid hormone (PTH; 242pg/ml). There were normal levels of phosphorus, calcitonin, osteocalcin and vitamin D3; kidney function was also normal. Chest and neck technetium-99 scintigraphy showed images suggestive of parathyroid hyperfunctioning tissue in the left lower thyroid lobe. Abdominal ultrasound showed normal urinary tract.

The nodule was surgically excised, with a confirmed intra-surgery PTH decrease (from 255 to 32). Pathology showed a parathyroid adenoma.

After surgery, the patient was discharged with vitamin D treatment. Calcium and PTH levels returned back to normal.

**Conclusions:** Although rare, primary hyperparathyroidism has been described in patients with TS and should be considered and investigated in the presence of hypercalcemia, even when it is mild and the patient is asymptomatic. Our patient is one of the youngest reported with this association and our

case illustrates how a high level of suspicion and consequently an early diagnosis of primary hyperparathyroidism can prevent a severe and irreversible damage due to untreated chronic hypercalcemia.

P1-215

#### **HYPOPHOSPHATASIA: THREE NEW MUTATIONS IN ALPL GENE DESCRIBED IN TWO PATIENTS WITH UNCOMMON CLINICAL MANIFESTATIONS**

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**Objectives:** Hypophosphatasia (HPP) is a rare genetic disease due to inactivating mutations of ALPL gene, which encodes the non-specific tissue alkaline phosphatase enzyme -ALP. We report on three new ALPL gene mutations in two patients who presented unusual clinical manifestations.

**Methods:** The ALPL gene sequencing was performed through PCR amplification and Sanger sequencing. New mutations went through in silico analysis by pathogenicity prediction softwares (PoliPhen; Mutation Taster).

**Results:** Description of cases and comments:

(1) Male, 21 year-old, diagnosis of PPH at 2 years of age, after surgery for correction of craniosynostosis. He presents extremely short stature and obesity, height 130.5 cm / 4ft 3in (Z-score:-6.3 SDS), body mass index (BMI) 34.3 kg/m<sup>2</sup> and waddling gait. At 20 years of age his laboratory evaluation showed: ALP 5 IU/L (reference: 30-120 IU/L), vitamin B6: 170.9 mcg/L (reference: 5.2-34.1 mcg/L). Three ALPL gene mutations were found: exon 11, c.1307A> G (deleterious, maternal inheritance; previously described); exon 3, c.97G> C (deleterious, PoliPhen) and c.112A> C (benign, PoliPhen), being last both of paternal inheritance and not previously described. Unusual manifestations: obesity, hepatic steatosis, autoimmune thyroiditis; asymmetric kidneys, hyperuricemia, hypocitraturia and proteinuria. There was no history of bone fractures. It is questioned whether such findings are part of a not yet known wider HPP spectrum or just coincidental.

(2) Female, 26 year-old, presents Turner syndrome (ST), karyotype 45,X/46Xi(X)(q10). Height 149 cm / 4 ft 11in (Z-score -2.2 SDS), BMI 40 kg/m<sup>2</sup>, hepatic steatosis, severe scoliosis. Despite a history of ALP dosages consistently low for age since adolescence, the suspicion and diagnosis of PPH was only made at 25 years of age: ALP 20 IU/L, vitamin B6 250 mcg/L. It was found a ALPL gene mutation in heterozygosity, exon 11, c.1238T> C, not previously described (pathogenic variant, Mutation Taster). There was no other clinical findings typical of HPP nor history of bone fractures. For this patient, the unusual manifestations were the severe obesity and ST-HPP association.

**Conclusions:** These two cases illustrate the breadth of the

potential clinical and biochemical genotype related-expression in patients with HPP.

P1-216

#### **AUTOSOMAL DOMINANT HYPOCALCEMIA TYPE 1 AND LITERATURE REVIEW**

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**Objectives:** To explore the clinical manifestation of patient with autosomal dominant hypocalcemia type 1 and to sequence the related CaSR gene of the patient.

**Methods:** A children with ADH1 was reported in regard to clinical manifestation, laboratory examination and genetic mutation. Some related literatures were reviewed.

**Results:** The patient was a girl, 1 months 11 days old, and had recurrent seizures for more than three weeks, aggravating for three days. Laboratory work-up revealed hypocalcemia, hypomagnesemia, hyperphosphatemia, suppressed PTH, increased urinary calcium-to-creatinine. The child was clinically highly suspected of ADH1. Targeted sequencing showed a reported mutation in exon 3 of CaSR Gene, c.392G>A, p.cys131Tyr, and both parents did not harbor the child's mutation, indicating that her mutation had arisen de novo.

**Conclusions:** ADH1 is a rare endocrine disease caused by gain-of-function mutations in the CaSR gene, manifests familial or sporadic hypercalciuric hypocalcemia, that should receive more attention to avoid missing diagnosis. One pathogenic mutations (c.392G>A, p.cys131Tyr) in CaSR gene was found.

P1-217

#### **CLINICAL OUTCOMES WITH EARLY INITIATION OF TREATMENT IN A PATIENT WITH INCIDENTALLY DIAGNOSED INFANTILE HYPOPHOSPHATASIA**

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**Objectives:** To describe an unusual presentation of hypophosphatasia and the outcomes of treatment when initiated early in the disease course

**Methods:** Chart review was performed to obtain details related to the clinical case.

**Results:** A 4-week-old, term male was found to have a hip click bilaterally on exam by his primary care provider. Hip films were interpreted as having an abnormal appearance of the proximal femurs concerning for non-accidental trauma. Subsequent skeletal survey revealed cupping and metaphyseal irregularities in the majority of the long bones, in addition to rachitic rosary most consistent with rickets. The patient had normal calcium (9.7 mg/dL), normal parathyroid hormone (25 pg/mL), only mildly elevated phosphorous (5.8 mg/dL), and significantly low alkaline

phosphatase level (33 units/L). Additional testing was consistent with hypophosphatasia, including elevated urine phosphoethanolamine (2228 nmol/mg creatinine, normal 0–372) and elevated vitamin B6 (1030 mcg/L, normal range 5–50).

The patient was started on asfotase alfa 2 mg/kg three times weekly at 7 months of age. After 1 month of therapy, his laboratory findings had normalized. Repeat imaging revealed grossly normal long bone appearance with no evidence of low bone mineralization or metaphyseal flaring or widening. At 11 months of age, four months following initiation of therapy, he continued to have no apparent bony abnormalities or respiratory insufficiency. His only notable clinical symptom was premature loss of two primary teeth.

**Conclusions:** Infantile hypophosphatasia is a rare disorder that is life-threatening and frequently diagnosed late in the clinical course. Without treatment, mortality is greater than 50% by 9 months of age. This case report describes a unique presentation of infantile hypophosphatasia in which the diagnosis was incidentally made following evaluation to rule out congenital hip dysplasia, prior to the development of any clinically evident symptoms. Treatment with enzyme replacement therapy was initiated early, after which significant radiographic and laboratory improvement was demonstrated. Findings from this case emphasize the importance of early diagnosis and argue for timely implementation of enzyme replacement therapy.

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#### **CYP3A4 INDUCTION BY RIFAMPIN: AN ALTERNATIVE PATHWAY FOR VITAMIN D INACTIVATION IN PATIENTS WITH CYP24A1 MUTATIONS**

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**Objectives:** The P450 enzyme CYP24A1 is the principal inactivator of vitamin D metabolites. Biallelic loss-of-function mutations in *CYP24A1* are associated with elevated serum levels of 1,25-dihydroxyvitamin D<sub>3</sub> with consequent hypercalcemia and hypercalciuria, and represent the most common form of idiopathic infantile hypercalcemia (IIH). Current management strategies for this condition include a low calcium diet, reduced dietary vitamin D intake and limited sunlight exposure. CYP3A4 is a P450 enzyme that inactivates many drugs and xenobiotics and may represent an alternative pathway for inactivation of vitamin D metabolites. The aim of this study was to determine if rifampin, a potent inducer of CYP3A4, can normalize mineral metabolism in patients with IIH due to mutations in *CYP24A1*.

**Methods:** We treated two IIH patients with daily rifampin (10 mg/kg/day, up to a maximum of 600 mg). Serum calcium, phosphorus, parathyroid hormone, (PTH), liver and adrenal

function and vitamin D metabolites, as well as urinary calcium excretion, were monitored during treatment for up to 11 months.

**Results:** Prior to treatment, both patients had hypercalcemia (10.5–10.7 mg/dL), hypercalciuria and nephrocalcinosis with elevated serum 1,25-dihydroxyvitamin D<sub>3</sub> (55–99 pg/ml) and suppressed serum PTH (2–3 pg/ml). Daily treatment with rifampin was well tolerated and led to normalization or improvement in all clinical and biochemical parameters. At 10 months, serum calcium was 9.6–19 mg/dL, and serum PTH was 16–31 pg/ml. One patient stopped treatment for 2 months and serum calcium increased to 11.5 mg/dL with suppression of PTH to 3 pg/ml.

**Conclusions:** These observations suggest that rifampin-induced overexpression of CYP3A4 provides an alternative pathway for inactivation of vitamin D metabolites in patients who lack CYP24A1 function.

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#### **TWO NOVEL IN-FRAME DELETIONS OF COMP IN PATIENTS WITH PSEUDOACHONDROPLASIA**

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**Objectives:** Pseudoachondroplasia (PSACH) is a rare autosomal dominant skeletal disease which is exclusively caused by mutations in cartilage oligomeric matrix protein (*COMP*) gene. Mutations in the *COMP* gene are known to cause PSACH and multiple epiphyseal dysplasia (MED). Eighty-five percent of the *COMP* mutations are located in the type 3 thrombospondin (TSP) like repeat region, which is coded by exons 8–14. Approximately 76% of in-frame deletions in the type 3 TSP repeat region are responsible for PSACH, whereas 36% for MED. The genotype-phenotype correlation of *COMP* is still under investigation.

**Methods:** Our study involved two Japanese boys with sporadic PSACH. Case 1 was a 6-year-old boy. He had shown no signs of skeletal disease, until his growth retardation was evident at 2 years of age. He was diagnosed as having PSACH at 4 years, based on short stature (–2.8 SD), waddling gait, and specific radiologic findings including oval shaped platyspondyly, anterior breaking of vertebrae, small and irregular epiphyses, and irregular metaphyses. Case 2 was a 2-year-old boy. His mother noticed gait disturbance since he started walking. Radiologic survey revealed metaphyseal irregularity and epiphyseal hypoplasia of femur and tibia. He was diagnosed as having PSACH, based on short stature (–2.2 SD), waddling gait, and the radiologic findings. We extracted DNA from lymphocytes of both cases and examined all coding exons and flanking regions of introns of *COMP* by PCR-based Sanger sequencing.

**Results:** We identified a 12 base in-frame deletion in the exon 13 (c.1426\_1437del12bp, p.476\_479delGMPD) for Case 1 and a 9 base in-frame deletion in the exon 9 (c.934\_942del9bp, p.312\_314delCDP) for Case 2. The parents of both cases did not consent for familial analyses. Both deletions are located on type 3 TSP repeat region of *COMP* gene and have not been reported previously.

**Conclusions:** We identified two novel in-frame deletions in the type 3 TSP repeat region of *COMP* gene. Our findings support the notion that in-frame deletions of type 3 TSP repeat region preferentially cause PSACH rather than MED.

P1-220

### NOVEL TRPM6 MUTATION IN HSH SYNDROME WITH INFANTILE SEIZURES

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#### Objectives:

- *Hypomagnesemia with Secondary Hypocalcemia (HSH-OMIM\*602014)* is a rare autosomal-recessive disease that appears in early infancy and is characterized by very low serum Magnesium ( $Mg^{2+}$ ) levels. It manifests as generalized convulsions preceded sometimes by other signs of increased neuromuscular excitability like muscle cramps and agitation.
- Mutations in the *TRPM6* gene, encoding the epithelial  $Mg^{2+}$  channel TRPM6 (transient receptor potential melastatin 6), have been proven to be the molecular cause.

#### Methods:

- 5 month old male child was referred for multiple hypocalcemic seizures. First episode was at 20 days of life
  - Investigations-
    - Low serum Calcium-6.5mg/dl (8.5-10.6),
    - Low Ionised Calcium- **1.07**(4.6-5.1),
    - Normal Phosphorus- 6.78mg/dl (4.2-9),
    - Low Vitamin D- 15.28ng/ml (>20ng/ml)
    - Neuroimaging and Newborn Metabolic Screening was normal.
- He was suspected to have Vitamin D resistant rickets and was being treated for the same.
- At the time of presentation, child was receiving oral Calcium/ Phosphorus/ Vitamin D supplements and multiple anti-convulsants.
- Lab Investigations showed –
  - Calcium- 9.9mg/dl,
  - Ionised Calcium ( $Ca^{2+}$ )- **4.74**,
  - Phosphorus- 5.5mg/dl,
  - **Magnesium- 1.0mEq/L (1.8-2.4)**,
  - PTH- 49.5pg/ml (15-65pg/ml)
  - Vitamin D- 55.9ng/ml

- Hypomagnesemia with Secondary Hypocalcemia (HSH) was suspected and genetic testing was done.

#### Results:

- **Targeted sequencing analysis- an unreported homozygous splice site mutation in Intron 30 (Chr9:77365579; C>T) of the TRPM6 gene.**
- As no other oral Magnesium supplements were available in our country, child was started on 50%  $MgSO_4$  (orally) along with Calcium & Phosphorus supplements and doses were gradually adjusted based on serum calcium and magnesium levels.
- Currently child is seizure free and off anti-convulsants.

#### Conclusions:

- As hypomagnesemia can be multifactorial and multigenic, studies of isolated monogenic disorders represent a valuable tool to disclose the role of a single gene for  $Mg^{2+}$  metabolism and will eventually improve current clinical treatments to enhance patient's quality of life.

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### SLC34A1 MUTATION IN 2 CHINESE PATIENTS WITH IDIOPATHIC INFANTILE HYPERCALCEMIA

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**Objectives:** Idiopathic infantile hypercalcemia (IIH) is a rare condition, which is characterized by severe hypercalcemia with failure to thrive, vomiting, dehydration, and nephrocalcinosis. The gene mutation of SLC34A1 can involve IIH, which encoding renal sodium-phosphate cotransporter 2A.

We first reported 2 cases with IIH from 2 non consanguineous families in China due to SLC34A1 mutation. The purpose of this study is to pay enough attention on this disease and to identify at early stage, so as to avoid the occurrence of severe renal damage.

**Methods:** Clinical manifestations and biochemical data of the patients were collected.

Genomic DNA of the probands and their family members was isolated from peripheral blood cells.

The next generation genomic analysis identified with SLC34A3 gene mutation.

**Results:** One boy was 1 month old. He complained of poor feeding, failure to thrive, vomiting with early-onset nephrocalcinosis. The other was a 6 months old girl and complained of failure to thrive, vomiting, dehydration, and nephrocalcinosis. Both patients received vitamin D supplements from birth according to the country's recommendations.

We found they had polyuria after admission. Renal ultrasound demonstrated medullary nephrocalcinosis in both infants. The analysis of laboratory data at the time of initial manifestation revealed hypercalcemia and suppressed intact parathyroid hormone (iPTH) levels. The blood calcium level of the boy was high up to 5.35mmol/l, while of the girl was up to 4.16mmol/l. The iPTH values were low as 0.01pg/ml with

the boy and 1 pg/ml with the girl (normal range 10-69pg/ml). The ratios of calcium to creatinine were up to 2.72 and 2.25 respectively (normal range below to 0.2). The level of phosphorus was low to 0.68 mmol/l and 0.57mmol/l (1.1-1.8). During hypercalcemia, the levels of active 1, 25-(OH)2D3 and 25-(OH) D3 were determined normal.

During acute treatment of hypercalcemia, vitamin D supplements were stopped in both patients. The therapeutic measures included intravenous rehydration and furosemide. A low calcium diet was initiated in boy. Thereafter, serum calcium levels decreased but continuously elevated in the following days. After both patients were proven *SLC34A1* mutations, they were treated with oral phosphate supplementation. Both patients were normocalcemic and free of clinical symptoms in 3 days and, while hypophosphatemia were corrected. The ratios of calcium to creatinine both decreased to 0.25.

The boy carried with heterozygous *SLC34A1* mutation of c.1697\_c.1698(exon13), ins T , p.P566Pfs\*39. The girl carried with heterozygous *SLC34A1* mutation of c.1322A>G, p.Y441C.

**Conclusions:** The patient with Idiopathic infantile hypercalcemia had severe renal calcification that may eventually lead to severe damage kidney function. The clinical and laboratory findings persist despite cessation of vitamin D prophylaxis, but rapidly respond to phosphate supplementation. Therefore, early identification of *SLC34A1* defects appears critical for targeted therapy in patients with IIH.

P1-222

#### ALTERNATIVE TREATMENT OF MULTIPLE GIANT CELL LESIONS (MGCL) IN TWO BOYS WITH NOONAN SYNDROME (NS)

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**Objectives:** To report the alternative treatment of two cases of NS caused by mutation in the *PTPN11* and *SOS1* genes.

**Methods:** A 9.3-year-old and 5.7-year-old boys with Noonan syndrome were referred to dentistry center for evaluation of a mandibular swelling causing facial asymmetry. The lesion was first noted about ten months before the first evaluation. The first boy was previously diagnosed with NS and identified mutation in *SOS1* gene (p.M269R), dysmorphic face, pulmonary valve stenosis, and learning disabilities. The second one was a patient with NS and mutation in *PTPN11* (p.Q510P), dysmorphic face, learning disabilities and no heart defects.

**Results:** Clinical examination revealed moderate facial asymmetry, secondary to an expansive mandibular growth, covered by intact mucosa. Both patients showed normal bone metabolism profile, except for the low level of vitamin D in the first patient. Panoramic radiography disclosed bilateral cystic lesions in the maxilla and mandible. Tomography showed large multilocular lesions bilaterally in the mandible

and the paranasal region causing expansion of the cortical and displacement of the teeth. The mandibular canal was not evident. Based on images and previous NS diagnosis, MGCL was suspected. Regarding systemic risks and undesirable damage to the jaw and teeth, surgical curettage was not the choice for both patients. We opted for an alternative therapy with daily administration of salmon calcitonin nasal spray that was given for two years. No calcification has occurred after the treatment in both boys. The youngest patient showed discrete expansion of the lesions. To promote calcification of the lesions, we opted for once-yearly intravenous therapy with zoledronic acid. After one year, calcification was also inadequate despite no lesions progression. Bone turnover markers showed improvement from 1 to 6 months after zoledronic acid but rose again after one year.

**Conclusions:** Benign MGCL should be considered as a clinical feature of Noonan syndrome caused by dysregulation of the RAS-MAPK pathway. Calcitonin and zoledronic acid do not seem to improve calcification and lesion volume in this condition.

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#### AN INFANTILE HYPOPHOSPHATASIA CASE DUE TO A NOVEL MUTATION IN *TNSALP* GENE

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**Objectives:** It is a rare congenital metabolism disease characterized with defective bone mineralization related with serum and bone alkaline phosphatase activity due to mutation in hypophosphatasia tissue nonspecific alkaline phosphatase (*TNSALP*) gene.

**Methods: Case:** The infant was born as the first alive baby of a 29 year old mother from her first pregnancy with a birth weight of 3370 gr through C/S in the 40th week of pregnancy and she was hospitalized in an external center due to the seizure and respiratory difficulty starting on the postnatal first day. The metabolic scannings, cranial usg and brain MR were reported as normal for the patient who was previously hospitalized for 12 days in the intensive care due to convulsion and respiratory difficulty. She was discharged with antiepileptic drugs. Our patient referred to us when she was 52 days old. She had seizures, respiratory problem and groaning. Her parents were not relatives. According to the physical examination, her body weight was 4250 gr, height was 54 cm and head circumference was 36 cm. She had frog pose and hypotonia. In the head examination FF was open 4x5 cm and the sutures were open. Ca was 9.9 mg/dl, P was 5.1 mg/dl and ALP was 1 U/L. Spread rickets findings were observed in bone graphies. Plasma PLP:>500 µg/L (0-50) level was detected high. Infantile hypophosphatasia was considered for the patient with these findings and results.

**Results:** *TNSALP* gene and neighboring intronic areas were examined for possible mutations through DNA sequence

analysis. p.I218S (C.653T>G) homozygote mutation was detected in TNSALP gene.

**Conclusions:** Patients are normal at birth in infantile hypophosphatasia cases and clinical findings appear in the first six months. Demineralization and rachitic changes are observed in metaphyses. There may be respiratory problems due to rachitic deformities and the patients generally die due to this. Hypophosphatasia should be considered in distinctive diagnosis in cases with persistent convulsions and respiratory problems in newborn period.

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#### SEVERE HIPERPARATIROIDISM DUE TO MULTIPLE ADENOMA IN A MALE TEENAGER: RESPONSE WITH CINACALCET.

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**Objectives:** Parathyroid adenoma is the most common cause of primary hyperparathyroidism (PHPT). In most cases it is unique and the treatment is surgery. In adults, cinacalcet, a calcium-sensing agent that increases the sensitivity of the calcium sensor (CaRS), has been successfully used. In paediatric patients, cinacalcet is a common drug for treatment of secondary hyperparathyroidism, but its use in PHPT it's exceptional.

**Methods:** Case report

**Results:** Our patient was a 13-year-old teen from Senegal who underwent a medical examination at his arrival. Hypercalcemia 13.8mg/dL, hypophosphoremia 2.9mg/dl, parathormone (PTH) 1250 pg/dL, alkaline phosphatase 1587 UI/L and severe vitamin D deficiency (7.9ng/mL) were reported. The study was completed with calciuria 9.7mg/kg/day and normal urine catecholamine excretion. There was no familiar history of hypercalcemia. Physical examination showed height at -4 SDS, sable deformity in forearms and bilateral *genus valgus*. In whole-body skeletal X-ray, *Looser-Milkman* lines were observed in both tibias and also diffuse osteoporosis with bone reabsorption signs in clavicles, phalanges and metacarpals. Nephromegaly and nephrocalcinosis were reported in the abdominal ultrasound. Ultrasonography, cervical scan and sestamibi-Tc99m scintigraphy showed a left parathyroid adenoma of 12x10x45cm.

Patient received intensive treatment for hypercalcemia (maximum levels of 16 mg/dL) with hyper-hydration, diuretics, methylprednisolone, two calcitonin doses and surgical excision of the adenoma without incidences. CaRS and MEN-1 genetic studies were performed with both negative results.

Follow-up showed normal calcium and vitamin D but PTH (250 pg/dL) was persistently elevated. Cervical MRI and scintigraphy were performed again and a 12x8x4.9 cm right parathyroid adenoma was found. Given the complex surgical approach and the normality of calcium values, treatment with cinacalcet was initiated. After one year follow-up, patient has

normal serum calcium, a decrease in PTH levels (50 pg/dL) and a 0.61 mg/mg calcium/creatinine ratio.

**Conclusions:** Severe hyperparathyroidism, such as in this case, causes bone and metabolic alterations that cause morbidity. In our patient, treatment with cinacalcet allowed to avoid a new surgery on the parathyroid gland.

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#### PERINATAL SEVERE OSTEOGENESIS IMPERFECTA TYPE VIII DUE TO A NOVEL HOMOZYGOUS LEUCINE PROLINE-ENRICHED PROTEOGLYCAN 1 (LEPRE1) MUTATION: A CASE REPORT.

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**Objectives:** Osteogenesis imperfecta (OI) type VIII is a rare, autosomal recessive form of OI caused by a mutation in the Leucine proline-enriched proteoglycan 1 (*LEPRE1*) gene which encodes prolyl 3-hydroxylase 1 protein, a component of the collagen prolyl 3-hydroxylation complex, leading to altered post-translational collagen modification. Most cases are perinatal lethal, although some live into childhood or even rarely into adulthood. Severity of the disorder cannot always be determined by the genotype. OI type VIII can be difficult to distinguish clinically and radiographically from the autosomal dominant forms OI type II and type III, although characteristic features of OI type VIII include white to light blue sclera, rhizomelia, undertubulation of the long bones, gracile ribs without beading, and small to normal head circumference. OI type VII and type VIII are indistinguishable in infancy and early childhood.

Our objective is to summarize distinguishing characteristics of OI type VIII compared with other similar types of OI.

**Methods:** We present a case of OI type VIII with a novel homozygous mutation in *LEPRE1* gene (c1354delC) and review existing literature.

**Results:** Our patient was a 2 day old term female infant who presented with multiple bony deformities and fractures. She had IUGR and was born SGA at 38 weeks with light blue sclera, rhizomelia, mesomelia, microcephaly, and bowed legs. Skeletal survey revealed multiple fractures, a small, thin rib cage, and diffuse osteopenia. Lab analysis was unremarkable except for low vitamin D levels. At one month of age she was intubated for deteriorating respiratory status but ultimately extubated and weaned to nasal cannula. Due to new fractures she was treated with cyclic IV pamidronate but continued to have fractures and died at 5 months. Since her clinical signs and symptoms could not allow for differentiation between other perinatal lethal forms of OI, genetic testing was performed which revealed a novel homozygous mutation in *LEPRE1* gene (c1354delC).

**Conclusions:** This is a fatal case of OI type VIII with a novel homozygous mutation in *LEPRE1* gene (c1354delC). Genetic evaluation would be very helpful to differentiate OI type VIII from other perinatal lethal and severe forms of OI.



# INFANTILE HYPERCALCEMIA IN A CASE WITH NEUROFIBROMATOSIS TYPE 1 TIBIAL PSEUDARTHROSIS

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**Objectives:** Tibial pseudarthrosis is a serious but infrequent osseous manifestation of neurofibromatosis 1 (NF1). The pathogenesis of the skeletal abnormality of this disorder is not well understood. Although infantile hypercalcemia is caused by various condition, no report is so far available on the association with NF1.

**Methods:** Case report.

**Results:** The patient is a 3 year-old boy born at 32 weeks' gestation. His birth weight and length was 1496 g (-1.1SD) and 49.5 cm (-0.4SD), respectively. Physical examination showed some café-au-lait spots, left tibial bone bowing and mild bilateral ptosis leading to diagnosis of NF1. Although he was admitted to NICU because of prematurity, the clinical course was favorable and he was discharged at 2 months of age. However, he was admitted to the hospital again because of inability to sit without support and failure to thrive with emesis at 9 months of age. The laboratory data then revealed hypercalcemia (serum total calcium, 15.4 mg/dl) and hypercalciuria (a calcium/creatinine ratio of urine, 0.95 and fractional excretion of calcium, 1.3%). Intact PTH (1.5 pg/ml) and PTHrP (<1.1 pmol/l) were low. 1,25 (OH)<sub>2</sub>D (5 pg/ml) was low and 25OHD (44 ng/ml) was normal, indicating that CYP24A1 deficiency was unlikely. ALP activity of 303 IU/l was slightly low (age-adjusted reference range: 420-1580). Therefore, *ALPL* gene was analyzed but no mutation was identified. Williams-Beuren syndrome was also ruled out by FISH analysis for 7q11.23. Skeletal radiographic study showed no abnormal findings except for left tibial pseudarthrosis, which had been noticed since birth. Treatment with intravenous fluid infusion and furosemide was effective for normalizing serum calcium levels. He took a low calcium milk until 2 years of age. His serum calcium levels have been within normal range after discontinuation of calcium restriction.

**Conclusions:** Hypercalcemia in this patient seems to result from the unexplained elevated calcium absorption because all of PTH, PTHrP and 1,25(OH)<sub>2</sub>D levels were low. We speculate that the pathology might be relative elevated bone resorption due to possibly reduced bone mineralization as seen in the mouse model for NF1 skeletal dysplasia.

# HEREDITARY HYPOPHOSPHATAEMIC RICKETS WITH HYPERCALCIURIA: CASE SERIES HIGHLIGHTING VARIABLE PHENOTYPE

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**Objectives:** Hereditary hypophosphatemic rickets with hypercalciuria (HHRH – OMIM #241530) is a rare autosomal recessive renal phosphate wasting disorder which results from a loss-of-function mutation in the *SLC34A3* gene. HHRH usually manifests in childhood or early adolescence with severe rickets, skeletal deformity and short stature. Rarely, HHRH may present as idiopathic hypercalciuria, nephrocalcinosis or nephrolithiasis without apparent bone disease. We aim to describe the variable clinical phenotype and genotype of four cases from our institution.

**Methods:** There are less than 50 reported cases of HHRH worldwide. Here we present 4 cases of HHRH from three kindred who presented with variable clinical phenotype.

**Results:** As shown in the attached table, all of our cases had typical biochemistry suggestive of HHRH i.e. low serum phosphate, elevated alkaline phosphatase, low parathyroid hormone, reduced tubular resorption of phosphate, hypercalciuria and elevated 1,25(OH)<sub>2</sub>D levels. However, all cases differed in their clinical presentation. Case one and case two had severe bone fragility phenotype with low trauma fracture and low bone mineral density. However, cases three and four (siblings) had normal bone phenotype but progressive severe nephrocalcinosis.

Parental carriers in the first two cases had no demonstrable clinical or biochemical abnormality except borderline elevation in 1,25(OH)<sub>2</sub>D. Parental carrier of the siblings had a history of recurrent nephrolithiasis.

**Conclusions:** The cases demonstrate wide variation in clinical presentation of HHRH. Importantly, HHRH may present as idiopathic hypercalciuria, nephrocalcinosis or osteoporosis and hence a high index of suspicion is necessary for appropriate diagnosis and management. Variations in clinical phenotype may be due to the genotype variations, although further studies are needed to determine genotype-phenotype correlation.

PLEASE SEE TABLE ON NEXT PAGE

Table: Hereditary Hypophosphatemic Rickets with Hypercalciuria: phenotypic variations.

	Case 1 (10.7 y) Male	Case 2 (12 y) Male	Case 3 (14 y) Female	Case 4 (10 y) Male
Serum phosphate	Low	Low	Low	Low
Urine Ca/creatinine	Elevated	Elevated	Elevated	Elevated
TmP/GFR	Low	Low	Low	Low
Parathyroid hormone 1,25(OH) <sub>2</sub> D	Low	Low	Low	Low
Skeletal deformity	<b>Genu Valgum Bone pain</b>	Nil	Nil	<b>Genu Varus Knee pain</b>
Rickets	<b>Mild</b>	Nil	Nil	Nil
Recurrent fracture	Low trauma Single fracture	<b>Multiple fractures</b>	Nil	Nil
Bone mineral density	Low	<b>Very Low</b>	Normal	Normal
Nephrocalcinosis	Grade II	Absent	<b>Grade III progressive</b>	<b>Grade I</b>
SLC34A3 mutation	c.1046_47delTG homozygous	c.560+ 27_561- 38del/c.TTC13 57del	R468W homozygous	R468W homozygous

Calcium levels improved, but increased to maximum of 14 mg/dL. Glucocorticoids were started for treatment of hypercalcemia as bisphosphonates were not an option given acute kidney injury. Patient's 25 hydroxy vitamin D levels normalized 4 months later.

**Conclusions:** This case demonstrates the importance of diligence when treating vitamin D deficiency as vitamin D toxicity can occur in the pediatric population. It is important to verify the correct dose and duration is being prescribed in addition to recommendations on monitoring levels following treatment.

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## VITAMIN D STATUS IN TURKEY BETWEEN 2011 AND 2016

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**Objectives:** Recently, requesting serum 25-hydroxyvitamin D (25OHD) measurement and prescribing vitamin D are increasing in Turkey. In this study, the status of vitamin D in our country was analysed using a database of reliable and nationwide private laboratory.

**Methods:** Data analysis was carried out using serum 25OHD measurements performed by liquid chromatography tandem mass spectrometry (LC-MS/MS) method between January 2011 and December 2016. In total 110774 serum 25OHD measurements were analysed according to years, age groups and threshold vitamin D levels (0-11 ng / ml, 12-19 ng / ml, 20-49 ng / ml, 50-70 ng / ml and > 70 ng / ml). The correlation between 25OHD level and ALP and PTH was also assessed in cases which Alkaline Phosphatase (ALP) (14971 samples) and / or Parathyroid Hormone (PTH) measurement (7013 samples) were performed simultaneously.

**Results:** The mean 25OHD level was 37,80 ng/mL. Median 25OHD level was 37.80 ng / mL under 1 year, 29.00 ng / mL in 1-3 years, 21.79 ng / mL in 4-8 years, 19.74 ng / mL in 9-13 years, 16.9 ng/mL in 14-18 yr, 15.40 ng/mL in 19-30 yr, 17.50 ng / mL in 31-50 yr, 19.50 ng / mL in 50-71 yr, and 18.34 ng / ml, in > 70 yr group. Mean 25OHD level under 3 years was significantly higher than the other age groups (p <0.01). The frequency of serum 25 OH D measurement has increased approximately 2.60 times (260%) in the ages of 0-18 years and 32% in the age of 18 years between 2011-2016. However, mean serum 25OHD level at these age groups did not show a significant difference over the years. Frequency of Vitamin D deficiency/insufficiency (<20 ng / mL) was the lowest in less than 1 year (13.4%) and highest in 19-30 years (62.4%) (table).

**Conclusions:** Serum 25OHD levels in our country were similar to those of National Health and Nutrition Examination Survey (NHANES) carried out in 2001-2006, except under 1 year and 1-3 years age groups. These results support The Institute of Medicine (IOM) recommendations. The relatively high

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## VITAMIN D TOXICITY IN A PEDIATRIC PATIENT: AN IMPORTANT LESSON ON TREATMENT AND MONITORING

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**Objectives:** Identify barriers in treatment of vitamin D deficiency that can lead to vitamin D toxicity and potentially be prevented.

**Methods:** Vitamin D toxicity is rare in children, however over the past decade or so the benefits of vitamin D on bone health and other diseases has led providers to evaluate vitamin D states in children more commonly. There are an increasing number of different vitamin D formulations, recommended doses for daily requirements and treatment that place children at risk for vitamin D toxicity, in addition to, a lack of consensus on optimal levels and monitoring. This case is a great example of common pitfalls in treatment and monitoring of vitamin D deficiency that can lead to vitamin D toxicity requiring intervention.

**Results:** 8 year old female with complex congenital heart disease admitted for fatigue, heart failure and multiple electrolyte abnormalities. Patient was noted to have vitamin D deficiency in 2010 with 25 hydroxy vitamin D level of 19 ng/mL. Patient was reportedly started on 5,000 units of ergocalciferol daily, however review of prescription revealed ergocalciferol 50,000 units daily. Unclear duration of this treatment. 25 hydroxy vitamin D level was rechecked in 2011 and was replete at 82 ng/dL, no change in management. Serum calcium levels were normal until 2015. Labs on admission were serum calcium 13 mg/dL, ionized calcium 1.4 mmol/L, phosphorus 8 mg/dL and PTH at 9 pg/mL. 25 hydroxy vitamin D level was 727.12 ng/mL and 1, 25 dihydroxy vitamin D level was >600 pg/mL. All exogenous forms of vitamin D were discontinued, hydration was optimized and she was continued on Lasix. Repeat levels in 1 week were downtrending, 25 hydroxy vitamin D 335.5 ng/mL.

median 25OHD level in the first 3-year period and the low frequency of vitamin D deficiency and inadequacy were considered as positive effects of free D vitamin supplement program applied in our country.

Age groups	Serum 25-hydroxyvitamin D (25OHD) level				
	0-11	12-19	20-49	50-70	>70
	ng/mL	ng/mL	ng/mL	ng/mL	ng/mL
	(%)	(%)	(%)	(%)	(%)
<1	7.9	5.5	62.5	18.2	6.0
1-3	5.0	14.2	73.0	5.7	2.1
4-8	10.2	29.2	57.3	2.1	1.3
9-13	17.3	32.0	48.7	1.3	0.8
14-18	28.5	30.5	38.4	1.4	1.1
19-30	35.2	27.2	33.8	2.2	1.5
31-50	29.3	25.5	40.7	2.8	1.8
51-70	25.7	22.9	45.1	3.8	2.5
>70	32.6	18.6	41.7	4.0	3.1

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### LONG-TERM GROWTH HORMONE TREATMENT AUGMENTS FINAL ADULT HEIGHT IN PATIENTS WITH ACHONDROPLASIA

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**Objectives:** The objective of this study was to assess the gain in final height of achondroplasia (ACH) patients with long-term growth hormone (GH) treatment.

**Methods:** All patients had visited our hospital for treatment and were clinically diagnosed with ACH due to severe rhizomelic short stature, trident hands, characteristic facial features, and characteristic bone X-ray features. *FGFR3* gene analysis was performed by direct sequencing and the typical p.Gly380Arg mutation was detected in all tested patients. Medical records and/or questionnaires from 22 adult ACH patients (8 males and 14 females) that underwent GH treatment at a dose of 0.05 mg/kg/day were included in the retrospective analysis. Optionally, the Ilizarov method was used to perform tibial lengthening (TL) in 15 patients, and TL as well as femoral lengthening (FL) in 6 patients. Concomitant gonadal suppression therapy with buserelin acetate was applied in 13 patients.

**Results:** GH treatment was started at the mean age of 5.2±3.9 years and 5.5±2.7 years for boys and girls, respectively. GH treatment augmented final height +0.60±0.52 SD (+3.5 cm) and +0.51±1.29 SD (+2.8 cm) in boys and girls, respectively, compared to non-treated ACH patients. Final height of ACH patients that underwent GH and TL increased

+1.72±0.72 SD (+10.0 cm) and +1.95±1.34 SD (+9.8 cm) in males and females, respectively. GH, TL, and FL further increased final height +2.97 SD (+17.2 cm) and +3.41±1.63 SD (+17.3 cm) in boys and girls, respectively. Gonadal suppression therapy seemed to have no effect on final height. **Conclusions:** Long-term GH treatment as well as GH in combination with limb lengthening improved final height in ACH patients.

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### ASSESSMENT OF RESTLESS LEGS SYNDROME DEVELOPMENT AND POOR SLEEP QUALITY IN NON-ANEMIC CHILDREN WITH VITAMIN D DEFICIENCY

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**Objectives:** Restless legs syndrome (RLS) is a sensorimotor disorder that often has a profound impact on sleep. The aim of this study is to investigate the relationship between vitamin D (VitD) deficiency and RLS development and sleep quality in children.

**Methods:** Two hundred and ten children aged between 10 and 16 years were recruited for the study. VitD deficiency was defined as a serum 25-hydroxyvitamin D3 [25(OH)D] concentration

**Results:** RLS was diagnosed in 22 (10.4%) of the children and was more prevalent in VitD deficient group 13.6% (n=12) compared to the VitD insufficient 9.4% (n=8) and VitD sufficient groups 5.4% (n=2) (p<0.001). Total PSQI scores were significantly higher in VitD deficient subjects than VitD sufficient group (5.58 vs. 4.47, p=0.03). Lower VitD levels were negatively associated with age (r:-0.18, p:0.01) as expected and also negatively correlated with sleep characteristics such as sleep quality scale (r:-0.17, p: 0.02) and sleep duration (r:-0.16, p: 0.03).

**Conclusions:** VitD deficiency is common in childhood and may be the cause of or a contributor to RLS and RLS related poor sleep quality. Therefore, children with RLS need to be assessed for the VitD levels and to support regarding sleep quality

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### CONTINUOUS SUBCUTANEOUS INFUSION OF PTH FOR AUTOSOMAL DOMINANT HYPOCALCAEMIA.

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**Objectives:** Autosomal Dominant Hypocalcaemia (ADH) is due to gain-of-function mutations of the *CASR* resulting in

constitutive activation of the GPCR Calcium Sensing Receptor (CaSR) leading to hypercalciuric hypocalcaemia, hypoparathyroidism and occasionally Bartter syndrome type V. Patients usually present with hypocalcaemic seizures at young age. Conventional treatment is with Alfacalcidol and Calcium or PTH injections. We aimed to assess whether continuous subcutaneous treatment with PTH using insulin pumps is able to stabilise calcium concentrations and symptoms.

**Methods:** Five patients with ADH in whom stabilization of calcium concentrations could not be achieved with conventional treatment, were started on continuous subcutaneous PTH infusion (CSPI) using Medtronic and Omnipod patch pumps to deliver diluted PTH(1-34). Treatment was started in an inpatient setting and adjusted to achieve low-normal calcium concentration. Outcome parameters were number of seizures, hospital admissions, nephrocalcinosis, and calciuria.

**Results:** *CaSR* mutations were p.Thr828Asn, not previously described, and p.Ala843Glu, p.Tyr829Cys, p.Phe821Leu. In vitro functional analysis showed constitutive activation of the P.Thr828Asn variant. Patients presented with hypocalcaemic seizures or tetany in the first weeks of life. Additional features were bilateral cataracts, hypomagnesaemia, Bartter type V. Two patients had nephrocalcinosis before CSPI. Age at start of CSPI was 3 weeks, 6 weeks, 6 months, 6 years and 20 years. Duration of CSPI treatment is currently 1-3 years. PTH requirement was 0.21, 0.13, 0.15, 0.5 and 3 mcg/kg/day. Calcium concentration stabilised and patients continue to require weekly or bi-weekly blood tests. Number of admissions reduced during CSPI. Seizures stopped in all patients on CSPI. Current calcium concentrations range from 1.75-2.15mmol/l. Current urine Calcium/creat ratios are 1.2- 2.5 mol/mol. Nephrocalcinosis has remained stable. One patient stopped pump treatment temporarily due to instable calcium concentrations.

**Conclusions:** Continuous subcutaneous PTH infusion is a suitable treatment for ADH that cannot be controlled conventionally. Longer follow up is required to assess whether continuous sc PTH treatment delays the progression of nephrocalcinosis.

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#### ADAPTIVE VITAMIN D METABOLISM AT THE EQUATOR CAN PREDISPOSE TO INSUFFICIENCY IN CHILDREN OF FIRST GENERATION AFRICAN IMMIGRANTS IN THE US

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**Objectives:** The goal of this multi-center international cross-sectional observational study was to define vitamin D status in Somali immigrants living in northern US

**Methods:** Healthy children aged 6 months to 7 years living in Minnesota (US-born of Somali descent, n=55) or Uganda (n=95) were enrolled. 25OHD and other vitamin D metabolites (24,25(OH)2D) were measured by immune-affinity extraction and liquid chromatography-tandem mass spectrometry. Parathyroid hormone (PTH) and hypocalcemia status were used as primary markers of vitamin D insufficiency. DBP haplotypes were determined.

**Results:** Compared to the Ugandan group, and despite superior nutritional status (vitamin D fortified milk intake), MN Somali children had lower 25OHD (23.7 vs 30.1 ng/mL; p<0.0001), calcium levels (9.1 vs 9.5 mg/dL; p<0.0001), and higher PTH levels (47 vs 36 pg/mL; p<0.0001). Ninety-one percent of the MN Somali participants had 25OHD levels <30 ng/ml (vs 48% in Ugandans). Somalis had higher frequency (57% vs 14% in Ugandans; p<0.001) of calcium in the lower level of normal even at 25OHD levels >20 (American Academy of Pediatrics [AAP] cutoff for sufficiency) and this was not significantly different from the Somali group with 25OHD <20 ng/mL (p=0.3). The high-affinity allele Gc1f (which limits free forms of vitamin D) was the predominant DBP variant in both MN Somalis and Ugandans, but Somalis had a higher percentage of low serum calcium status. The Somali group had a higher level of vitamin D inactivation (greater 24,25(OH)2D, less 1,25(OH)2D levels, p=<0.001) despite having lower 25OHD levels raising a concern of maladaptive vitamin D metabolism and inherent susceptibility to vitamin D deficiency independent of limited cutaneous vitamin D synthesis as a result of darker skin tone.

**Conclusions:** These results suggest that even at the AAP cutoff for sufficiency (>20 ng/mL), clinically significant low 25OHD levels were common in African immigrant children. Also, while African children at the equator possess adaptive mechanisms to protect against excessive acquisition and utilization of vitamin D, but those same mechanisms may render them susceptible to low 25OHD when migrating to high-latitude regions such as Minnesota.

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#### THE TRPM6 GENE MUTATIONS IN TWO SIBLINGS OF GENETIC HYPOMAGNESEMIA WITH HYPOCALCEMIA AND HYPOPARATHYROIDISM

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**Objectives:** Magnesium is essential to the proper functioning of numerous cellular processes. Hypomagnesemia can cause neuromuscular irritability, seizures and cardiac arrhythmias. Mutations in the gene for the DCT- and colon-specific apical Mg2+ channel, TRPM6, cause the most profound genetic hypomagnesemia. We described two siblings with TRPM6 mutations.

**Methods:** First case was applied with seizure at 5-month old and hypomagnesemia, hypocalcemia and low level of parathyroid hormone were detected. Second case had also seizure with hypomagnesemia, hypocalcemia on newborn period.

**Results:** The molecular analysis confirmed the genetic cause of hypomagnesemia in these siblings by identifying the pathological homozygous variants c.2667+1G>A in TRPM6 gene.

**Conclusions:** To conclude, magnesium levels should also be checked in cases with hypocalcemia and hypoparathyroidism, genetic causes should be considered in case of hypomagnesemia and molecular analysis should be prioritized for early diagnosis.

## POSTER SESSION 1

Thursday, September 14, 2017, 5:45-6:45pm

### P1 - Fetal and neonatal endocrinology and metabolism, including hypoglycemia

P1-500 – P1-526

P1-500

#### SEVERE HYPERINSULINISM IN INFANTS WITH BECKWITH-WIEDEMANN SYNDROME AND HETEROZYGOUS KATP CHANNEL MUTATIONS: MORE THAN FOCAL OR DIFFUSE DISEASE

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**Objectives:** Congenital hyperinsulinism (HI) causes severe hypoglycemia, most often due to mutations in the beta cell ATP-gated potassium ( $K_{ATP}$ ) channel. Homozygous  $K_{ATP}$  mutations result in Diffuse HI (dHI), while paternally-inherited heterozygous mutations ( $K_{ATP}^{pMut/+}$ ) can cause Focal HI (fHI) when paternal uniparental isodisomy (pUPD) of chromosome 11p15 occurs in a specific pancreas region. Chromosome 11p15 includes the  $K_{ATP}$  genes and an imprinted region that is affected in Beckwith-Wiedemann Syndrome (BWS). BWS is a spectrum of overgrowth disorders associated with HI via an unclear mechanism. We compared clinical and biochemical features of HI in infants with pUPD BWS and  $K_{ATP}^{pMut/+}$  to those with fHI, dHI, or BWS alone.

**Methods:** Medical records were reviewed. Fresh pancreatic tissue resected during therapeutic pancreatectomy (Px) was collected for islet isolation and functional testing.

**Results:** We identified 6 infants with HI associated with  $K_{ATP}^{pMut/+}$  and pUPD BWS. All subjects were born large for gestational age (4,040-5,946 g), presented within 24 hours with severe hypoglycemia, required a high glucose infusion

rate (max 13-34 mg/kg/min), and did not respond to diazoxide. 18-fluoro-DOPA PET showed enlarged pancreas in 4 cases and focal uptake in 2 cases. All subjects underwent extensive (70-100%) Px, after which 3 of the infants did not require additional treatment, 2 required continuous enteral dextrose, and 1 required enteral dextrose and octreotide. Histology in all cases revealed increased endocrine tissue in multiple areas of the pancreas with variable numbers of islet cell nucleomegaly. Functional testing of islets from 3 cases showed elevated basal intracellular calcium and/or insulin secretion, increased responsiveness to amino acids, and minimal or no response to glucose.

**Conclusions:** We found that pUPD BWS with  $K_{ATP}^{pMut/+}$  caused severe HI requiring aggressive intervention. Islet functional assays demonstrated features of both  $K_{ATP}$  HI and BWS HI, indicating that both pathophysiologic mechanisms contribute to clinical severity. Histologic features distinguish this clinical entity from dHI, fHI, and BWS HI. It is important to identify these cases early by  $K_{ATP}$  mutation analysis and SNP array karyotyping.

P1-501

#### INCREASED NUMBERS OF SEPTAL ISLETS REPRESENT A PHASE SHIFT IN PANCREATIC DEVELOPMENT IN CONGENITAL HYPERINSULINISM

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**Objectives:** Congenital Hyperinsulinism of Infancy (CHI) is a disease of islet cells associated with excessive secretion of insulin leading to profound hypoglycaemia in affected children. During pancreatic ontogeny, some islets are formed within the septum of the pancreatic tissues, and remain in the septum until following birth. Little is known about the organization of septal islets (SI) or their association with the pathobiology of disease.

**Methods:** We characterized the general properties of SI in post-natal neonatal tissue (n=7 cases; n=48 SI), adult control tissue (n=4), and CHI tissue following surgery from either diffuse (n=16 patients; n=378 SI) or focal (n=11 patients; n=102 SI) cases. Tissue samples were fixed in 4% paraformaldehyde and embedded in paraffin wax; 5  $\mu$ m thick sections were prepared for immunostaining. Images were acquired and digitized by a 20x/0.80 Plan Apo objective using the 3D Hitech Panoramic 250 Flash II slide scanner. Panoramic Viewer and HistoQuant software packages were used for data analysis and high-content cell counting (3DHISTECH Ltd, Hungary).

**Results:** SI were on average 2-fold larger than non-SI (range 1831.9-122946.5  $\mu\text{m}^2$  (n=531) vs. 1589.5-39907.6  $\mu\text{m}^2$  (n=257)) and associate with expression of insulin, glucagon and somatostatin. SI appear to be more highly vascularized than non-SI and establish close connections with neural branches; however these are similar in proximity to non-SI. In control tissue, SI were only seen in neonatal tissue, but their incidence was found to be >2-fold higher in CHI tissue compared to controls;  $2.1 \times 10^{-7}$  SI per  $\mu\text{m}^2$  (n=480) vs.  $9.32 \times 10^{-8}$  SI per  $\mu\text{m}^2$  (n=48). The incidence of SI was higher in the non-lesion parts of the pancreas of focal CHI cases ( $3.33 \times 10^{-7}$  per  $\mu\text{m}^2$  (n=102)) than in diffuse CHI ( $1.47 \times 10^{-7}$  per  $\mu\text{m}^2$  (n=378)). The role of SI in the pathobiology of CHI has not been determined, but in addition to an increased incidence in the hyperinsulinism pancreas, SI were also found to be proliferative (Ki67<sup>+</sup> expression) and associated with nucleomegaly; a feature only seen in SI from CHI tissue.

**Conclusions:** Our findings that SI are more prevalent in CHI tissue supports previous observations that the CHI pancreas is naïve and more closely aligned to the foetal pancreas rather than age-matched control tissue.

P1-502

#### PERSISTENT HYPERINSULINEMIC HYPOGLYCEMIA, SERIES OF CASES IN 20 YEARS IN A SINGLE HOSPITAL IN MEXICO.

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**Objectives:** To describe clinical, biochemical, medical and / or surgical treatment and complications in patients with persistent hypoglycemia hyperinsulinemic over a period of 20 years (January 1997 to January 2017).

**Methods:** Case series. Descriptive statistics were used for the analysis of data with measures of central tendency, dispersion and frequency. SPSS Program 22.

**Results:** Out of 55 records reviewed, we were able to confirm the diagnosis of hyperinsulinemic. Found a higher prevalence in males 52% (n = 12). The medications used to control hypoglycemia were octeotride (83.75%), hydrocortisone (42.1%) and diazoxide (41.65%), 60.2% required subtotal pancreatectomy of 95%. The most common sequelae were psychomotor retardation (82.6%), seizures (34.7%), secondary diabetes (13%), hypoglycemia (8.7%).

**Conclusions:** The clinical picture and the sequelae of this disease are similar in what is reported in other series worldwide. Treatment differs since steroid used as the drug of choice in the acute control of hypoglycemia. We have a greater number of patients with neurological sequelae probably secondary to the late diagnosis. The use of glucagon as a first line medication for the control of hypoglycemia in the acute period of the disease is required.

P1-503

#### CALCIUM/CALMODULIN DEPENDENT PROTEIN KINASE 2 (CAMKK2) MUTATION – A NOVEL GENETIC CAUSE OF CONGENITAL HYPERINSULINISM

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**Objectives:**  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase 2 (CaMKK2) belongs to the Serine/Threonine protein kinase family and alternative splicing results in multiple transcripts encoding distinct isoforms. *CaMKK2* mRNA has been shown to express in mouse pancreatic islets and loss of *CaMKK2* increases the glucose mediated insulin secretion. We report, for the first time, *CaMKK2* mutation as a novel genetic cause of congenital hyperinsulinism (CHI).

**Methods:** A Caucasian child born to non-consanguineous parents at 33 weeks gestation presented with hypoglycaemic seizures at 7 months of age requiring intravenous glucose load up to 15mg/kg/min. The investigations confirmed CHI [plasma insulin concentration of 37pmol/L and suppressed  $\beta$  hydroxy butyrate (<100mmol/L) during hypoglycaemia]. No mutation was identified in *ABCC8*, *KCNJ11* or *GCK*. The 18-Fluro-DOPA PET CT scan suggested diffuse CHI and the patient responded well to diazoxide therapy. At the age of 5 years, the patient requires 10mg/kg/day of diazoxide and has features of developmental and speech delay.

**Results:** Whole exome sequencing was performed on the genomic DNA of the patient and the biological parents. A de novo heterozygous frameshift mutation (p.G539fs\*4) was found at the terminal exon (exon 16) of *CaMKK2* (NM\_001270486.1) (isoform-7). *CaMKK2* isoform-7 (WT) and the pG539fs\*4 mutant were expressed in COS7 cells and the pG539fs\*4 mutant was noted to have significantly higher basal and  $\text{Ca}^{2+}$ -CaM dependent kinase activity compared with WT isoform-7. Both isoform-7 and the pG539fs\*4 mutant have elevated basal activity compared with isoform-1, the major *CaMKK2* isoform expressed in most tissues.

**Conclusions:** We describe for the first time, *CaMKK2* mutation as a novel genetic cause of persistent CHI. The potential mechanism is likely to involve alteration in the AMPK (substrate for *CaMKK2*) regulated insulin secretion driven specifically by isoform 7. This has wider implications in understanding the molecular genetic aetiology of CHI as well as monogenic diabetes mellitus.

### INSULIN-LIKE GROWTH FACTOR I IN CORD BLOOD IS PREDICTIVE FOR FINAL HEIGHT IN MONOZYGOTIC TWINS WITH DISCORDANT GROWTH

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**Objectives:** We investigated catch-up growth and final height of monozygotic twins with discordant birth-weight and the predictive value of birth-weight, birth-length, and concentration of IGF-I in cord-blood and at the age of 4 yrs.

**Methods:** 25 monozygotic twin-pairs [16 discordant with an intra-twin birth-weight SD score (SDS) difference >1] were studied at birth, at 4 yr, and at final height. Several parameters including IGF-I serum concentration were analyzed in cord blood. In 20 pairs parameters were re-analyzed at 4 yr of age and at final height. Intra-twin differences ( $\Delta$ ) in birth weight, birth length, and longitudinal growth until final height were correlated with  $\Delta$  in concentration of the respective biochemical parameters.

**Results:** We found a gradual reduction of intra-twin  $\Delta$  height SDS from birth to final height, with the main catch-up growth of the smaller twin occurring during the first year of life. In the formerly concordant twin-pairs final height was nearly identical ( $\Delta$  0.03 SDS) whereas in the discordant group the former smaller twin was still an average of 0.74 SDS shorter than the co-twin. Correlation coefficients were used to identify factors predicting existing differences at final height. Birth-weight difference ( $r=0.45$ ;  $P=0.01$ ) and  $\Delta$  IGF-I in cord blood ( $r=0.4$ ;  $P=0.01$ ) were both of similar predictive value. Although there was still a significant difference for intra-twin  $\Delta$  height-, weight-, and BMI-SDS at four years there was no intra-twin difference but a highly significant intra-twin correlation for IGF-I serum concentration ( $r=0.88$ ;  $p<0.001$ ). In contrast to cord-blood IGF-I, IGF-I at the age of 4 yrs was of no predictive value for further catch-up growth until final height of the smaller twin.

**Conclusions:** Genetically identical twins with discordant birth-weights showed gradual convergence in height with still a remaining significant difference at final height. Predictive of catch-up growth until final height were difference in birth-weight and in cord-blood IGF-I, but not IGF-I at the age of four years.

P1-505

### GLUCOCORTICOIDS IN NEONATAL HAIR: REFLECTION OF INTRAUTERINE HPA-AXIS ACTIVITY?

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**Objectives:** The value of glucocorticoids (GCs) measured in neonatal hair is not known, although it might provide a retrospective view of fetal HPA-axis activity. We aimed to describe factors associated with infant hair GC levels in early life, as well as their relation with maternal HPA-axis activity.

**Methods:** Mother-infant pairs donated hair samples directly pp ( $n=108$ ,  $GA=39.5\pm 1.8$ , 54.5% male), and during an outpatient visit (OPV) at  $43\pm 13$  days pp ( $n=72$ ). Cortisol and cortisone levels were determined by LC-MS/MS. Analyses were performed with regard to (1) factors associated with infant hair GCs directly pp, (2) the course of GC levels pp, and (3) associations between maternal and infant HPA-axis activity.

**Results:** (1) Infant hair GCs directly pp were positively associated with gestational age (GA) (log-transformed  $\beta$  [95%CI]: cortisol: 0.07 [0.05-0.10]; cortisone: 0.03 [0.01-0.06]) and perinatal infection (cortisol: 0.15 [0.03-0.26]; cortisone: 0.21 [0.12-0.29]). Other neonatal and maternal factors (e.g., gender, birth weight, respiratory distress, pre-eclampsia) did not influence infant hair GCs directly pp.

(2) Between birth and the OPV, infant hair GCs decreased, although they were still 5-15 times higher compared to maternal levels. Longer gestation was associated with a steeper cortisol decrease and higher hair cortisol at the OPV. Infection was associated with a steeper decrease in cortisone. (3) Maternal hair cortisol was positively associated with infant hair cortisol directly pp ( $r: 0.31$ ,  $p=0.001$ ;  $\beta: 0.21$  [0.08-0.33]) and at the OPV ( $r: 0.47$ ,  $p<0.001$ ;  $\beta: 0.38$  [0.20-0.56]), while associations between maternal and infant hair cortisone were not found.

**Conclusions:** Our findings suggest that infant hair GCs are mainly influenced by the positive feedback loop, a placenta-driven phenomenon causing an increase in GCs in the third trimester, represented by a positive association with GA. Perinatal complications and maternal HPA-axis activity had minor influences on infant hair GCs. At 1.5 month pp, infant hair GCs seemed to reflect both the intra- and extra-uterine period. From our data, it is not possible to discern at which point pp infant hair GCs represent the extra-uterine environment only.

P1-506

### NEONATAL HYPOGLYCEMIA DIAGNOSES BEFORE AND AFTER GUIDELINE RELEASE: A PEDIATRIC HEALTH INFORMATION SYSTEM DATABASE INQUIRY

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**Objectives:** The Pediatric Endocrine Society (PES) updated the hypoglycemia guidelines in August 2015. Our primary aim is to assess change in hypoglycemia diagnoses in neonates,



infants, and children after guideline release. Our secondary aim is to evaluate institutional variation in implementation.

**Methods:** We queried the Pediatric Health Information System database to determine the frequency of hypoglycemia diagnoses in 49 US Children’s Hospitals before (Jan 1-June 30, 2015) and after (Jan 1-June 30, 2016) guideline release.

The rate of hypoglycemia was determined by dividing cases of hypoglycemia by total number of admissions. Cases were defined by the presence of an ICD9 or ICD10 diagnostic code for hypoglycemia, excluding those for diabetes patients. This analysis was completed for 3 age groups: neonates (0-30 days), infants (31 days-1 year), and children (1-18 years). We tested for statistical significance using binomials.

**Results:** In the neonatal group, there were 11.8 cases per 100 admissions in the six months preceding guideline release (5,973 cases for 53,175 admissions). There were 13.5 cases per 100 admissions for the six months after guideline release (6,707 cases for 52,429 admissions). Therefore, neonatal hypoglycemia cases increased by 1.7 per 100 admissions after guideline release ( $p<0.01$ ). There was no significant increase in hypoglycemia diagnoses in either the infant ( $p=0.64$ ) or children ( $p=0.30$ ) group overall.

In the neonatal group, 14 of 49 institutions had a significant increase in hypoglycemia diagnosis rates ( $p<0.05$ ), while 35 of 49 institutions showed no significant change. No institution had a significant decrease in neonatal hypoglycemia.

**Conclusions:** A national increase in neonatal hypoglycemia diagnoses followed release of the PES guidelines. Just under a third of institutions are responsible for the increase. Explanations for institutional variation include: inadequate guideline dissemination, disagreement with the guidelines, and high pre-guideline diagnosis rates. There was no concurrent rise in hypoglycemia diagnoses in older infants or children, in whom it is less common and easier to diagnose. The incidence of neonatal hypoglycemia in this database inquiry is consistent with published estimates of 5-15%.

P1-507

**CLINICAL PRESENTATION AND INSULIN MANAGEMENT IN 88 PARTICIPANTS DIAGNOSED WITH DIABETES UNDER 1 YEAR OF AGE**

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**Objectives:** To characterize diabetes diagnosis presentation and insulin management of participants diagnosed  $\leq 1$  year of age in the US Monogenic Diabetes Registry and to compare features by type of diabetes (genetic cause versus likely type 1 diabetes).

**Methods:** Participants enrolled through the US Monogenic Diabetes Registry were included if they were diagnosed with diabetes  $\leq 13$  months of age and had a valid medical record release form on file. Medical records from time of diabetes diagnosis were requested. Data was analyzed using Stata

Version 14 (StataCorp, 2015). For group comparisons, Kruskal-Wallis tests and Fisher’s exact tests were performed. The relationship between age at diagnosis and days hospitalized (Spearman rank correlation) and diabetic ketoacidosis (DKA) (logistic regression) was also determined. Study data was collected and managed using REDCap electronic data capture tools.

**Results:** 301 participants met eligibility criteria for this study and 88 had substantive records from time of diabetes diagnosis. The majority were male (52.3%), Caucasian (62.5%), alive at time of analysis (97.7%), and had permanent forms of diabetes (86.4%). The most common genetic cause was KCNJ11-related diabetes (37.5%) followed by unknown genetic cause/likely type 1 diabetes (21.6%). Median age at diagnosis of diabetes was 10.4 weeks (IQR: 5.2-26.5 weeks). Several parameters were significantly different among subgroups, including DKA (Table 1). The most common signs/symptoms at diagnosis were polyuria and tachypnea. Therapies used were not significantly different by mutation subtype. Earlier diagnosis age was associated with more days spent in the hospital ( $r_s=-0.64$ ). Participants diagnosed at a later age had a greater likelihood of DKA at diagnosis (OR: 1.23 [95% CI 1.04, 1.45]).

**Conclusions:** Severe presentation of diabetes was common in this young population. Prevalence of DKA at diabetes diagnosis in this study was  $>1.5$  times higher than one previous study of children diagnosed between 0-4 years old. This may be due to delay in diagnosis, since later age at diagnosis increased likelihood of DKA. Efforts to reduce any possible delay in diagnosis may help to prevent diabetes-related morbidity in this vulnerable population.

Table 1: Details of diabetes diagnosis by mutation subtype								
	KCNJ11/ ABCC8 n=41	INS/ EIF2AK3 n=13	6q24 n=10	IL2RA/ FOXP3 n=3	GATA6/ PDX1 n=2	Unknown n=19	Total n=88	p-value
Glucose, mg/dl n=73	716.5 (563-870)	435 (319-625)	408 (300-502)	920 (342-1600)	411 (355-467)	736 (526-840)	618 (477-800)	<0.001*
pH n=49	7.07 (6.87-7.26)	7.41 (7.4-7.43)	7.43 (7.39-7.46)	6.95 (6.9-7.0)	7.11 (6.9-7.31)	7.08 (7.0-7.27)	7.08 (6.98-7.31)	0.02*
Bicarbonate, mEq/L n=58	6.0 (4.6-11.0)	16.4 (15.0-25.0)	21.1 (20.0-21.8)	13.0 (6.0-20.0)	16.0 (7.0-25.0)	5.0 (4.0-10.4)	7.0 (5.0-18.8)	0.001*
HbA1c, % n=27	12.0 (9.3-13.6)	9.9 (8.5-10.9)	Not available	4.9	Not available	8.8 (6.9-9.8)	9.9 (8.3-12.2)	0.04*
DKA, yes (%) n=71	26 (78.8)	3 (30)	0 (0)	3 (100)	1 (50)	14 (87.5)	47 (66.2)	<0.001*
Days in hospital n=66	7.0 (4.0-10.0)	4.0 (3.0-14.0)	22.0 (13.0-28.0)	10.5 (6.0-15.0)	6.0	4.0 (3.0-6.0)	6.5 (4.0-14.0)	0.02*

All data presented as median (IQR) unless otherwise specified  
\*HbA1c <6 months are underestimated due to fetal hemoglobin. \*Statistically significant by Kruskal-Wallis test or Fisher's exact test

P1-508

**INFANTS BORN SMALL-FOR-GESTATIONAL AGE HAVE DIFFERENT PLACENTAL EXPRESSION OF MICRORNAS**  
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**Objectives:** To investigate the placental microRNA expression profile in children born small-for-gestational age (SGA) and exposed to low maternal gestational weight gain (GWG).

**Methods:** 13 full-term newborn babies with birth weights  $< -2$  SD from the population mean exposed to maternal GWG  $\leq$

10 kg (group 1) were identified in a placental biobank. 9 children with birth weights < - 2 SD and GWG 11.5–16.0 kg constituted group 2. 20 children with normal birth weights but GWG ≤ 10 kg constituted group 3 and 26 children with both normal birth weights and GWG constituted group 4. The infants in groups 2–4 were matched with group 1 with respect to gender, gestational age, maternal parity, and maternal age.

Total RNA were extracted from the placental biopsies. After microRNA preparation, next generation sequencing using Illumina technology was performed. Comparisons between the groups were done with ANOVA for unequal variances and Benjamini-Hochberg's correction for multiple testing.

**Results:** The mean (SD) birth weight and maternal GWG in group 1 were 2,834 (296) g and 9.2 (1.2) kg, respectively. The corresponding numbers in group 2 were 2,636 (211) g and 13.6 (1.0) kg, respectively, in group 3 3,696 (355) g and 9.1 (1.0) kg, respectively, and in group 4 3,747 (356) g and 15.0 (1.2) kg, respectively. 48 of the 68 children were boys.

The minimum reads/sample were 9.2 millions. The expression of 16 microRNAs differed significantly between group 1 and group 2. The expression of 12 microRNAs differed significantly between group 2 and 4. Ten of the differentially expressed microRNAs differed in both comparisons (miR-3679-5p, miR-4532, miR-335-3p, miR-379-3p, miR-380-3p, miR-369-5p, miR-330-5p, miR-519e-3p, miR-105-5p, and miR-3065-5p).

**Conclusions:** The mechanism behind poor fetal growth may involve differential expression of microRNAs in the placenta. Low maternal weight gain during pregnancy seems to influence the placental microRNA expression in full-term in children born SGA but not in children with normal birth weights.

P1-509

#### MIRNAS IN UMBILICAL CORD OF SMALL-FOR-GESTATIONAL-AGE INFANTS AT BIRTH: ASSOCIATION WITH POSTNATAL CATCH-UP GROWTH

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**Objectives:** The vast majority of infants born small-for-gestational-age (SGA) develop spontaneous catch-up growth beyond birth. The mechanisms underpinning the presence versus absence of postnatal catch-up growth in SGA infants are poorly understood. We postulated that postnatal

catch-up growth in SGA infants may relate to prenatal miRNA profiles, and tested this hypothesis by studying miRNAs in the umbilical cord of SGA infants with versus without postnatal catch-up growth.

**Methods:** MicroRNA PCR Human Panels were used to study the miRNA profile in umbilical cord tissue, free of blood vessels, of SGA infants with (SGA-CU) versus without catch-up growth (SGA-nonCU). Relationships were studied between miRNAs differentially expressed (SGA-CU versus SGA-nonCU) in umbilical cord at birth and body size at the postnatal age of 1 year.

**Results:** 12 miRNAs were differentially expressed between SGA-CU and SGA-nonCU, 7 being upregulated in SGA-CU (miR-128-3p, miR-576-5p, miR-628-5p, miR-222-5p, miR-300, miR-940 and miR-374b-3p), and 5 being downregulated in SGA-CU (miR-876-3p, miR-873-5p, miR-770-5p, miR548c-5p and miR501-3p) (p between <0.05 and <0.0005). miR-300 and miR-548c-5p associated with Z-scores of weight and height at age 1 year (all p <0.05), and predicted catch-up growth (miR-300:  $\beta = 0.725$ ,  $R^2 = 0.53$ , p = 0.008; and miR-548c-5p:  $\beta = -0.721$ ,  $R^2 = 0.86$ , p = 0.004). *In silico* analysis suggests that these miRNAs share targets of metabolic pathways including WNT and TGF- $\beta$  which relate to cell growth and proliferation.

**Conclusions:** The miRNA profile in the umbilical cord of SGA infants at birth was found to relate to postnatal catch-up growth. The potential of prenatal miRNA profiles as predictors of postnatal growth deserves to be further explored.

P1-510

#### LANREOTIDE IS A SAFE AND EFFECTIVE TREATMENT FOR CONGENITAL HYPERINSULINISM

Katherine Lord, MD; Nicole Stewart, RN; David Langdon, MD; Diva D. De León, MD, The Children's Hospital of Philadelphia, Philadelphia, PA, United States

**Objectives:** Congenital hyperinsulinism (HI), resulting from dysregulated insulin secretion, causes severe and persistent hypoglycemia. Without effective treatment, children with HI are at risk of poor neurologic outcomes. However, few medical therapies exist. These include diazoxide, to which many patients fail to respond, and octreotide, which requires multiple daily injections. Lanreotide is a long-acting somatostatin analogue, which is administered every 28 days and has been shown to improve glycemic control in children with HI. We describe a single center's experience with the use of lanreotide to treat congenital HI.

**Methods:** We conducted a retrospective chart review of patients with HI treated with lanreotide at the Children's Hospital of Philadelphia

**Results:** Between June 2015 and December 2016, 18 children (10M) with HI initiated therapy with lanreotide. Fourteen children had mutations in the  $K_{ATP}$  channel genes, 1 had Beckwith Wiedemann syndrome and 3 had no mutations identified. Nine children (50%) had a history of near-total pancreatectomy (n=7) or partial pancreatectomy (n=2). The median age at initiation of lanreotide was 2.3 yrs (1-7.6 yrs).

At initiation of lanreotide, medical therapy included: octreotide and overnight enteral dextrose (n=16); octreotide, diazoxide and overnight enteral dextrose (n=1); diazoxide (n=1). Initial lanreotide dosing was 30 mg (n=10); 60 mg (n=7); 90 mg (n=1). Twelve patients (71%) were able to discontinue octreotide and 6 (35%) were able to discontinue enteral dextrose. Five children are treated with lanreotide alone, 7 with lanreotide and overnight enteral dextrose and 1 with lanreotide and diazoxide. Five subjects failed to respond to lanreotide and discontinued treatment. Side effects included irritation at the injection site (n=2) and headaches (n=1).

**Conclusions:** Lanreotide provides convenient and effective treatment for children with HI. The majority of children were able to transition from multiple daily octreotide injections to monthly lanreotide. Future studies are needed to determine protocols for transition from octreotide to lanreotide and to identify risk factors for lanreotide failure.

P1-511

#### REDUCING ERRORS IN HYPOGLYCAEMIC SCREENS IN A TERTIARY NEONATAL INTENSIVE CARE UNIT - OPTIMISING THE SYSTEM

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**Objectives:** Neonatal hypoglycaemia is a common physiological phenomenon in the first days of life. However, persistent hypoglycaemia requires investigation. A hypoglycaemic screen ("critical sample") taken during spontaneous hypoglycaemia can diagnose underlying endocrine or metabolic conditions. However, resource limitations and educational deficits compromise the speed and accuracy with which these critical samples are taken. We designed a quality improvement project to optimise the system underlying the critical sampling process, aiming to reduce the number of errors associated with hypoglycaemic screens in our NICU from 100% to 50% over six months.

**Methods:** A series of "Plan, Do, Study, Act" (PDSA) cycles guided the project. The first cycle involved process mapping to understand the system of critical sampling. In the second cycle, a retrospective audit was performed of critical samples taken between August 2014 and December 2016. A Pareto diagram was then constructed to identify key areas of improvement. The third cycle is ongoing and measures the impact of these changes over time using re-audit and run charts. Data analysis utilised SPSS software.

**Results:** Process mapping revealed the critical sampling process to be multidisciplinary, involving doctors, nurses, biochemists, and lab technicians. Our audit demonstrated that 257 errors had been made in 45 critical samples performed on 36 patients over a 53-month period. The Pareto diagram revealed major contributing errors to be:

- A delay in receiving results > 1 week (Median time until formal reports available 22 days (7-239))

- Incomplete hypoglycaemic screens (97.8% (n=44) of screens)
- A delay >15 minutes from low point-of-care blood glucose to time of critical sample (Median time 45 minutes (1 minute - 5 hours))

Other significant issues stemmed from haemolysed samples (22.2% of all screens), insufficient samples (77.8% of all screens), or incorrectly timed samples (40% of all samples).

**Conclusions:** Improvement efforts targeting key areas were implemented:

- Standardised checklist to record results
- Hypoglycaemic "packs", containing blood bottles numbered in order of priority
- Guidelines on timing of hypoglycaemic screens
- Educational session for neonatal team

P1-512

#### 18F-DOPA MANUFACTURED BY A MODIFIED ONE POT METHOD IS OF HIGH ENOUGH SPECIFIC ACTIVITY TO PRODUCE QUALITY IMAGES OF THE PANCREAS WHEN INJECTED UP TO 6 HOURS POST MANUFACTURE.

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**Objectives:** PET imaging with 18F-DOPA is the only currently effective available imaging technique in patients with CHI. Most centers throughout the world manufacture the 18F-DOPA in close proximity to the imaging center because 18F-DOPA has a short half-life of 110 minutes. We report our experience with a novel nucleophilic manufacturing process that allows us to inject between 4-6 hours after end of synthesis (EOS). The aim of this study is to determine if we could generate high quality images of the pancreas using 18F-DOPA with a higher specific activity (SA) that is manufactured at a distance of 200 miles away and injected 4-6 hours later.

**Methods:** We modified a previously reported one pot technique to manufacture 18F-DOPA. Two doses of 18 F-DOPA designed to be injected at 30 minutes apart were shipped. A dose of 0.12-0.16 mCi/kg was administered IV and the patients had a low dose attenuation CT, followed by 10 minute PET scans at 20, 30, 40, and 50 minutes with a contrast CT between the 30 and 40 minute scans. The 18F-DOPA was manufactured and administered under an IND held by the PI.

**Results:** 33 patients underwent the 18F-DOPA PET CT. All 33 images were good quality exams. The mean SA at EOS was 259.2 mCi/mg DOPA. The mean SA at the time of injection

was 41.4 mCi/mg DOPA. The mean injection time from EOS was 292.5 minutes. The total synthesis time was about 120 minutes, the radiochemical yields of 18F-FDOPA produced were about 10±7%. The radiochemical and enantiomeric purities were about 98±2%. 26 of 33 patients went to surgery. There were 15 focal surgeries, 13/14 of which were cured with minimal pancreatectomy. One had persistent hypoglycemia despite removal of head and pancreatico-jejunosomy. Overall, focal surgery had a 93% cure rate. There were two LINE surgeries performed. Both patients were cured with pancreatectomy of 30-50%. Six patients had diffuse surgery with hypoglycemia post 98% pancreatectomy. There were 3 patients with atypical focal surgeries who also had hypoglycemia post-op with 50-98% pancreatectomy.

**Conclusions:** This modified novel production method of 18F-DOPA results in a product with higher specific activity which allows it to be transported by ground up to 200 miles and injected up to 6 hours after EOS and results in excellent quality images.

P1-513

#### IMPACT OF 2015 PES GUIDELINES ON CLINICAL FEATURES OF NEONATAL HYPOGLYCEMIA

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**Objectives:** After the 2015 Pediatric Endocrine Society (PES) recommendations for evaluation of hypoglycemia in neonates, infants and children, our Department of Pediatrics revised its protocol for evaluating persistent hypoglycemia in neonates ≥72 hours of age. Previously, a glucose of >2.6 mmol/L (47 mg/dL) was the target at any age. The new protocol stated that a glucose of <3.3mmol/L (60 mg/dL) at ≥72 hours of age would trigger a critical sample and consult to Pediatric Endocrinology.

The primary objective of this study was to determine if there was a significant increase in the number of consults to Pediatric Endocrinology post-protocol implementation. Our secondary objectives were to evaluate the etiologies of persistent hypoglycemia, and the number of infants requiring treatment for hyperinsulinemia. Other variables collected were: gestational age, sex, age at presentation, presenting signs, maternal hypertension and lifestyle, consanguinity, anthropometric data, critical lab values, dextrose requirements, presence of genetic syndromes, and length and type of treatment.

**Methods:** A retrospective chart review was conducted for all consults to Pediatric Endocrinology for neonatal hypoglycemia from November 2012 to October 2016 at our two tertiary care centers. All referrals for hypoglycemic infants included with no exclusion criteria.

**Results:** Sixty percent of consults (33/56) occurred after implementation of the new protocol (in the last 12 of 48 mo.), a statistically significant increase over time. Mean age of infants was 8.2 days and half were IUGR (27/54). Approximately 80% were males (44/56). Half (27/54) of

mothers reported smoking in pregnancy. The average blood glucose at ≥72 hours of age was 2.8 mmol/L (50.5mg/dL). Hyperinsulinemia was the most common etiology for hypoglycemia (51/56 infants). Diazoxide treatment was utilized in more than 50% (26/56) of infants, with an average length of treatment of 95 days (range 5-219). Two infants developed pulmonary hypertension with diazoxide.

**Conclusions:** There has been an increase in the number of consults to Endocrinology since implementation of PES guidelines. Hyperinsulinemia is the most common cause of hypoglycemia with significant proportions requiring treatment with diazoxide.

P1-514

#### GLYCATED ALBUMIN LEVEL DURING LATE PREGNANCY AS A PREDICTIVE FACTOR FOR NEONATAL OUTCOMES OF WOMEN WITH DIABETES

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**Objectives:** Investigate association between glycated albumin in diabetic mothers and complications in their children, and determine glycated albumin cut-off values for predicting complications in infants

**Methods:** This hospital based case control study involved Japanese 71 mothers with diabetes and their children. The mean glycated albumin of mothers were compared between mothers of infants with complications and those without complications. Receiver operating characteristic analysis was conducted to set the glycated albumin cut-off values with respect to complications of infants. The relation between glycated albumin and the numbers of complications of infants was investigated by Pearson's correlation coefficient.

**Results:** Glycated albumin was significantly higher in mothers of infants with hypoglycemia ( $15.8 \pm 3.2$  vs.  $12.6 \pm 1.2\%$ ,  $p < 0.001$ ), respiratory disorders ( $15.7 \pm 3.6$  vs.  $12.9 \pm 1.9\%$ ,  $p < 0.001$ ), hypocalcemia ( $15.9 \pm 3.7$  vs.  $13.1 \pm 1.8\%$ ,  $p < 0.001$ ), polycythemia ( $15.7 \pm 2.3$  vs.  $13.8 \pm 2.1\%$ ,  $p = 0.009$ ), myocardial hypertrophy ( $16.1 \pm 3.7$  vs.  $13.1 \pm 2.3\%$ ,  $p < 0.001$ ), and large-for-date status ( $15.8 \pm 2.4$  vs.  $13.7 \pm 3.1\%$ ,  $p = 0.006$ ). The cut-off values of glycated albumin were as follows: hypoglycemia (13.6%), respiratory disorders (13.9%), hypocalcemia (14.2%), polycythemia (14.5%), large-for-date status (14.7%), myocardial hypertrophy (14.2%). Glycated albumin showed significant a positive correlation with the numbers of complications of infants ( $r=0.704$ , 95%CI: 0.579-0.797,  $p<0.001$ ).

**Conclusions:** Glycated albumin is useful for considering pregnancy outcome of mothers with diabetes during pregnancy. To keep glycated albumin lower is important to prevent complications in infants. The relationship between glycated albumin and the numbers of complications of infants was strong.

**RELATIONS OF BIRTH HEAD CIRCUMFERENCE / BIRTH CHEST CIRCUMFERENCE RATIO TO CIRCULATING INSULIN-LIKE GROWTH FACTOR-I IN THE NOT-LIFE-THREATENED NEWBORN: ROLE OF BIRTHWEIGHT AFTER CONTROLLING FOR THE PRESENCE OF PRETERM BIRTH, RESPIRATORY SUPPORT MEASURES AND FOR CALORIC INTAKE**

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**Objectives:** The ratio of birth head circumference(HC) to birth chest circumference(CC)(HC through CC, HC/CC) is related to birth gestation age(GA) in the human newborn(NWB). We intended to evaluate the relevance of birthweight(BW) to correlations of HC/CC with blood serum Insulin-like Growth Factor-I(IG1) after control for gender(SEX), preterm birth(birth at  $\leq 36$  completed weeks GA; PTB) postnatal age(PNA), respiratory oxygen supplementation(O2S), assisted ventilation of any kind (AV) and caloric intake(KT) in not-life-threatened NWBs.

**Methods:** NWBs with any among total parenteral nutrition, life-threatening disease, diabetes mellitus(DM), endocrine diagnosis out of DM, malformation, clinically relevant trunk trauma, and mother with DM were excluded. Each of 78 included NWBs had available data for: 1) SEX, GA(range=28-42 completed weeks), BW(range=1200-4150g), HC(range=27.0-36.0cm), CC(range=22.0-39.0cm), HC/CC(range=0.82-1.28cm/cm) and BW $\leq$ 10th centile for GA(SGA) and 2) same-day records at one of the first 5 postnatal days(x), 5 days after x(y) and 10 days after x(z) for PNA(unit:day), O2S, AV, KT(as KCal/kg/24h or, for PNA $<$ 24h, KCal/kg/PNA) and IG1 RIA measurements(unit:uM/dl)(male SEX, n, 43; PTB, n, 46; SGA, n, 20; O2S, n, x=22, y=11, z=1; AV, n, x=8, y=4, z=1). Natural-log-transformed IG1(IG1-LN) was near-normally distributed. Multiple Linear regression(MLR) was used to predict IG1-LN at x-y-z(computations; male SEX, PTB, O2S, AV, condition present=1, condition absent=0).

**Results:** MLR showed 1) a significant partial correlation(PC) coefficient(r) of HC/CC PCs with outcome IG1-LN at x-y when including together as predictors O2S-AV-KT-PNA chronologically corresponding to IG1-LN, as well as SEX, PTB and HC/CC(HC/CC vs IG1-LN; x,  $r=-.240$ ,  $p=.0422$ ; y,  $r=-.255$ ,  $p=.0305$ ) but 2) no significant HC/CC PC with outcome IG1-LN when including together as predictors O2S-AV-KT-PNA chronologically corresponding to IG1-LN, as well as SEX, PTB,

HC/CC and BW(each considered MLR model was significant; MLR R2 range=.27-.55).

**Conclusions:** BW could be involved in negative HC/CC relations to IG1-LN not explained by SEX, PTB, PNA, O2S, AV and KT in the not-life-threatened NWB.

**TRANSIENT HYPERINSULINISM IN INFANCY : A SINGLE CENTER EXPERIENCE**

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**Objectives:** Transient hyperinsulinism (THI) can occur without underlying genetic defects and may be associated with perinatal stress. However, limited information on the clinical characteristics in this group is available. The objective of this study is to describe the clinical characteristics and natural history on infants with THI in a single institute.

**Methods:** The records of all infants diagnosed with 'hyperinsulinism' (HI) in our unit between 2006 and 2015 were retrospectively reviewed. HI was diagnosed if infants had hypoketotic hypoglycemia concomitant with high plasma insulin and required high intravenous glucose infusion rate (IV GIR) of  $>8$  mg/kg/min. Those with transient, diazoxide-responsive HI were included, while those with maternal gestational diabetes and underlying genetic conditions were excluded.

**Results:** Thirty-two patients were included (Male: Female = 27: 5). Mean gestation age was  $38.1 \pm 1.9$  weeks. Birth weight percentile was  $16.0 \pm 28.9$ th and 72% were small for gestation age. There was no apparent perinatal stress, including maternal pre-eclampsia, fetal distress, sepsis or chorioamnionitis in 14 patients. Mean age and blood glucose at presentation were 3.0 days and 1.6mmol/L correspondingly. Most were discovered during routine blood glucose monitoring (n = 21), while some presented with seizure (n = 4) or other non-specific symptoms (n = 7). Mean IV GIR was 14.2mg/kg/min. Diazoxide and hydrochlorothiazide was started at a mean age of 11.9 days, at 14.2mg/kg/day and 2.9mg/kg/day respectively. Hyponatremia was observed in 24 patients and 12 required oral sodium supplements. No other side effect was observed. Diazoxide was stopped at a mean age of 11.8 months. Mean age at last follow-up was 5.0 years. Two had autistic spectrum disorder and one had developmental coordination disorder. Others had normal development.

**Conclusions:** While perinatal stress was described to be associated with THI, it was not apparent in most patients in this cohort. Hyponatremia was a common side effect and serum sodium should be monitored after initiation of medical treatment. THI resolved mostly before the age of two years. Some were observed to have developmental issues. Regular follow-up on their developmental outcome is necessary.

**SALIVARY CORTISOL IN LATE PRE-TERM INFANTS**

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**Objectives:** Salivary cortisol is a non-invasive, easy to collect and cost effective marker of HPA axis function and stress.

Limited data exist on salivary cortisol values in pre-term infants. As part of studies (including a crossover randomized controlled trial on the impact of silence or empathetic vocal soothing on infant stress) we obtained salivary cortisol results, adding to normative data.

**Methods:** We studied healthy 32-35 week gestation infants between days 5 and 10. Heelsticks were for bilirubin or glucose monitoring. Salivary cortisol samples were collected using a Salivette™ swab in the infant's mouth for 3 minutes and measured by in-house ELISA (intra-/inter- assay CV 7.6%/8.6%), requiring >50 µL saliva. In pilot studies we determined saliva volumes with/without a stimulant and non-interference of the stimulant with the assay. In the main study 50 infants were studied in each condition on 2 separate days at 3 timepoints: before the heelstick, at 20 mins (peak) and at 50 mins (recovery).

**Results:** In pilot studies, saliva volumes were too low without stimulant use in all but 2 subjects. One drop of 5% citric acid solution improved saliva volume significantly (150±99.5 vs 76±31.4 µL, p=0.043) with no difference in cortisol values in 8 adult volunteers when samples were collected with/without stimulant.

Cortisol levels from the main study are reported in the table. Baseline values on the 2 days did not correlate significantly (r=0.05,p=0.77).

Table: Salivary cortisol results (nmol/L)

	Baseline	Day 1 Peak	Recovery
Minimum	11	11	8
25 <sup>th</sup> centile	14	18	17
<b>Median</b>	<b>24</b>	<b>28.5</b>	<b>27</b>
75 <sup>th</sup> centile	52.3	41.5	46
Maximum	199	506	119

**Conclusions:** Salivary cortisol is a useful non-invasive measure of the HPA axis and stress in late pre-term infants. Care with sample collection and a non-interfering salivary stimulant are required at this gestation. These normative salivary cortisol values in late pre-term infants, at baseline and following a painful procedure, indicate substantial intra-individual variability.

**CO-INHERITANCE OF DOMINANT AND RECESSIVE ABCC8 MUTATIONS IN A CASE OF FAMILIAL CONGENITAL HYPERINSULINISM (CHI):- MOLECULAR AND FUNCTIONAL STUDIES.**

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**Objectives:** A male with CHI was born to an unaffected mother. His father had CHI with incomplete diazoxide response in infancy, then maintained on diazoxide (ceased at 7 years). The neonate had intensive medical support, a more severe phenotype, less diazoxide response (ceased due to pulmonary hypertension) and required surgery (diffuse disease).

Objective (i) Molecular analysis: *ABCC8*, *KCNJ11*; (ii) Functional studies of likely pathogenic variants

**Methods:** (i) Targeted massively parallel sequencing with Sanger sequencing confirmation (ii) COSm6 cells (green monkey kidney) transfected with wild type (WT) SUR1 and WT Kir6.2, or mutant SUR1 and WT Kir6.2. Western blots to assess SUR1 protein expression with processing efficiency estimated by core- and complex-glycosylated bands. Inside-out patch-clamp recording assessed channel gating properties (MgADP stimulation).

**Results:** (i) Two heterozygous *ABCC8* variants were detected. A paternal *ABCC8* missense variant (c.4532T>C, p.Ile1511Thr) was predicted to have potentially damaging functional effects (previously reported monoallelic variant in diazoxide-responsive diffuse CHI). A maternal *ABCC8* nonsense variant (c.742C>T, p.Arg248\*) resulting in a premature stop codon was predicted to have loss of function (previously reported recessive variant in diffuse CHI).

(ii) I1511T SUR1: reduced protein bands compared to WT SUR1. R248\* SUR1: no protein bands.

Paternal (I1511T SUR1 co-expressed with WT SUR1 at 1:1 molar ratio; with Kir6.2): SUR1 bands similar intensity to WT SUR1. Maternal (R248\* SUR1 with WT SUR1): reduced SUR1 bands. Proband: (I1511T SUR1 with R248\* SUR1): reduced SUR1 bands.

I1511T channels: reduced MgADP response. R248\* channels: no detectable channel activity. I1511T and R248\* channels: little MgADP response.

**Conclusions:** Paternal mutation reduces channel function (reducing expression and MgADP response), predicting a dominant-negative effect. Maternal mutation affects WT allele expression, but residual WT channels reaching the cell surface respond to MgADP, hence mother clinically unaffected. The proband likely had an additive effect: maternal truncation mutation does not make it into the channel; paternal allele, although expressed, has lower maturation efficiency and reduced MgADP response compared to WT allele.

### DIAZOXIDE-RESPONSIVE HYPERINSULINISM ASSOCIATED WITH NEUROBLASTOMA

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**Objectives:** Neuroblastoma-associated paraneoplastic syndromes include opsoclonus myoclonus syndrome or secretion of vasoactive intestinal peptide. Excess secretion of insulin is uncommon although the association of hyperinsulinism and neuroblastoma has been reported in the setting of Beckwith Weidemann syndrome (BWS) and described in other cases as a type of complex neurocristopathy with associated nesidioblastosis. We describe a case of hyperinsulinism associated with neuroblastoma, with negative genetic testing for both BWS and congenital hyperinsulinism.

**Methods:** Non applicable

**Results:** Our patient presented at 2 months of age with abdominal distension, hepatomegaly and elevated urine VMA and HVA. Further work up led to the diagnosis of neuroblastoma stage 4S and chemotherapy was initiated. Hypoglycemia initially occurred during hospital admission after an 8.5 hour fast with a glucose level of 37 mg/dL. He required a glucose infusion rate (GIR) of 10.2 mg/kg/min to maintain euglycemia. Biochemical markers showed non-ketotic hyperinsulinism with insulin level of 10 mU/L and Beta-hydroxybutyrate

**Conclusions:** To our knowledge, this is the first reported case of neuroblastoma and hyperinsulinism presenting at two months of age and responsive to diazoxide therapy. This atypical presentation of hyperinsulinism and neuroblastoma, along with negative genetic testing, indicates that the underlying association requires further investigation.

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### CONTINUOUS GLUCOSE MONITORING IN POST-OPERATIVE MANAGEMENT OF CONGENITAL HYPERINSULINISM

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**Objectives:** Congenital Hyperinsulinism (CHI) is the leading cause of severe, persistent hypoglycemia in newborns. CHI due to KATP channel mutations is particularly severe and in the case of diffuse disease, requires subtotal pancreatectomy. Post-operatively, only 25% of patients are considered "cured", with 50% remaining hypoglycemic and 25% developing diabetes. Close monitoring of blood glucose (BG) levels is necessary to detect glycemic fluctuations due to dysregulated insulin secretion from residual pancreatic tissue. Using periodic point of care (POC) BG is the standard

of care to monitor glycemic control; however, glycemic variability may be unrecognized with infrequent measurements.

**Methods:** We report a case series of 3 term infants (2 males, 1 female) with diffuse CHI due to ABCC8 mutations, requiring near total pancreatectomies whose post-operative management was guided by the use of continuous glucose monitoring (CGM).

**Results:** In case 1 and 2, consistent patterns of hypoglycemia identified on CGM directed both octreotide initiation and dose titration. CGM trends also led to the recognition of tachyphylaxis and the discontinuation of octreotide. To achieve and maintain euglycemia, CGM was utilized to adjust continuous enteral glucose infusion rates and timing. In case 3, we identified initial pre-prandial hypoglycemia and then persistent post-prandial hyperglycemia with CGM, which re-directed management from octreotide injections to introducing insulin therapy. Without CGM, persistent hypoglycemic or hyperglycemic episodes may have gone unrecognized, delaying changes in medical management.

**Conclusions:** Management of CHI is challenging as patients have chaotic insulin secretion leading to unpredictable glycemic control, which is particularly critical for neurocognitive outcomes in developing infants. Our experience demonstrates the tremendous potential of CGM for both acute and long term management. CGM was used to identify individual glucose trends that otherwise would not be easily recognized with standard POC BG monitoring. This ultimately led to personalized medical management. Our case series highlights the need for larger studies to optimize the use of CGM in post-operative management of CHI.

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### LONG ACTING OCTREOTIDE AND NEONATAL CONGENITAL HYPERINSULINISM

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**Objectives:** Congenital hyperinsulinism is a rare inherited disease. Its incidence is estimated 1 in 50000 newborns. It's a major cause of persistent hyperinsulinimic hypoglycemia of infancy. This inappropriate oversecretion of insulin from pancreatic beta-cells induces severe and irreversible brain damage. Therefore, an aggressive treatment to prevent neurologic damage is required. In our report, we give prominence to the role of long acting octreotide in the treatment options of congenital hyperinsulinism. Respectively, we described and followed a case of severe hypoglycemia in a newborn over a period of 9 years.

**Methods:** A 32 gestational week boy was admitted to the NICU for respiratory distress with a glycemia of 0 mg/dl in the first hour of life. A progressive oral feeding and intravenous infusion of glucose up to a 25 mg/kg/min was administered, but he remained hypoglycemic. Glucagon and hydrocortisone infusion were required. During hypoglycemic episodes, the highest documented insulin level was 82.8 microU/ml. Thus, a



neonatal congenital hyperinsulinism was confirmed whereas metabolic diseases, hypopituitarism, GH and cortisol deficiency were eliminated.

**Results:** After 45 days of hospitalization, our patient was discharged home on diazoxide 15 mg/kg/day and octreotide 50 microg/kg/day. He had a regular medical monitoring and adjustment of the treatment dosing. At the age of 6 months, genetic studies revealed a mutation of the gene ABCC8; the same mutation was identified in his father. Pet-scan showed a diffused form of hyperinsulinism. Diazoxide was discontinued due to its multiple side effects, and only octreotide remained at 57 microg/kg/day. At 2 years of age, we switched to octreotide long acting 20 mg every 3 weeks. Currently our patient is receiving the same dose every 7 weeks.

**Conclusions:** In conclusion, congenital hyperinsulinism is a heterogeneous disorder. The response to pharmacologic therapy is variable. To the best of our knowledge, neonates with autosomal recessive mutations respond most likely to surgical therapy than to pharmacologic and dietary therapy. However in our case, long acting octreotide therapy was successful and our patient maintained a normal psychomotor development.

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#### RECURRENT HYPOGLYCEMIA IN TODDLER WITH BETA-BLOCKERS THERAPY

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**Objectives:** Hypoglycemia is a well-known side effect of propranolol. However, it seems to rarely be associated with severe and recurrent hypoglycemia in older children. We describe the case of a girl presenting with atypical features of propranolol associated hypoglycemia.

**Methods:** A four year old girl experienced four episodes of severe hypoglycemia. She was born from an uneventful pregnancy and diagnosed with permanent junctional reciprocating tachycardia on her first day of life. She was started on propranolol, digoxin and amiodarone. She first presented to us at 20 months of age with altered level of consciousness following a viral episode. Her serum glucose was 1.3mmol/l at that time. Between the ages of 3 to 4 years, she presented three episodes of morning seizures. Each time she was found to have serum glucose around 1mmol/l. Notably only one of these episodes was associated with diminished food intake the night before. Her physical exam revealed short stature. On investigation, the critical sample showed an appropriately elevated cortisol and GH level, an appropriately suppressed insulin and normal metabolic work up with only mildly elevated ketones. She didn't respond to glucagon challenge, but each episode responded rapidly to glucose boluses. Between the episodes, glucose monitoring was normal, even on CGM for five days. She had no other episode of hypoglycemia for the past 1 1/2 year.

**Results:** Propranolol is a non-selective beta adrenergic blocking agent. It blunts the adrenergic response which is normally induced by low glucose level therefore promoting hypoglycemia. Those hypoglycemic episodes are generally associated with prolonged fasting periods and ketosis which was not the case of our patient.

**Conclusions:** This case illustrates the high risk of beta blocker associated hypoglycemia in a patient considered low risk. It also emphasizes unusual associated features such as low ketones production.

P1-523

#### AN UNUSUAL CASE OF FOCAL CONGENITAL HYPERINSULINISM

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**Objectives:** Congenital Hyperinsulinism (CHI) is a heterogeneous condition caused by dysregulation of insulin secretion. Mutations in *ABCC8* and *KCNJ11* are the most common cause of CHI. Focal CHI (CHI-F) involves the inheritance of a paternal *ABCC8/KCNJ11* mutation and somatic loss of the maternal chromosome in the 11p15 allele. CHI-F is limited to a small area of the pancreas and is generally cured after selective lesionectomy.

**Methods:** We investigated focal CHI by initial genetic analysis, followed by 18 F DOPA PET-CT scanning and pancreatic tissue analysis to understand the pathophysiology of focal CHI.

**Results:** Our patient presented with hypoglycaemic seizures in the first day of life and CHI was subsequently confirmed. She showed partial response to diazoxide and was managed with continuous octreotide infusion as well as oral diazoxide. She was found to be negative for the known genetic mutations associated with CHI and was transferred to our centre for 18 F FOPA PET-CT scan at the age of 2.8 years. 18 F DOPA PET-CT showed a possible focal lesion in the tail of the pancreas.

Histopathology following partial pancreatectomy showed abnormal increase in islet tissue within the lesion, interspersed with normal exocrine pancreas. Analysis of pancreatic tissue from the lesion showed maternal loss of heterozygosity (LOH) at the 11p15 locus. In vitro studies showed that 0.1 mM diazoxide inhibited 20mM glucose induced secretion and insulin release initiated by 10 mM leucine. Following the surgical procedure the patient was initially hyperglycaemic for 48 hours and then returned to euglycaemia, thereby achieving cure.

**Conclusions:** Our case represents deviation from the paradigm of focal CHI due to paternally inherited

heterozygous mutations in *ABCC8/KCNJ11*. Pancreatic LOH confirmed the mechanism of focal CHI in the absence of mutations identified in the peripheral blood DNA analysis. In CHI patients with persistent need for medical treatment but without mutations in *ABCC8/KCNJ11*, it is important to perform 18F DOPA- PET-CT scan to exclude or detect a possible focal lesion that could potentially be cured with selective lesionectomy. Our case may represent an alternative mechanism for focal CHI which needs to be replicated in other cohorts.

P1-524

**A MATERNAL ANTIBODY (AB) CAUSING FALSE POSITIVE NEWBORN SCREENING (NBS) RESULTS FOR CONGENITAL HYPOTHYROIDISM (CH)**

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**Objectives:** NBS programs for CH have existed for over 40 years. NBS methods include primary TSH, primary T4, or combination screening. The assays used are immunoassays, employing two different Abs: capture and label. TSH bridges the two Abs causing a quantifiable result. Assays are subject to interference from both heterophile and anti-thyroid hormone Abs, and are transferable to a NB from the mother during pregnancy. Assays using different Abs, capture and detection systems, may be affected by other interfering substances and Abs.

**Methods:** An infant was born to a mother with no history of thyroid disease. The NBS lab reported a TSH >555 IU/L and tT4 of 10 mcg/dl. Repeat labs, via Siemens Vista assay confirmed a TSH >500 IU/L but a normal fT4 of 1.99 ng/dl. The baby was started on L-T4. Imaging revealed a normal appearing gland, normal uptake, and a normal position. Due to the lack of correlation between imaging and labs, a Siemens Centaur chemiluminescence assay was performed and reported a TSH of 23 IU/L and fT4 of 11.7 mcg/dl. L-T4 was discontinued, and a maternally transferred Ab was postulated.

**Results:** See Tables: Testing of maternal serum via Siemens Vista assay 2 weeks post partum revealed a TSH of 178 IU/L and fT4 of 0.72 ng/dl. Siemens Centaur assay noted a near normal TSH of 7.3 IU/L. No anti-thyroid or anti-TSH receptor antibodies were present in either mother or NB. Neither the mother nor NB's samples showed linear dilution; treatment to remove HAMA did not restore dilutional linearity.

**Conclusions:** While TSH assays are generally reproducible, and not routinely subject to interference from competing substances, there are rare reports of heterophile or HAMA Abs interfering with TSH assays. The discordant TSH values from the various assays are consistent with a yet to be identified circulating Ab. As NBS relies on whole blood assays,

there is a theoretic increase in the likelihood for interfering substances to affect the assay. One additional case from an unrelated adult is being investigated. In the patient described, neither the T4 level nor the results of imaging were consistent with the markedly elevated TSH; an alternative explanation was considered and discovered, reminding the clinician to always consider the whole clinical picture when evaluating a laboratory finding.

TABLE:

1: Infant Lab Results

Age TSH Assay	NBS Perkin-Elmer Neonatal TSH	DOL 6 Siemens VISTA	DOL 20 Siemens CENTAUR	1 month Roche ELECSYS	2 months Siemen CENTAUR	3 months Siemen CENTAUR	3.5 months Siemens CENTAUR (on L-T4)
TSH (IU/L)	>555	>500	23	332.6	22	21	6.8
Free T4 (ng/dl)	10	1.99	--	1.22	--	0.92	1.0
Total T4 (mcg/dl)	--	17.7	11.7	--	--	11.4	12.2
Total T3 (ng/dl)	--	126	180	--	--	--	--

2: Maternal Lab Results

Time Postpartum Assay	5 weeks Siemens VISTA	5.5 weeks Siemens CENTAUR	4 months Siemens CENTAUR
TSH (IU/L)	178	7.3	10
Free T4 (ng/dl)	0.72	0.88	0.77
Total T4 (mcg/dl)	6.9	--	5.3

P1-525

**A NEWBORN WITH DIABETES MELLITUS**

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**Objectives:** Neonatal diabetes mellitus is a rare condition affecting approximately 1 in 300,000-500,000 live births. It can be classified into transient and permanent types, depending on the duration of initial insulin requirement.

**Methods:** We reported a case of transient neonatal diabetes mellitus.

**Results:** A baby girl was born at 38 weeks weighing 2.2 kg. She was first-born of non-consanguineous parents. Antenatal course was uneventful, and there was no family history of diabetes mellitus. She was found to have non-ketotic hyperglycemia shortly after birth. She has no facial dysmorphism, skeletal anomalies, kidney diseases, cardiac defects, nor epilepsy. Investigations showed insulin <2.5 mIU/L and C-peptide 0.2 microgram/L while plasma glucose was 25.1 mmol/L. Anti-islet cell antibody was negative. Rapid-acting insulin infusion was started on day 1 up to 0.004 unit/kg/hour, and was successfully weaned off on day 4. Blood glucose ranged 5.4-11.9 mmol/L at glucose load of 8.4 mg/kg/minute. However, blood glucose rose to 19.4 mmol/L again on day 11, requiring resumption of insulin infusion at 0.0009 unit/kg/hour. Breast feeding was started while glycemia control was stable with insulin infusion. Route of insulin administration was changed to subcutaneous on day 13. Diluted insulin detemir was started at 0.04 unit twice daily (~0.04 unit/kg/day). Glycemic control was suboptimal with blood glucose ranged 16.8-23.5 mmol/L. Diluted insulin

detemir was gradually stepped up to 0.14 unit every 8 hourly (~0.15 unit/kg/day). Blood glucose was successfully controlled at 4.8-10.3 mmol/L without hypoglycemia. Insulin was gradually titrated down since day 35, and successfully weaned off on day 48. Repeated testing after weaning off insulin found C-peptide of 0.5 microgram/L. Blood glucose was well controlled between 4.3-9.4 mmol/L, and baby was discharged on day 57. Mutational analysis showed a methylation defect in 6q24 locus due to paternal uniparental disomy.

**Conclusions:** Transient neonatal diabetes mellitus is a rare imprinting disease due to over-expression of 6q24 with paternal expression. The initial hyperglycemic phase was successfully managed with subcutaneous diluted insulin analog. Although the condition went into remission, it might recur later in life.

P1-526

**NEONATAL DIABETES : MUTATION ANALYSIS, ROLE OF ORAL SULFONYLUREAS AND OUTCOME**

*Garima Chawla , MD, Sir GangaRam Hospital , New Delhi, India; Vasundhara Chugh, MD, Sir Ganga Ram hospital , New Delhi , India; Archana Arya, DO, Sir Ganga Ram Hospital, New Delhi., New Delhi, India*

**Objectives:** Neonatal diabetes(NDM) has an incidence of 1: 200000 to 1: 400000. Sulfonylurea therapy proves to be an effective measure to achieve euglycemic status and thereby reduce the insulin requirement and improve the quality of life in the affected infants. Objective of our case series is to lay emphasis on genetic testing for this rare entity thereby, introducing oral sulfonylureas, replacing insulin injections wherever possible and improving the quality of life of young infants.

**Methods:** We report herein ten cases of neonatal diabetes being treated at Sir Ganga Ram Hospital, a tertiary care hospital in Northern India.

All ten patients had onset of hyperglycemia within first 6 months of life. Five patients had diabetic ketoacidosis(DKA) at presentation. Blood sample for genetic mutation was sent in nine out of ten patients.

**Results:** Two patients showed mutation in KCNJ11 gene and two patients had mutation in ABCC8 gene. In these four patients insulin was stopped and euglycemia was achieved with glibenclamide alone. One patient had insulin (INS) gene mutation and is being treated with isophane insulin. In rest of the four patients, no common mutation was detected. Three patients had transient neonatal diabetes and are maintaining euglycemia without any medication. One female patient in whom mutation was not detected has positive tissue transglutaminase antibody, thyroid peroxidase antibody but negative GAD 65 and Islet cell antibodies and is receiving insulin injections to maintain euglycemia. One patient had Sensorineural deafness & Megaloblastic anaemia along with diabetes at 6 months of age. Multiple

system involvement may be present depending upon the gene mutation. Cases have been summarized in the attached table.

**Conclusions:** Neonatal Diabetes, though rare, should be kept in mind while dealing with infantile onset diabetes mellitus. Molecular understanding helps in switching over the treatment from insulin to sulfonylureas. Mutation can be detected in 82% of the cases. Prognosis depends upon early recognition and treatment , severity of the disease, associated malformations and metabolic control. Pharmacogenomic approach improves in a tremendous way the quality of life of the young diabetic patients.

Seria I No	Age at Diagnosis and Sex	Age of presentation to our clinic	Birth weight and associated anomalies	Developmental delay and associated anomalies	DKA at diagnosis	Family History	Genetic Mutation	Antibody profile	Insulin +/-or Glibenclamide
1.	2month/ M	3mth	34wk, 1.130kg SGA	Hyothyroid No ism Grade 3-4 VUR	No	Pat gm	Mutation not tested	Gad65, Insulin, islet cell No	Transient NDM Negative treatment ongoing
2.	3months/ M	3.5mth	3.15kg AGA	None	Yes	Father	heterozygosity for a novel missense mutation , L213P in exon 5 of the ABCC8 gene	Gad65, Insulin, de at islet cell 0.3mg/kg/d negative ay	Insulin stopped at 3y11m
3	3 days/ F	6y1m	1.9kg SGA	None	No	Mother, mat gf, mat gm, mataunt, pat aunt and uncle	heterozygous for a NA missense mutation, R201H, in the KCNJ11 gene.	Glibenclamide at 0.24mg/kg/ day Ins stopped at 11mth	
4	5 month/ F	5mth	2.35kg SGA	Seizure episode, Milestones normal	Yes	Mat gf	heterozygous mutation c.601 C>T[Arg201Cys] in KCNJ11 gene in the proband	Ins and GAD 65 de at negative 0.1mg/kg/d ay	Glibenclamide at 0.1mg/kg/d
5	2month/ F	2mth 8days	1.8kg 36wk AGA Consanguin ous	None	Yes	pat gf, pat gm	novel homozygous intron mutation c.187+5G>C(IVS 2+5G>C) in INS gene.	Gad65, Isophane Islet cell Insulin a/b negative	
6	4 days/ M	1.5mth	1.4kg IUGR	None	No	Pat GM, Mat GP, Mat aunts	No mutation detected Methylation: normal	NA	Transient NDM No treatment ongoing
7	3month/ F	3 month	2.55kg, AGA, non consanguin ous	None	Yes		Heterozygous for two previously reported ABCC8 missense mutations (p.Met115Val (inherited from father) and p.Arg1183Ttp (de novo) }	GAD 65, Insulin antibody negative 0.14mg/kg/ d	Insulin stopped at 4mth Glibenclamide at 0.14mg/kg/ d
8	2.5mth/ M	6mth	2.7kg, non consanguin ous	None	No	None	No mutation in ABCC8, KCNJ11, INS detected	NA	Transient neonatal diabetes, no treatment ongoing
9	5mth 27d/ F	6mth 1wk	normal, non consanguin ous	Celiac, Thyroid Peroxidase	Yes	Pat gf	No mutation in ABCC8, KCNJ11, INS detected	Gad65, Islet cell a/b neg	Insulin

**POSTER SESSION 1**  
**Thursday, September 14, 2017, 5:45-6:45pm**  
**P1 - Growth and GH/IGF Axis**  
**P1-800 – P1-860**

P1-800

**COMPARISON OF THE EFFECTS OF L-DOPA AND INSULIN TOLERANCE TESTS ON CORTISOL SECRETION**  
*Sezer Acar, MD, Dokuz Eylül University, Faculty of Medicine, Izmir, Turkey; Ahu Paketçi, MD; Hale Ü Tuhan, MD; Korcan Demir, Assoc. Professor; Ece Böber, MD; Ayhan Abacı, MD, Dokuz Eylul University, Faculty of Medicine, Izmir, Turkey*

**Objectives:** Adrenal insufficiency, which is one of the life-threatening diseases, is assessed by several pharmacological tests. There is growing evidence that L-dopa may increase cortisol secretion by activating hypothalamus-hypophysis-adrenal (HPA) axis and thus, L-dopa is suggested to use in assessment of HPA axis. The aim of this study is to evaluate the effect of L-dopa on secretion of cortisol and ACTH in short children, and to compare its performance with ITT in a large number of patients.

**Methods:** A total of 29 short but otherwise healthy children who had inadequate GH response to ITT, which was performed as the first test, were consecutively enrolled to the study. GH, cortisol, and ACTH were measured just before administration of L-dopa and then at 30-min intervals for a total of 120 minute. Peak concentrations of cortisol and ACTH exceeding 18 µg/dL (496 mmol/L) and 46 pg/mL (10.2 pmol/L), respectively, were defined as an adequate response.

**Results:** Twenty-nine otherwise healthy cases [mean age, 9.5±3.1 years (range, 3.7-14.9 years)] with short stature were studied. Twenty-six out of the 29 children (89.7 %) found to have a peak serum cortisol >18 µg/dL after L-dopa test, while 23 children (79.3 %) had an adequate cortisol response after ITT. Normal ACTH response (>46 pg/mL) were found in 24 (82.8 %) patients in L-dopa test. Peak cortisol levels were higher, but statistically insignificant, in children with normal ACTH response than those with subnormal ACTH response (25.6±6.2 vs 19.5±6.4 µg/dL, p=0.054).

**Conclusions:** This is the first time to demonstrate that L-dopa test is superior to ITT, as a gold standard test, in terms of effective cortisol stimulation, lack of life-threatening side effects, and convenience for the assessment of HPA axis during evaluation of suspected GH deficiency. As a result, L-dopa test can be used safely instead of ITT.

P1-801

## VARIATION IN ADULT HEIGHT EXPLAINED BY QEPS GROWTH FUNCTIONS, SIZE AT BIRTH AND PARENTAL HEIGHTS.

Kerstin Albertsson-Wikland, MD, PhD; Aimon Niklasson, MD, PhD; Anton Holmgren, MD; Andreas FM Nierop, PhD, Sahlgrenska Academy; University of Gothenburg, Gothenburg, Sweden

**Objectives:** To explain variation in adult height and the relative importance of size at birth, parental heights and QEPS growth functions.

**Methods:** Multivariable regression analyses including the variables known at birth i.e. gestational age, birth length/weight, mother/father heights and the QEPS growth model function estimates Emax, Etimescale (Exponential), Qmax (Quadratic), Pmax, Ptimescale, AgeP05 (Pubertal).

**Material:** The healthy cohorts *GrowUpGothenburg* born 1974 (n 2280; 1139 girls, 1141 boys) and born 1990 (n 1901; 929 girls, 972 boys), with 95 419 measures from birth to adult height, mean 22/24 per child. Adult height for 1974/1990 cohort was for girls 167.7/168.3cm and for boys 180.7/181.7cm with for girls & boys in 1974/1990 cohort Emax 63/63 & 65/65cm, Qmax 98/98 & 104/105cm,

Pmax 13/13 & 17/17cm and with T(QEPS)pubgain during ageP05-95 of 26/27 & 29/29cm.

**Results:** In girls (Fig left) variation in adult height of 1974/1990 cohorts was to 45/51% explained by information available at birth (only size 14/19% and parental heights); to 73/72% explained adding QE-function estimates (only Q 66/69%); to 78/79% explained adding age at onset of puberty; to 99.3/99.2% explained adding P-function estimates.

In boys (Fig right) variation in adult height of 1974/1990 cohorts was to 46/45% explained using information available at birth (only size 18/15% and parental heights); to 76/75% explained adding QE-functions estimates (only Q 71/71%); to 79/78% by adding age at onset of puberty; to 99.5/99.5% explained adding P-function estimates.

The QE-function (Emax, Qmax) could already in early-childhood be estimated with acceptable accuracy.

**Conclusions:** With information available at birth around half of the variation in adult height could be explained. Adding information of prepubertal growth functions another 25% could be explained, whereas adding age at onset of puberty only explained another 5%. Finally, adding also the specific pubertal growth function explained the remaining 25% of variation in adult height. QE-functions, possible to estimate in early childhood, could information available at birth when missing.

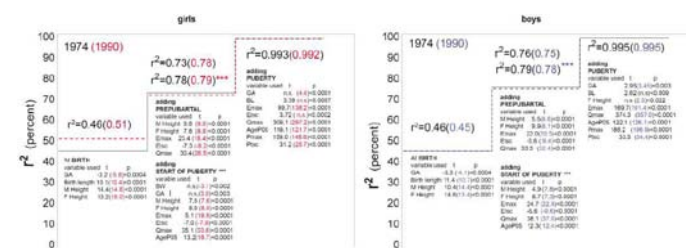


Figure. Multivariable regression analysis explaining the variations in adult heights in the GrowUp 1974 (black solid lines) and 1990 (dotted lines) cohorts.

P1-802

## FINAL ADULT HEIGHT OF ADOLESCENTS WITH BETA THALASSEMIA MAJOR: RELATION TO THEIR GH SECRETION.

Noura Alhumaidi, MD; Mohamed Yassin, MD; Noura Alhumaidi, MD, Hamad Medical Center, Doha, Qatar

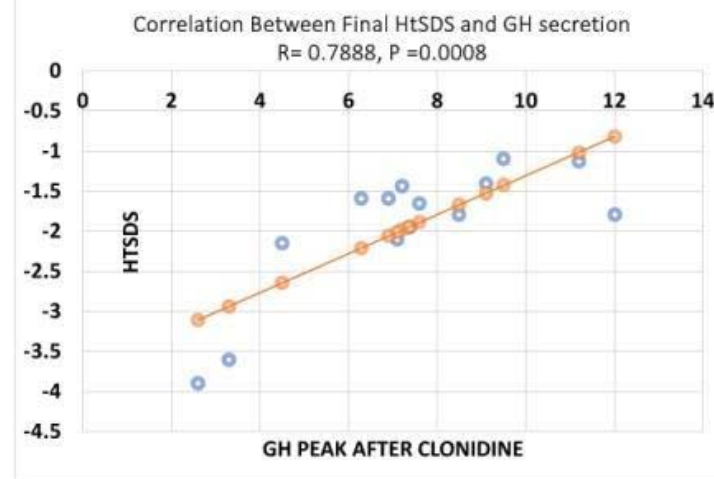
**Objectives:** To evaluate the effect of growth hormone status and iron overload on their final adult height in patients with Beta Thalassemia Major (BTM). Our study is a cross-sectional analysis of data on growth in a group of patients with Beta thalassemia Major (BTM) who have completed puberty spontaneously and have attained their adult height.

**Methods:** 15 adolescent patients with BTM (6 females and 9 males) on regular blood transfusion and iron chelation using desferrioxamine administration since the age of 2 years that was changed to Exjade oral therapy for the past 3 years were studied. Growth parameters (height, weight) were measured and BMI and HtSDS were calculated. Bone age showed complete fusion of the hand and wrist epiphyseal plates. We measured their Free T4, TSH, fasting and 2h blood glucose levels after oral glucose load (75g), fasting insulin and C-peptide, and IGF-I concentrations. Patients

were categorized according to their peak GH response to clonidine provocation into : 9 patients with normal GH secretion (GHN) and 6 patients with GH deficiency (GHD) (Peak GH < 7 ng/ml) .

**Results:** All patients had normal thyroid function and glucose homeostasis. Two females and 3 males on hormonal replacement therapy for hypogonadotropic hypogonadism started at 13 and 14 years of age respectively. The final stature of adolescents with BTM = 159.1 +/- 6.42 cm, with HtSDS = -1.94 +/- 0.83 which had been spontaneously achieved at an age ranging from 21 +/- 3 years. The HtSDS of patients with GHD was significantly lower than those with NGH with a mean difference of 1SD. IGF-I, fasting insulin and C-peptide concentrations, fasting and 2h blood glucose after oral glucose load (75 g) did not differ among the two groups. The final HtSDS were correlated significantly with the Peak GH secretion (  $r = 0.788$ ,  $p = 0.0008$ ). Neither ferritin level nor IGF-I concentrations were correlated with the HtSDS. HtSDS were positively related to their mid-parental height ( $r=0.58$ ,  $P<0.01$ ).

**Conclusions:** The final adult height of patients with BTM and GHD is significantly shorter compared to their peers with GHN. rhGH therapy is recommended in thalassemic children with GHD in addition to proper blood transfusion and intensive chelation to improve their adult height



P1-803

#### BONE AGE DETERMINATION BY ULTRASOUND (BAUS): VALIDATION IN BRAZILIAN STUDENTS

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**Objectives:** Validation of Bone Age Determination by Ultrasound (BAUS)

**Methods:** We evaluated 248 students (F:131; M:117), age range 6-17y, and BMI between  $\pm 2$ SDS. BAUS was performed employing the SonicBone Medical device and BARx was done using a portable Rx device. BARx was established after

reading of 3 experienced investigators (2 pediatric endocrinologists and 1 radiologist).

**Results:** Discordant BARx occurred in 4/131 girls and 11/117 boys; the final BA was established after review and concordance of at least two investigators. A significant correlation between BAUS and BARx was identified both in girls ( $r=0.91$ ;  $p<0.001$ ) and boys ( $r=0.92$ ;  $p<0.001$ ). A significant correlation was also detected between chronological age (CA) and BA methods (BAUS:  $r=0.9$  and BARx:  $r=0.94$ ,  $p<0.001$ ). Differences between both methods were predominantly detected in the upper age limits. In girls older than 13y, BAUS was around 2y less than BARx and CA; in boys older than 15y, BAUS was similar to CA, but 8 months delayed in comparison to BARx.

**Conclusions:** We concluded that there are significant positive correlation among BAUS, BARx and CA. BAUS determination in Brazilian students needs a formula adjustment in ages older than 13y and 15y in girls and boys, respectively. BAUS is a safe and practical method of bone age determination, and seems to have a potential clinical applicability.

P1-804

#### SHORT CHILDREN BORN SMALL FOR GESTATIONAL AGE (SGA) TREATED WITH GROWTH HORMONE (GH): ADULT HEIGHT AND FACTORS IMPLICATED IN LONG-TERM RESPONSE.

Anunciación Beisti Ortego, PhD, Calahorra's Hospital, Calahorra, Spain; Antonio De Arriba Muñoz, PhD, Miguel Servet's Hospital, Zaragoza, Spain; Cristina Fuertes Rodrigo, MD, Calahorra's Hospital, Calahorra, Spain; Marta Ferrer Lozano, MD; Jose Ignacio Labarta Aizpun, PhD, Miguel Servet's Hospital, Zaragoza, Spain

**Objectives:** The aim of this study was to evaluate height gain, puberty and adult height (AH) during rhGH treatment and factors related with long-term response such as pubertal stage at start, treatment duration before puberty, diagnosis of GH deficiency (GHD) or familiar short stature (FSS) and combined treatment with GnRH analogues.

**Methods:** Retrospective, longitudinal cohort study of 139 short children born SGA treated with rhGH; 115 reached AH (28 males) and 36 received GnRHa.

**Results:** Auxological data are presented in Table 1.

Prepubertal children at start of treatment reached higher AH compared with pubertal children ( $-1.4 \pm 0.6$  vs  $-1.9 \pm 0.6$  respectively,  $p<0.01$ ). Patients treated  $\geq 2$  years in pre-puberty showed a significantly higher height gain than those treated < than 2 years ( $1.32 \pm 0.5$  vs  $0.99 \pm 0.6$ , respectively,  $p<0.05$ ). Height gain does not depend on the presence of GHD or FSS. Factors associated with higher height gain were: a) lower height ( $r = -0.59$ ,  $p<0.001$ ), weight ( $r = -0.58$ ,  $p<0.001$ ), and BMI ( $r = -0.42$ ,  $p<0.001$ ) at onset of treatment b) younger chronological age ( $r = -0.23$ ,  $p=0.013$ ) and bone age ( $r = -0.49$ ,  $p<0.001$ ), c) lower pre-treatment IGF-I values ( $r = -0.45$ ,  $p<0.001$ ), d) greater distance with target height ( $r = -0.53$ ,  $p<0.001$ ), e) higher first year ( $r = 0.47$ ,  $p<0.001$ ) and second year ( $r = 0.55$ ,  $p=0.032$ ) growth velocity f) and higher



prepuberty and puberty height gain ( $r=0.42$ ,  $r=0.49$ , respectively,  $p<0.001$ ). Compared with reference population, patients treated with rhGH had less height gain during puberty (males  $23.19\pm4.23$  vs  $26.20\pm4.2$  cm, females  $17.94\pm3.93$  vs  $20.30\pm4.4$  cm,  $p<0.001$ ). However, females treated with combined rhGH/GnRHa showed higher height gain during puberty than reference population ( $23.78\pm0.60$  vs  $20.30\pm4.4$  cm,  $p<0.05$ ). No differences were observed in AH SDS or adult BMI SDS between the two treatment groups.

**Conclusions:** rhGH treatment in short SGA children results in variable height gain but allows in most of them to reach their target height. Best results are found in prepubertal children with longer treatment duration before puberty. Patients with early puberty and poor adult height prediction can benefit from combined rhGH/GnRHa treatment.

Table 1. Auxological data and comparison between treated with rhGH and combined rhGH/GnRHa.

	rhGH			combined rhGH/GnRHa			P value
	N	MEAN	SD	N	MEAN	SD	
Target Height SDS	100	-1,31	0,79	35	-1,38	0,74	n.s
Age at start	103	9,05	3,07	36	9,81	2,79	n.s
Height at start SDS	103	-2,72	0,69	36	-2,3	1,12	*
Growth Velocity First Year SDS	103	2,42	1,77	36	0,99	1,96	***
First Year Height gain SDS	103	0,55	0,48	36	0,3	0,41	**
Growth Velocity Second Year SDS	95	1,77	1,58	33	1,04	1,71	*
Second Year Height gain SDS	95	0,34	0,41	33	0,18	0,38	**
Adult Height Prediction at start of Puberty	69	-1,63	0,93	28	-2,82	0,59	***
Adult Height SDS	80	-1,63	0,65	35	-1,85	0,89	n.s
Adult BMI SDS	79	-0,33	0,9	35	-0,15	1,13	n.s
Height gain SDS	80	0,96	0,7	35	0,44	0,98	**
TH-corrected AH SDS	80	-0,22	0,76	34	-0,41	1,14	n.s

\* p<0,05    \*\* p<0,01    \*\*\*p<0,001    n.s. not significant

P1-805

**THE GH RECEPTOR GENE EXON 3 DELETION IS ASSOCIATED WITH POSTNATAL SPONTANEOUS GROWTH IN SMALL FOR GESTATIONAL AGE CHILDREN.**

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**Objectives:** The GH receptor gene (GHR) contains an unusual genetic polymorphism caused by deletion of exon 3 that mimics alternative splicing. The exon 3 deletion has been linked to increased responsiveness to rhGH treatment in small for gestational age (SGA) patients. However, the association between spontaneous catch-up growth and GHR polymorphism has been poorly addressed in this population. The aim of this study is to determine the association between GHR polymorphism, postnatal catch-up growth and serum IGF-I levels in SGA children.

**Methods:** We conducted an observational cross-sectional study. Fifty prepubertal and early pubertal children (30 boys) aged 4-12.41 yr were evaluated at a tertiary center for pediatric endocrinology. Ninety-four appropriate for gestational age (AGA) children served as a control group. The GHR polymorphism was genotyped by polymerase chain reaction (PCR) duplex assay. Anthropometric measures were recorded, while age of pubertal onset was assessed by clinical examination and serum gonadotropin, estradiol and testosterone levels. Serum IGF-I levels prior to the rhGH treatment were also evaluated. Those patients who have reached height  $>-2$  SDS without treatment, were defined as spontaneous catch-up group.

**Results:** The *GHRd3/d3* genotype was underrepresented in the SGA group (2%) when compared with the control group (13.8%)  $p=0.03$ . No difference in the frequency of the *GHRfl/fl* or *GHRfl/d3* genotype was found between SGA patients and the control group. The percentage of SGA patients that achieved spontaneous catch-up growth was greater in those with at least one d3 allele ( $n=10/18$ ; 55%) when compared with the *GHRfl/fl* group ( $n=6/31$ ; 19%),  $p=0.01$ . A tendency towards greater IGF-I levels expressed as SDS was found in the exon 3 deleted genotype ( $0.22\pm1.1$ ) when compared with those with *GHRfl/fl* group ( $-0.35\pm0.82$ ),  $p=0.06$ .

**Conclusions:** In SGA children, the *exon 3* deletion was associated with greater catch up growth, and higher serum IGF-I levels. Thus, we propose that this common polymorphism could play a role in, postnatal spontaneous growth in SGA children.

P1-806

**CHANGES OF THYROID FUNCTION DURING HGH THERAPY IN GROWTH HORMONE DEFICIENCY CHILDREN**

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**Objectives:** Growth hormone deficiency (GHD) is an important cause of short stature in childhood and the goal of growth hormone (GH) therapy is to promote linear growth, restore body composition and improve the quality of life. Normal thyroid hormone secretion or appropriate L-thyroxine (L-T<sub>4</sub>) substitution is necessary for the optimal effect of the GH administration.

**Aim:** To evaluate the effect of rhGH administration on thyroid function in children with GHD during one year of therapy, as well as to assess its influence on rhGH therapy effectiveness and potential indications to thyroid hormone supplementation.

**Methods:** The study enrolled 55 children (36 boys, 19 girls, 4–14 years old) with confirmed GHD (decreased or low GH, two negative tests). All of them were treated with a mean dose of GH=0.04+/-0.005 mg/kg/day and followed for at least 1 year. Clinical (body height, height velocity) and hormonal (IGF1, TSH, fT<sub>4</sub>) data, as well as radiographic bone age assessments were documented at the beginning, 6 months and after one year of treatment.

**Results:** Before treatment, all patients had the height SDS less than -2.5, delayed bone age, decreased or low normal IGF1 and normal thyroid function. During the initial 6 and 12 months of rhGH administration, a moderate decrease of fT<sub>4</sub> (p=0.428, respectively p=0.013) without significant changes of TSH (p=0.074) was observed. In 6 children, either the decreased fT<sub>4</sub> level, increased TSH or both led to administration of L-T<sub>4</sub> substitution. After 1 year of rhGH, HV improvement was significantly lower in those children who were hypothyroid even for a relatively short period (mean 0.47 vs 0.78, p<0.05).

**Conclusions:** Impaired thyroid function during the first year of rhGH treatment in children with GHD and the negative effect of even transient thyroid hormone deficiency on growth rate should be taken into account while beginning rhGH. Our study highlights the importance of a closer monitoring of thyroid function in these patients.

P1-807

#### COMPARATIVE STUDY OF SAFETY, EFFICIENCY AND BIOCOMPATIBILITY BETWEEN A MEXICAN RECOMBINANT GROWTH HORMONE AND GENOTROPIN, IN CHILDREN WITH GROWTH HORMONE DEFICIENCY

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**Objectives:** To investigate safety, efficiency and biocomparability of recombinant human growth hormone from a Mexican pharmaceutical laboratory PiSA.

**Methods:** Phase III, prospective, randomized, parallel and comparative study during 12 months.

Inclusion criteria: prepubertal male and female, proven diagnosis of GH deficiency, height less than -3SD, bodily proportions, growth velocity less than 10 percentile, naive to rGH treatment and parents informed consent signature. Exclusion and elimination criteria: chronic and/or systemic disease, genetic syndrome, intrauterine growth retardation, active or past oncology disease-radiotherapy-chemotherapy, use of drugs that interfere with growth hormone action.

The study was approved by the Investigation and Ethical Committees of the National Institute for Pediatrics. 54 patients were included (80% power and alpha 0.05 = 50 patients), and ended the study 24 patients in PiSA (rGH-1) and 26 patients in Genotropin (rGH-2). Every two months a complete somatometry and biochemical safety profile (blood cytometry, blood chemistry, electrolytes, thyroid, lipid and hepatic profiles, urine analysis, pre and postprandial glucose and insulin, oral glucose tolerance test, IGF-1, IGFBP-3), were performed.

**Results:** Growth velocity increased (10.82cm/year in rGH-1, 10.24cm/year in rGH-2, p<0.001), and height gain was suitable (0.944SD in rGH-1 and 0.877SD in rGH-2 p<0.001), and there was not statistical significance between rGH-1 and rGH-2 (p>0.05).

No alterations were observed in biochemical safety profile, and no severe adverse events were reported, and the two more frequent non-related adverse events were viral upper airway infections, and transient headache, without differences between the two groups (p>0.05).

ANOVA (CI 95%) was used for efficiency analysis, with subgroups adjusted by Bonferroni method; U-Mann-Whitney and Fisher test were used for safety analysis.

**Conclusions:** There are not statistical differences in efficiency, safety and biocomparability between rGH-1 and rGH-2. PiSA rGH is a safety, efficient and biocompatible option for the treatment of growth hormone deficient children.

P1-808

#### SHOX DEFICIENCY: GENETICS ALTERATION AND THERAPEUTIC EFFICACY AND SAFETY OF GROWTH HORMONE TREATMENT.

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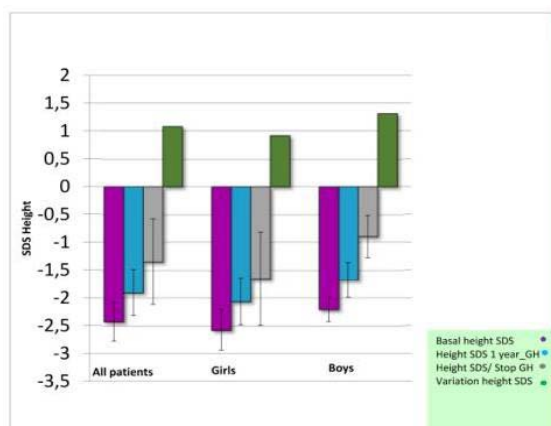
**Objectives:** SHOX deficiency (SHOX-D) is a frequent cause of short stature. The *SHOX* gene resides in the telomeric PAR1 region on the short arm of both sex chromosomes and escapes X inactivation. The diagnosis of SHOX deficiency has acquired relevance in the last decade due to advances in the knowledge of the genetic and molecular mechanisms involved in its aetiopathogenia and also due to the recent use of growth hormone therapy to improve the height of these patients.

**Objectives.** 1) To detect the genetic alteration in the *SHOX* gene for the SHOX-D diagnosis. 2) To assess auxological and clinical data as well as therapeutical efficacy and safety after one year and at the end of treatment with growth hormone (GH).

**Methods:** Monocentric retrospective observational study. Data were examined for 19 GH-treated SHOX-deficient children (10 girls and 9 boys). Genetic study: PCR and direct sequencing of *SHOX* coding exons and flanking regions plus MLPA for detection of deletions.

**Results:** All patients had some type of genetic alteration in *SHOX* or in its regulatory areas. The deletion of *SHOX* was the most frequent genetic alteration and 26.31% presented *SHOX* missense mutations (p.Arg178Trp, p.Tyr199Stop, p.Phe1136Leu and p.Ala170Pro). At the beginning of the GH treatment, the mean height of all Growth Hormone-treated SHOX-deficient children was  $-2.43 \pm 0.35$  SDS with a mean chronological age (CA) of  $9.88 \pm 2.95$ ; girls CA:  $8.91 \pm 2.65$  and height SDS  $-2.58 \pm 0.36$  and boys CA:  $9.84 \pm 3.42$  and height SDS  $-2.21 \pm 0.22$ . After one year of GH treatment, the mean height in girls was  $-2.07 \pm 0.42$  SDS and in boys  $-1.68 \pm 0.31$  SDS. The mean height of the patients at the end of GH treatment was  $-1.35 \pm 0.77$  SDS: girls  $-1.66 \pm 0.84$  SDS and boys  $-0.9 \pm 0.38$  SDS. Overall, the height increased throughout the treatment being higher in boys than in girls (figure 1). Likewise no serious adverse effects were observed during the GH treatment.

**Conclusions:** The results obtained indicate that the treatment with growth hormone is safe in SHOX-D and improve the growth of these patients, since it increases the height not only during the first year of GH therapy but also at the end of the treatment. On the other hand, the most frequent genetic alteration was the *SHOX* deletions.



## THE RISK OF METABOLIC SYNDROME ACROSS TERTILE OF DELTA CHANGES IN SDS-HEIGHT DURING GROWTH HORMONE THERAPY IN PRE-PUBERTAL CHILDREN WITH GROWTH HORMONE DEFICIENCY (GHD)

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**Objectives:** Growth hormone deficiency (GHD) in adults is associated with metabolic and cardiovascular (CV) complications. Obesity, dyslipidemia, hypertension, insulin resistance are components of the Metabolic Syndrome and in adults are positively affected by growth hormone (GH) treatment. Few data are available in youth especially evaluating the metabolic effects across changes of sds-height (sds-h) at the end of GH treatment. To evaluate changes in insulin resistance index, lipid profile and blood pressure in pre-pubertal GHD children across tertiles of sds-h changes at the end of GH replacement therapy.

**Methods:** 15 pre-pubertal normal weight children with GHD (age:  $11.4 \pm 2.3$  years; sds-h:  $-2.25 \pm -1.94$ ). In all children IGF-1, lipid profile (total cholesterol [TC], triglycerides [TG], HDL-cholesterol [HDL]), glucose metabolism (fasting glucose [FG] and insulin [FI], HbA1c levels), and insulin resistance index (HOMA, TG/HDL ratio) were evaluated before and at the end of GH treatment and delta changes were calculated for each variable. Subjects were divided according to tertile of delta-changes of sds-h (1<sup>st</sup> tertile:  $< 1.03$ ; 2<sup>nd</sup> tertile:  $1.03-1.37$ ; 3<sup>rd</sup> tertile:  $> 1.37$ ) at the end of therapy.

**Results:** In each tertile group a significant increase of sds-height was documented (all  $p < 0.05$ ). Delta changes of glucose metabolism (FG, FI, HOMA, TG/HDL, HbA1c) and lipid profile (TG, HDL, TC) indexes significantly improved across tertile groups showing the highest tertile a better metabolic pattern. Blood pressure was not different across the three tertiles.

**Conclusions:** GH therapy is associated with improvement of indexes of metabolic syndrome. Delta changes seem to be more evident in those children with a higher tertile of delta sds-h at the end of therapy. A tailored therapy aimed to reach a proper goal in sds-h at the end of GH therapy might be necessary in order to reduce cardiovascular risk in GHD children.

## GENETIC SCREENING OF PATIENTS WITH CONGENITAL GH DEFICIENCY IN THE GENESIS OBSERVATIONAL PROGRAM: CLINICAL INDICATORS FOR IDENTIFICATION OF MUTATIONS.

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Sobrier, PhD, Inserm US013, Paris, France; Christine Jones, PhD; Alan G Zimmerman, PhD, Eli Lilly and Company, Indianapolis, IN, United States; Roland W Pfäffle, MD, University of Leipzig, Leipzig, Germany

**Objectives:** Congenital GH deficiency (GHD) may be caused by mutations in genes involved in pituitary development, GH synthesis or secretion. Defects in *GH1* and *GHRHR* commonly cause isolated GHD (IGHD). Defects in genes for transcription factors (*GLI2*, *HESX1*, *LHX3*, *LHX4*, *SOX3*, *PROP1*, *POU1F1*) that shape the developing pituitary and specify hormone producing cells, cause multiple pituitary hormone deficiencies (MPHD). Using data from the DNA Analysis Sub-study of the GeNeSIS observational program of outcomes in children with short stature, we aimed to identify patient characteristics that predicted for a GHD causing mutation.

**Methods:** SSCP, dHPLC and direct sequencing analyses were performed based on a candidate gene approach in patients with IGHD or MPHD. DNA variants were classified as pathogenic according to American College of Medical Genetics and Genomics standards. Data submitted by physicians at baseline and during the course of follow-up were combined for statistical analysis. Logistic multivariable regression analysis (mutation yes = 1, no = 0) was performed with various cohorts and sets of variables.

**Results:** Data for the best regression model for patients with IGHD or MPHD are shown in the table. MPHD, low baseline height minus target height standard deviation score (SDS), low log stimulated GH peak were found to be significant indicators of a relevant mutation in the tested genes. When the analysis focused on patients with IGHD (N = 398), significant indicators of *GH1* or *GHRHR* mutation were low baseline age (odds ratio 0.74; 95% confidence interval 0.60–0.92; *P* = 0.005) and low log stimulated GH peak (0.37; 0.21–0.66; *P* < 0.001). In patients with MPHD (N = 259), the only significant indicator of mutation in *GLI2*, *HESX1*, *LHX3*, *LHX4*, *POU1F1*, *PROP1* or *SOX3* was low baseline height minus target height SDS (0.71; 0.58–0.87; *P* < 0.001). Sex, baseline bone age SDS, or baseline IGF-I SDS were not significant indicators of mutations in any models.

**Conclusions:** The most relevant clinical indicators for a mutation in the investigated genes are MPHD, younger age at start of GH therapy, low baseline height minus target height SDS, and low GH peak in stimulation testing. These data may assist in identifying patients with GHD for DNA testing.

PLEASE SEE TABLE IN NEXT COLUMN

Table: Logistic multiregression modelling of impact of selected baseline variables in patients with IGHD or MPHD on likelihood of mutation<sup>a,b</sup> in tested genes (N = 462)

Variable	Class	Estimate	P-value	OR	95% CI	P-value <sup>c</sup>
Intercept		-3.11	<0.001			0.715
Sex	M vs F	0.11	0.790	1.11	0.50-2.46	
MPHD	Yes vs No	1.45	<0.001	4.28	1.86-9.85	
Baseline chronological age (y)		-0.15	0.004	0.86	0.78-0.95	
Baseline bone age SDS		-0.04	0.729	0.96	0.76-1.21	
Baseline Ht SDS minus TH SDS		-0.35	0.013	0.70	0.53-0.93	
Log (maximum GH peak [µg/L])		-0.43	0.004	0.65	0.48-0.87	

Abbreviations: CI = confidence interval; F = female; Ht = height; IGHD = isolated GH deficiency; M = male; MPHD = multiple pituitary hormone deficiencies; OR = odds ratio; SDS = standard deviation score; TH = target height; y = year.  
<sup>a</sup> DNA variants classified as pathogenic according to Richards S et al 2015. Genet Med; 17:405-424.  
<sup>b</sup> The response variable for IGHD or MPHD was "mutation of any of the investigated genes" = 1. Note for the IGHD population it was "mutation of *GH1* or *GHRHR*" = 1, and for the MPHD population it was "mutation of any of *GLI2*, *HESX1*, *LHX3*, *LHX4*, *POU1F1*, *PROP1* or *SOX3*" = 1.  
<sup>c</sup> Lack of fit (Hosmer and Lemeshow goodness-of-fit test).

P1-811

CHANGES IN THE CIRCULATING INSULIN-LIKE GROWTH FACTOR SYSTEM IN RESPONSE TO SHORT-TERM HIGH FAT INTAKE

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**Objectives:** The insulin-like growth factor (IGF) system is important for growth and metabolism during development, while in adulthood it maintains tissue integrity and continues to be involved in metabolic control. However, little is known regarding the effect of diet on more recently identified members of this family such as pregnancy-associated plasma protein-A2. This metalloproteinase cleaves IGF binding protein (IGFBP) 3 and 5 to release IGF-1 from the ternary complex.

Our aim was to analyze the changes in the circulating levels of members of the IGF in response to a short-term dietary change.

**Methods:** Male and female Wistar rats were given a high fat diet (HFD, 60% fat, 5.1 kcal/g), low fat diet (LFD, 10% fat, 3.76kcal/g) or normal rat chow (Ct, 3.1 % fat, 2.9 kcal/g) for 1 week (n = 6). Food intake and weight gain were monitored and total IGF-1 (tIGF1), free IGF-1 (fIGF1), IGFBP-3, IGFBP-5 and PAPP-A2 levels measured in serum by ELISA at 70 days of age.

**Results:** Energy intake was higher in rats on HFD and LFD compared to Ct diet in both sexes, with HFD males ingesting more kcal than LFD males. HFD males gained more weight than those on LFD or chow. In females diet had no effect on weight gain. Percent visceral fat was not significantly affected by diet. Males had higher tIGF1 levels than females on all diets ( $p<0.0001$ ). In males HFD and LFD tended to decrease tIGF1, but increase it in females ( $p<0.05$ ). Males had higher fIGF1 than females on all diets ( $p<0.0001$ ). In males LFD decreased fIGF-1 ( $p<0.02$ ). Diet had no effect on IGFBP3 levels with higher levels in males than females ( $p<0.0001$ ) on all diets. Males had higher levels of IGFBP5, but this was only significant under HFD ( $p<0.0001$ ). PAPP-A2 levels were unaffected by diet, but were higher in females than in males. See table.

**Conclusions:** After only one week of dietary change modifications in body composition and the circulating IGF1 system can be observed, with males more affected than females. The circulating IGF1 system is sexually dimorphic with males having higher levels of all factors measured compared to females except PAPP-A2, where females had higher levels. Whether changes in the IGF system affect the long-term response to dietary challenges remains to be determined.

	MCt	NHFD	MLFD	FCt	FHFD	FLFD
Weight gain (g)	26.2±2.3	32.0±1.2 <sup>a</sup>	26.8±1.1	8.5±1.0 <sup>a</sup>	12.3±2.0 <sup>a</sup>	14.7±2.6 <sup>a</sup>
Visceral fat (%)	1.4±0.2	1.7±0.3 <sup>b</sup>	1.6±0.08 <sup>b</sup>	0.7±0.01	1.0±0.1	0.9±0.1
Intake (Kcal/day)	58.7±3.7	96.2±5.5 <sup>b</sup>	79.5±1.5 <sup>b</sup>	39.9±2.1 <sup>a</sup>	57.0±3.9 <sup>a,b</sup>	56.4±3.0 <sup>a,b</sup>
Total IGF1 (ng/ml)	2329.7±123.6	2091.7±191.2	1768.0±148.1	1365.2±104.2 <sup>a</sup>	1748.0±129.0 <sup>a</sup>	1555.0±160.8 <sup>a</sup>
Free IGF1 (ng/ml)	9.7±0.8	9.8±0.8	6.9±0.4 <sup>b</sup>	3.8±0.5 <sup>a</sup>	4.7±1.0 <sup>a</sup>	3.2±0.3 <sup>a</sup>
IGFBP3 (ng/ml)	294.6±17.7	238.5±15.0	263.4±19.1	190.2±7.0 <sup>a</sup>	190.3±12.1 <sup>a</sup>	181.4±14.7 <sup>a</sup>
IGFBP5 (ng/ml)	98.0±4.0	104.5±3.0	100.9±8.6	86.5±4.1	75.9±4.4 <sup>a</sup>	81.0±9.9
PAPP-A2 (ng/ml)	0.8±0.3	0.7±0.1	0.8±0.1	1.3±0.4	1.5±0.5	1.6±0.6

Table 1. Effects of one week of a high fat diet (HFD) or low fat diet (LFD) compared to normal rat chow (CT) in male (M) and female (F) rats. Pregnancy-associated plasma protein-A2: PAPP-A2. a: different between sexes on same diet; b: different compared to Ct of same sex.

P1-812

**INCREASED ABDOMINAL PERIMETER (AP) AT BIRTH OF CHILDREN BORN SMALL FOR GESTATIONAL AGE (SGA) DUE IUGR (INTRAUTERINE GROWTH RETARDATION)**  
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**Objectives:**

The metabolic syndrome (MS) is related to central obesity and observed during infancy, in children born SGA. Since abdominal fat reflects the perivisceral fat, predisposing factor to MS, we wanted to study besides the classical parameters Height (H), Weight (W), Head Circumference (HC) at birth, also the non included in the neonatal exploration Abdominal Perimeter (AP) in a sample of newborns SGA.

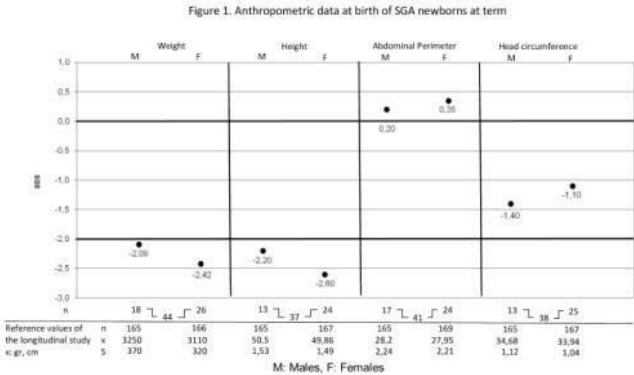
**Methods:**

41 SGA (H, W or both  $\leq$  SD) born at term (38-42 weeks of gestation) without confounding factors like syndromic cases, complicated pregnancies and being in good clinical condition, were measured by experienced nurses, just after having cut the umbilical cord. The obtained values were compared to our longitudinal Growth Study from birth until adulthood.

**Results:** Figure 1 shows the values of W, H, HC and AP compared to our normal standards and expressed in SD. H and W and in a lesser extent HC are clearly below the mean standards whereas as a new finding the AP is on the contrary very normal, even slightly above the mean. Other biochemical and ecographic signs suspicious of MS are now in process.

**Conclusions:**

Newborns SGA due to IUGR show an increased AP, even above the mean standards, with a clear difference to the H, W and HC. This increased AP is the expression of an intraabdominal obesity, as a consequence of a fetal thrifty energy expenditure. This clinical finding alerts about the risk to develop a MS at very early ages and advises to control it at birth specially in newborns SGA. In such cases an adequate nutrition and stimulation of physical activity are mandatory to avoid an MS. Also the early use of growth hormone not only for the growth but to prevent the MS must be taken into consideration.



P1-813

**HOW FREQUENT ARE PARTIAL AND COMPLETE ACID-LABILE SUBUNIT DEFICIENCY (ACLS) IN CHILDREN WITH IDIOPATHIC SHORT STATURE (ISS)?**  
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**Objectives:** Idiopathic short stature (ISS) is a clinical condition defined as height 2 SD below the mean in children without evidence of systemic, endocrine, nutritional, or chromosomal abnormalities. ISS children have normal birth weight and are GH sufficient. Several molecular defects have already been characterized in a subgroup of ISS children, including *GHR*, *GHSR*, *SHOX*, *NPR2*, *IGFALS* genes among others. The aim of this study was to characterize the *IGFALS* gene in normal and ISS children, identify potential pathogenic variants and determine their impact on the IGF system and the frequency of partial and complete ACLSD.

**Methods:** We have studied 125 normal prepubertal children (62 males; age  $6.67 \pm 2.89$ ; height  $-0.05 \pm 0.95$ ) and 103 ISS prepubertal children (76 males; age  $7.82 \pm 2.54$ ; height  $-2.77 \pm 0.45$ ). Levels of IGF-I, IGFBP-3 were determined by ICMA and ALS by RIA or ELISA and expressed as SDS. The *IGFALS* gene was sequenced in both controls and patients.

**Results:** Levels of IGF-I ( $-0.77 \pm 1.27$  vs.  $-0.01 \pm 1.02$ ), IGFBP-3 ( $-0.77 \pm 1.57$  vs.  $0.09 \pm 1.24$ ), and ALS ( $-1.24 \pm 1.36$  vs.  $-0.09 \pm 1.03$ ) were significantly lower in ISS compared to controls (all  $P < 0.0001$ ). While heterozygous synonymous variants (SV) were found in both controls and ISS children (5.6 vs. 1.9%), non-synonymous variants (NSV) were more frequent in ISS children (15.5 vs. 4.8%;  $P = 0.0039$ ). In those 16 ISS children

with NSV, one presented complete ACLSD (compound heterozygous for p.Glu35Glyfs\*17/p.Ser490Trp), and other 5, presented partial ACLSD (heterozygous carriers for p.Glu35Glyfs\*17, p.Arg277His, p.Pro287Leu, and 2 p.Arg548Trp). Only *IGFALS* variants p.Glu35Glyfs\*17 and p.Ser490Trp were classified as pathogenic by *in silico* bioinformatic tools and confirmed by *in vitro* expression.

**Conclusions:** Although *IGFALS* gene variants are frequently found in both normal and ISS children, NSV are much more frequent in ISS children. However, only a fraction of them (about 5% of ISS children) presented a biochemical profile suggestive of partial ACLSD and less of 1% presented complete ACLSD. Identification of partial ACLSD in ISS children could have practical implications, considering that these children have shown a positive response to rhGH treatment.

P1-814

## FIVE YEARS OF GROWTH HORMONE THERAPY AT CHILDREN WITH GROWTH HORMONE DEFICIENCY

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**Objectives:** Growth hormone (GH) has been available for more than 5 decades for the treatment of growth hormone deficiency (GHD); the growth velocities particularly rise during the first 5 years of GH therapy. Our aim has been to assess the growth and safety during the first 5 years of GH treatment in 38 GHD children.

**Methods:** We reviewed clinical data of 38 prepubertal children (26 boys, 12 girls): 34 with IGHD (isolated GH deficiency), 4 with MPPHD (multiple pituitary hormone deficiency). All of them were treated with a mean dose of  $GH = 0.036 \text{ mg/kg/d}$  and followed for at least 5 years (mean 6.74ys).

**Results:** The mean height gain in standard deviation score (SDS) was 2.15SDS; the change in height SDS decreased in time. The mean IGF-1 levels achieved remain within the normal range using age-appropriate standards. A significant acceleration of bone maturation was recorded after the first year of therapy and persisted until the fifth year.

**Table1-Growth data during first 5 years of GH therapy in 38 GHD children.**

Parameter	Baseline	1yr	2ys	3ys	4ys	5ys
Chronological age(ys)	8.79	9.79	10.79	11.79	12.79	13.79
Bone age(ys)	6.57	7.42	8.92	10.47	11.87	13.26
IGF-1 mean values (ng/ml)	73.1	248.3	221	284.4	378.5	529
Height SDS	-2.85	-2.19	-1.61	-1.08	-0.77	-0.7
Height velocity(cm/yr)	-	10.74	7.54	6.32	6.71	5.68
Weight SDS	-1.88	-1.24	-0.94	-0.89	-0.24	-0.15

Within first 5 years of therapy none of these children developed diabetes mellitus, 9 patients (23.68%) presented transient increase in fasting glucose, 2 patients (5.26%) had transiently impaired glucose tolerance, 5 patients (13.15%) developed hypothyroidism and 2 patients (5.26%) had transiently increased TSH levels. No malignancies were observed to date.

**Conclusions:** The onset of therapy was followed in all patients by an important height gain, which attained its zenith during the first year of treatment (10.74 cm/yr) and became progressively less evident during the next 4 years. Early diagnosis and therapy initiation optimized growth outcomes.

P1-815

#### **SOMATOTROPHIC AXIS FUNCTION IN ADOLESCENT GIRLS WITH HYPERANDROGENISM**

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##### **Objectives:**

Hyperandrogenism may develop during adolescence. It has been suggested that the somatotrophic axis may be related to the development of hyperandrogenism in non-obese adult women with PCOS.

To investigate the relationship between the function of the somatotrophic axis and ovarian hyperandrogenism in young postmenarchal girls.

##### **Methods:**

**Design:** Cross-sectional study of adolescent girls.

**Patients:** We studied non-obese adolescent girls with hyperandrogenism (HA; n=21) that were matched with control girls (C; n=25) for chronological age, age at menarche and body mass index.

**Methods:** We obtained a fasting blood sample for the measurement of serum glucose, insulin, 17-hydroxyprogesterone, dehydroepiandrosterone sulfate, androstenedione, SHBG, total testosterone, IGF-I, IGF-II, IGFBP-1, IGFBP-3, Ghrelin, leptin, AMH, LH and FSH during the follicular phase of the menstrual period. In addition, we performed an OGTT to determine blood glucose, ghrelin and insulin levels, and we collected urine samples to measure urinary GH levels.

##### **Results:**

As expected, HA had higher Ferriman scores ( $13 \pm 4$  in HA vs  $1 \pm 2$   $p=0.001$ ), and higher levels of basal total testosterone (nmol/L) ( $2.4 \pm 0.7$  in HA vs  $1.0 \pm 0.3$  in C,  $p<0.001$ ), FAI (FAI  $9.2 \pm 5.7$  in HA vs  $2.4 \pm 1.3$  in C,  $p<0.001$ ), androstenedione (nmol/L) ( $12.9 \pm 4.5$  in HA vs  $8.7 \pm 2.8$  in C,  $p<0.001$ ) and AMH ( $44.0 \pm 24.1$  in HA vs  $27.7 \pm 14.2$  nmol/L  $p=0.005$ ) compared with C. Serum IGF-I, IGF-II, IGFBP-III and

urinary GH did not differ between HA and C, but four HA with the highest serum testosterone ( $> 2.43$  nmol/L) had urinary GH  $> 10$  pg/mg creatinine. There was a correlation between urinary GH and FAI in the entire group of girls ( $r 0.29, p<0.05$ ). In addition, in HA girls FAI correlated with insulin, HOMA, and basal and stimulated ghrelin correlated with IGF-1, IGFBP-3 and basal insulin.

##### **Conclusions:**

We observed a correlation between urinary GH and Ghrelin with FAI in the hyperandrogenic and control girls. In addition, Ghrelin correlated with IGF-1 and IGFBP-3 in HA girls suggesting that the function of the somatotrophic axis may influence the secretion of androgens in adolescent girls.

P1-816

#### **CLINICAL CHARACTERISTICS OF CHILDHOOD ONSET GROWTH HORMONE SECRETING PITUITARY ADENOMA**

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**Objectives:** Despite growth hormone secreting pituitary adenoma (GHoma) is rare in childhood, correct diagnosis of pituitary gigantism is essential in treating the patients with tall stature. We report clinical characteristics of case series with childhood onset GHoma.

**Methods:** We performed retrospective review of five cases with GHoma diagnosed during 2011 to 2016. The diagnosis of GHoma was made based on excessively rapid growth and/or acral enlargement and acromegalic facial changes associated with elevated GH/IGF-1 and detection of pituitary adenoma with MRI.

**Results:** We included three males and two females. Mean age at diagnosis was 13.6 years (range 7.5~16.3 years). Their initial chief complaints were tall stature (2), visual disturbance (2) and dental problem (1). Mean height S.D. score at diagnosis were  $+2.8$  (range  $1.0 \sim 4.7$ ). The younger patient had the greater height S.D. score. Four patients, in whom the delay from symptom to diagnosis was longer than three years, had acral enlargement and acromegalic facial changes. Serum IGF-1 values were greater than  $+2SD$  of age and gender matched standards. All of the patients had macroadenoma and three were with cavernous sinus invasion. Somatostatin analogues (SSA) suppressed serum GH level and tumor size. All tumors were totally removed by trans-sphenoidal surgery (TSS) and IGF-1 levels decreased to normal range. AIP mutation was found in two patients, one was youngest boy and the other was familial GHoma.

**Conclusions:** In childhood onset GHoma, the younger patient had the greater height SDS. IGF-1 values were useful in diagnosis. Macroadenomas were controlled after SSA and TSS treatment but careful follow-up is required.

CLINICAL AND BIOCHEMICAL RESPONSE TO RHGH TREATMENT IN CHILDREN WITH HETEROZYGOUS VARIANTS IN THE IGFALS GENE.

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**Objectives:** Acid-labile subunit (ALS) is crucial to stabilize IGF-I in circulating ternary complexes. Complete ALS deficiency is characterized by short stature, severe reduction of serum IGF-I and IGFBP-3 levels and poor response to rhGH treatment. Less information is available on the response to rhGH treatment in children heterozygous carriers for IGFALS gene variants.

**Aim:** Evaluate auxological and biochemical responses to one year of rhGH treatment in short children homozygous wild-type (WT) or heterozygous carriers (HC) for non-synonymous IGFALS variants.

**Methods: Patients:** Short children (height ≤ -2.5 SDS) presenting normal stimulated GH levels (GH max ≥ 4.7 ng/ml) were recruited. Six patients (5 boys, aged 6.7±2.2) had heterozygous IGFALS gene variants: 4 probably pathogenic

by in silico or in vitro assessment: p.E35Gs\*17 (n=2), p.G506R (n=1), p.H128R (n=1), and 2 probably benign: p.R548W (n=1) and p.P22L (n=1). Other 6 idiopathic short stature (ISS) children (4 boys, aged 6.5±2.0) were homozygous WT. Height and IGF-I, IGFBP-3 levels were evaluated before and after one-year of rhGH treatment (dose of 0.33 mg/kg/week). ALS levels were evaluated only before treatment [HC: -1.95±0.15 (n=6); WT: 1.57±2.00 (n=4); NS].

**Results:** Auxological and biochemical data are shown in the Table.

**Conclusions:** Short children HC for IGFALS variants showed a satisfactory and similar response to one year rhGH treatment compared to WT-ISS children, although with a lower increase in IGF-I levels. This suggests that short children, carriers for IGFALS variants, could be more sensitive to IGF-I, that paracrine action of locally produced IGF-I has a more important effect on linear growth, or a combination of both. The impact of rhGH treatment on adult height in carriers for IGFALS variants remains to be determined.

Auxological and biochemical data

	HC (mean±SDS)	WT (mean±SDS)	T-test
Height SDS	-2.90±0.15	-2.82±0.53	NS
IGF-I SDS	-2.25±0.44	-0.44±0.95	p=0.008
IGFBP-3 SDS	-2.05±0.98	0.00±0.55	p=0.002
IGF-I SDS on rhGH	0.32±1.48	2.21±0.94	p=0.02
IGFBP-3 SDS on rhGH	0.16±0.92	1.14±0.82	NS
HV (cm/year)	9.93±1.49	10.72±1.53	NS
Delta height SDS	1.21±0.43	1.15±0.26	NS

GHR-EXON 3 AND -202 A/C IGFBP3 POLYMORPHISMS AND RESPONSE TO GROWTH HORMONE TREATMENT IN KOREAN CHILDREN WITH GROWTH HORMONE DEFICIENCY

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**Objectives:** The GHR-exon 3 and the -202 A/C IGFBP3 polymorphisms have been suggested to affect responses to recombinant human growth hormone (rhGH) therapy in some individuals with short stature. This study aimed to assess the influences of the two polymorphisms on treatment outcomes in patients with growth hormone deficiency (GHD).

**Methods:** In 72 (32 girls and 40 boys) children with confirmed diagnosis of GHD, genotyping and serial measurements of auxological and endocrinological parameters were performed. Forty-nine patients who remained in the prepubertal state after 1year of GH treatment were analyzed.

**Results:** Distribution of the GHR-exon3 genotypes was as follows: d3/d3 genotype 2.8%; d3/fl genotype 15.3%; and fl/fl genotype 81.9%. Frequencies of the -202 A/C IGFBP3 genotypes were as follow: A/A genotype 55.5%; A/C

genotype 38.9%; and C/C genotype 5.6%. In comparing the d3/d3 and d3/fl group with the fl/fl group, there was no significant difference in first-year height velocity. Likewise, comparing the A/A group with the A/C and C/C group, no significant difference was observed in height velocity. Combined analysis of the two polymorphisms showed no significant interaction on the first year height velocity.

**Conclusions:** Our results suggest that the GHR-exon3 and -202 A/C IGFBP3 polymorphisms are not major factors in the modulation of growth response to GH therapy in Korean children with GHD.

P1-819

#### **DELAYED BONE-AGE MAY ACCELERATE THE GROWTH RESPONSE TO TREATMENT IN SHORT SMALL FOR GESTATIONAL AGE (SGA ) CHILDREN**

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**Objectives:** SGA is one of major causes of short stature in children. It has been known that the effectiveness of growth hormone (GH) treatment for short SGA children depends on the GH dose, the age of the child and family-corrected individual height (Albanase A et al, Horm Res, 1997). This study was conducted to see the growth response to treatment by bone-age (BA) in short SGA children.

**Methods:** Study patients consisted of 29 short SGA children. Their age at diagnosis (yrs) was  $7.2 \pm 1.9$ . Male to female ratio was 10:17. Their medical records were reviewed retrospectively.

**Results:** Eighteen patients (67%) showed >2 yrs BA delay when compared with chronological age (delayed BA group). Nine patients (33%) showed < 2 yrs BA delay (control group). In delayed BA group, initial height SDS was significantly increased at 6 mo after treatment, when compared with 'control group',  $-2.45 \pm 0.34$  to  $-1.87 \pm 0.82$  in 'delayed BA group' ( $p=0.01$ ) vs  $-2.68 \pm 0.58$  to  $-2.50 \pm 0.61$  in 'control group' ( $p=0.538$ ). At 12 mo after treatment 'delayed BA group' showed significant height increase,  $-2.45 \pm 0.34$  to  $-1.63 \pm 0.65$  in 'delayed BA group' ( $p=0.001$ ) vs  $-2.68 \pm 0.58$  to  $-2.27 \pm 0.70$  in 'control group' ( $p=0.483$ ). Age at diagnosis, initial sIGF-I level and BMI were not significantly different between two groups.

**Conclusions:** Delayed BA (>2 yrs) could be one of factors related to the magnitude of the growth response to treatment in short SGA children. Further large-scaled long-term study is necessary.

P1-820

#### **DYNAMIC CHANGES IN IGF-I DURING SOMAVARATAN THERAPY IN PEDIATRIC SUBJECTS WITH GROWTH HORMONE DEFICIENCY FROM THE VISTA LONG-TERM SAFETY STUDY**

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**Objectives:** IGF-I response to daily rhGH has been described to increase over time, but the nature of the increment is not well understood. Somavaratan is a long-acting rhGH fusion protein under study as a twice-monthly alternative to daily rhGH for pediatric growth hormone deficiency (PGHD). To determine whether IGF-I response is stable during long-term treatment with somavaratan, IGF-I changes over time were assessed in ongoing PGHD subjects who completed 3 years of treatment, the last 2 years on 3.5 mg/kg twice-monthly dosing, in the VISTA long-term safety study.

**Methods:** IGF-I samples were collected at expected times for peak (Months 21, 27, and 33) and trough values (Months 24, 30, and 36). IGF-I SDS was calculated based on samples from healthy pediatric subjects with no active medical problems and normal physical exams. Time-related IGF-I changes were calculated as the slope from linear regressions of consecutive peaks and consecutive troughs for each subject. A t-test was used to test for mean slope of zero.

**Results:** From Months 21 to 36, multiple IGF-I samples were collected from 44 subjects (23 female [mean $\pm$ SD age:  $10.56 \pm 2.2$  years] and 21 males [mean age:  $10.99 \pm 2.7$  years]). The mean slope of consecutive peak IGF-I over time was 7.1 ng-month/mL (95% confidence interval [CI]: 4.46, 9.75;  $P=0.015$ ). In contrast, no definitive changes over time were noted in consecutive trough IGF-I ( $2.18$  ng-month/mL; 95%CI:  $-0.16, 4.52$ ;  $P=0.067$ ) or IGF-I SDS ( $-0.01$  SD-month/mL; 95%CI:  $-0.03, 0.02$ ;  $P=0.70$ ).

**Conclusions:** In this initial examination, both peak IGF-I and peak IGF-I SDS increased over time, but the increase in consecutive peak IGF-I concentrations was more prominent than that of peak IGF-I SDS, suggesting that effects were related more to age-related physiological changes than a cumulative drug effect. This suggests that peak IGF-I changes are developmentally driven during long term somavaratan treatment. The lack of changes in consecutive trough values of IGF-I and IGF-I SDS suggests that no accumulation or loss of drug effects occurred during this time period.

P1-821

#### **IMPACT OF THE UNDERLYING ETIOLOGY OF GROWTH HORMONE DEFICIENCY ON SERUM IGF-I SDS LEVELS DURING GH TREATMENT IN CHILDREN**

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**Objectives:** Regular monitoring of serum IGF-I levels during growth hormone (GH) therapy has been recommended, for



assessing treatment compliance and safety, in terms of potential long-term cancer risk. We aimed to investigate the serum IGF-I levels during GH treatment in children with GH deficiency, and to identify potential determinants of these levels.

**Methods:** This observational cohort study included all patients ( $n = 308$ ) with childhood-onset non-acquired or acquired GHD included in the database of a single academic paediatric care center over a period of 10 years for whom at least one serum IGF-I determination during GH treatment was available. These determinations had to have been carried out centrally, with the same immunoradiometric assay. Serum IGF-I SDS levels were expressed for sex, age and pubertal stage, according to our normative data.

**Results:** Over a median of 4.0 (2–5.8) years of GH treatment per patient, at a median initial dose of 36 (33–40)  $\mu\text{g/kg/day}$ , 995 serum IGF-I determinations were recorded with a median of 3.0 (2.0; 4.5) measurements per patient. Serum IGF-I SDS values were in the normal range for most patients, with wide individual variation. However, very low and high serum IGF-I SDS values were observed with 54 individual serum IGF-I determinations 2.5 SDS obtained from 56 patients, on at least one occasion during GH treatment. The multivariate model revealed that, throughout the study period and in addition to the positive effect of BMI SDS, height SDS and GH dose ( $p < 0.01$ ), etiological group ( $p < 0.01$ ) had a significant effect on serum IGF-I SDS levels, with patients suffering from acquired GHD having higher serum IGF-I SDS levels than those with non-acquired GHD, whereas sex, age, pubertal stage, treatment duration, hormonal status (IGHD vs MPHD) and initial severity of GHD, had no effect.

**Conclusions:** These original findings have important clinical implications for long-term management and highlight the need for careful and appropriate monitoring of serum IGF-I concentration and GH dose, particularly in patients with acquired GH deficiency, to prevent the unnecessary impact of potential comorbid conditions.

P1-822

#### COMPARISON OF GROWTH RATE RANGES IN CHILDREN USING FOUR DIFFERENT STUDIES

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**Objectives:** Normal variants of pubertal maturation shows differences in centiles of height during early adolescence. Tanner & Whitehouse & Tanner Davies charts are still in use not only in North America population showing these differences.

Recently Kelly et al. in a longitudinal multicenter study published data that differ significantly from Tanner Whitehouse & Tanner Davies charts.

Representative sampling to compare and validate our local result and compare to British and North American population, evaluating differences in pubertal time in height velocity,

considering standard, early and late maturers in both sexes in a healthy pediatric population.

**Methods:** Descriptive and comparative study, using similar parameters elaborated by Kelly et al. including data of healthy subjects both sexes located between 3 and 97th percentile followed for two yearly intervals (average) between 6 - 19 years obtained from 2004 to 2016.

In 2,193 girls, 5025 observations (average 2,29 years), and 1,803 boys, 5,759 observations (average 3,19 years) were made.

Data obtained of Height, height percentile, weight, body mass index percentile, annual height velocity, pubertal time.

Result was expressed as age in years, average, maximum, minimum and standard deviation.

**Results:** Early maturers girls reach the maximum height velocity between 10 and 11 years reaching a media of 7,3 cm/y, average girls between 11 and 12 years reaching a media of 6,7 cm/y and late maturers at 12 and 13 years reaching a media of 6,3 cm/y.

Early boys reached the media height velocity of 8,3 cms/y between 12 and 13 years, average boys 7,9 cms /y between 13 and 14 years, and late maturers reached 7,5 cm/y at age of 14 to 15 years.

**Conclusions:** Our results show that the pattern of pubertal growth differ to those expressed by Tanner & Whitehouse (1976) and NCHS data set for Tanner Davies (1984), being very similar to those presented by Kelly et al (2014).

Our data confirms variations in growth velocity *in tempo* as showed by Tanner and confirmed by Kelly, but differences in the amplitude and differences in time of pubertal peak is less than expected compared with Tanner.

Prospective studies are needed searching differences in different countries and also using BMI to evaluate the importance of body weight in these variations.

P1-823

#### THE LEIDEN EXPERIENCE IN DIAGNOSTICS FOR SHORT STATURE: GENE PANEL BASED MUTATION ANALYSIS BY NEXT GENERATION SEQUENCING ON THE ION TORRENT PGM

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**Objectives:** Short stature is usually classified based on phenotypic characteristics, such as pre- or postnatal onset, proportionate or disproportionate stature, and biochemical data. Defining a specific genetic diagnosis in a young child can have important therapeutic consequences. Furthermore, it

provides insight in recurrence risks, plays a role in family planning, contributes to knowledge on prognosis and surveillance and overall gives more insight in the regulation of longitudinal growth. Routine diagnostic procedures usually include targeted gene-by-gene testing using Sanger sequencing, MLPA and SNP-array analysis which is laborious and time consuming and often does not lead to a definite diagnosis. The LUMC in Leiden is one of the Dutch national centres of expertise for growth disorders. Here we present the results of the implementation of gene panel based analysis with which we aim to enhance the diagnostic efficiency and yield.

**Methods:** Gene panel based sequencing was implemented using a custom made Ion AmpliSeq™ kit followed by sequencing on the Ion Torrent™ Personal Genome Machine. Genetic variants are identified using the SeqNext module in Sequence Pilot software from JSI. Using this approach we simultaneously analyze 14 genes (*COMP, FGFR3, GH1, GHR, GHSR, IGF1, IGFALS, IGFBP3, IGF1R, NPR2, NPR3, PAPSS2, SHOX, STAT5B*). In addition MLPA for *GH1, GHR, IGF1, IGFALS, IGF1R, SHOX* and *STAT5B* was performed.

**Results:** With this approach we have so far identified (likely) pathogenic mutations in 24 out of 138 tested patients. Of these, 5 carried pathogenic mutations in *GH1, GHR* or *COMP* and 15 carried one or two variants of uncertain clinical significance (VUCS). Deletions/duplications were detected in 4 patients using MLPA (3 in *SHOX* and 1 in *GH1*). A total of 17 different VUCS in 8 different genes were detected. Four patients had a variant in 2 different genes which might have been missed in a classical gene-by-gene approach.

**Conclusions:** Although our approach has a similar diagnostic yield as conventional gene-by-gene analysis, it allows a more efficient and complete analysis of growth related genes. In 2 cases a combination of variants in 2 different genes illustrates the increased value of this strategy. The addition of other genes to our panel should further increase the yield.

P1-824

### TREATMENT WITH GROWTH HORMONE: EVALUATION OF THE RESPONSE AT FIRST YEAR OF THERAPY IN DIFFERENT PAEDIATRIC CATEGORIES

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**Objectives:** -To analyse the height gain obtained by our cohort of paediatric patients with idiopathic short stature after a year of treatment with growth hormone and to compare it with the other categories of patients treated with growth hormone in our hospital (partial GH deficiency, SGA and Turner syndrome) and with the criteria of good response to growth hormone therapy in the literature (figure 1). -To compare the growth hormone dose used by our hospital with doses proposed in the literature evaluating the

differences in terms of height gain obtained, biological risk, meant as an increase in IGF1 and HOMA-ir values, and economic costs.

**Methods:** Our study was conducted on 113 prepubertal patients (61 males and 52 females) of which 33 (29%) ISS, 34 (30%) GHD-p (partial, peak between 5-8 ng/mL), 33 (29%) SGA and 13 (12%) Turner. All patients (mean age 9aa at beginning of the study) were treated with rhGH for one year.

**Results:** In our population, all categories have respected the criteria of good response found in literature. The height gain of patients with ISS was lower than other categories although the different height gain is statistically significant only for GHD-p. This difference doesn't have an univocal interpretation, but is probably due to the low dose of growth hormone used in our centre. Our study shows that our dosage has a good safety profile because our patients have normal IGF1 values (only two patients have IGF1 values>2SDS) in contrast to the population of the literature that has IGF1 values ≥2SDS (value considered at risk).

**Conclusions:** -Despite the low dosage used in our patients, in the first year of rhGH treatment all categories have respected the criteria of good response of the literature, in particular the population of GHD-p and Turner syndrome; -Although the height gain of patients with ISS is below other paediatric categories, such as GHD-p (+0.53 SDS), SGA (+0.51 SDS), Turner syndrome (+ 0.74SDS), their growth is acceptable because it respect the criteria of good response, therefore treatment appears useful and justified; -Dosages used by our centre, above all for ISS, are equally efficient, more secure and cheaper.

<b>Bang et al.</b> (102) (126)	All categories	ΔHSDS>0,5 SDS
<b>Ranke et al.</b> (100) (125) (127)	GHD severe (<5ng mL)	ΔHSDS>0,4 SDS
	GHD partial (>5ng mL)	ΔHSDS>0,3 SDS
	SGA Turner	
<b>Bakker et al.</b> (128)	ISS	ΔHSDS>0,3-0,5 SDS ΔVC>1SDS o VC>3 cm/yr
	All categories	VC>1SDS of specific curve

Figure 1. criteria of good response in the literature

	ISS	GHD-p	SGA	Turner
EC baseline (yrs)	9,47	8,90	8,59	8,63
H baseline (SDS by Cacciani e Bernasconi)	-3,04	-2,62	-3,00	-2,69 Cacciani; 0,66 Bernasconi
IGF1 baseline (SDS by Cianfrani)	-1,23	-1,21	-0,96	-1,04
HOMA-IR baseline	0,85	0,84	0,81	0,89
G.V. baseline (SDS by Tanner)	-1,43	-1,79	-1,40	-1,66
Dose (mg/kg/sett)	0,20	0,20	0,21	0,27
ΔH (SDS by Cacciani e Bernasconi)	0,43	0,53	0,51	0,53 Cacciani; 0,74 Bernasconi
ΔIGF1 (SDS by Cianfrani)	1,68	1,67	1,86	2,15
ΔHOMA-IR	0,84	0,78	0,55	0,46
ΔG.V. (SDS sec. Tanner)	3,84	4,42	4,07	4,03

Figure 2. Data of our centre

# **HIGHLY INCREASED RISK OF GROWTH HORMONE DEFICIENCY (GHD) IN CHILDREN WITH A HISTORY OF SURGERY OF THE SELLAR OR SUPRASellar REGION OR ANOTHER ANTERIOR PITUITARY DEFICIENCY.**

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**Objectives:** Growth hormone stimulation testing (GHST) has been a standard practice required for the diagnosis of growth hormone deficiency (GHD). However, GHST may raise safety issues in a patient with co-morbidities.

The objective was to test whether there is an increased risk of GHD in patients having a history of surgery of the sellar and/or suprasellar region, one or more anterior pituitary hormone deficiencies associated with diabetes insipidus, congenital hypogonadism in males, neonatal hypoglycaemia, neonatal cholestasis, craniofacial midline defects or pituitary dysgenesis by imaging studies.

**Methods:** Case-control study to assess the association between highly suggestive risk factors and the existence of GHD.

Retrospective clinical chart review of all patients meeting the criteria for GHST, according to the Summary Statement of the GH Research Society, during a period 10 years (6/2004-5/2014). GHD diagnosis was based on maximal stimulated-GH < 6.0 ug/L (WHO 80/505) or < 4.7 ng/ml (WHO 98/574) after pharmacological stimuli of arginine (0.5 g/kg body weight) and/or clonidine (100 ug/m2 body surface) tests.

**Results:** A total of 671 patients were analyzed. Out of 142 patients with GHD, 93 had the postulated risk factors, while these were found in 7 of the 529 patients without GHD. There was a strong association between GHD and the existence of at least one of the postulated risk factors (Fisher's exact test  $P < 0.0001$ ); the risk of having GHD was approximately 6-fold higher (RR: 6,09, 95% CI: 4,49-8,27) in patients with one of the postulated risk factors, and the probability of having a risk factor was 141-fold higher (OR: 141, 95% CI 62-322) in the GHD group.

**Conclusions:** Our findings have clearly identified surgery of the sellar or suprasellar region and coexistence of congenital multiple pituitary hormone deficiencies with hypogonadism in males, neonatal hypoglycemia or cholestasis, diabetes insipidus or midline defects as major risk factors for GHD in pediatric patients. Our results suggest that GHST might not be necessary in these patients, thus avoiding unnecessary and invasive procedures.

P1-826

# **KINETIN IMPAIRS GH-1 SPLICING IN AN IN VITRO MODEL OF GROWTH HORMONE DEFICIENCY TYPE II**

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**Objectives:** Isolated GH deficiency type II (IGHD II), the autosomal dominant form of GHD, is primarily a splicing disorder which results from heterozygous splice-site mutations in *GH-1* gene that weaken recognition of exon 3 splice-sites and lead to mRNA missplicing. *In vitro* and transgenic animal data indicate that the IGHD II phenotype relates to the proportion of aberrant transcripts and suggest the pharmacologic correction of aberrant splicing as a possible therapeutic approach to IGHD II. In order to test this hypothesis we tested kinetin, a plant cytokine which was recently proven to act as a splicing modulator.

**Methods:** Rat pituitary cell line stably expressing hGrowth Hormone Releasing Hormone Receptor (GC-GHRHR) cells were transiently transfected with either *wt*-GH or different GH splice-site mutants, stimulated with GHRH (10nM) and/or treated w/wo different concentrations of kinetin. Twenty-four h after treatment extracellular GH secretion was measured in the cultured medium by DSL-GH ELISA and, after RNA extraction, the 17.5-kDa vs 22-kDa transcript ratio was determined by qRT-PCR. Further, to analyze the role of splicing regulators, the expression of several serine/arginine (SR)-rich proteins and SR-like splicing factors were assessed by Western blot. As a marker of transactivation via the GHRH activation, intracellular cAMP was measured.

**Results:** Treatment with kinetin impairs the correct splicing of *GH-1* by decreasing the 22-kDa mRNA by transcription activation. At the protein level, we could observe a decreased synthesis of the 22-kDa isoform ( $P < 0.05$ ) and therefore a

decreased 17.5/22-kDa ratio ( $P<0.05$ ). Overall, the imbalance between the two GH isoforms resulted in a statistically significant decrease of GH secretion ( $P<0.01$ ) in all GH splice-site mutants analyzed. Our data demonstrate that the kinetin does not directly activate GHRHR, as assessed through the lack of increase in cAMP levels after kinetin stimulation, suggesting that its action is mediated by a pathway different from that of GHRHR.

**Conclusions:** Our results demonstrate that this approach might be useful to identifying drugs able to revert abnormal splicing, and could open the way for novel therapeutic strategies for IGHD II and potentially other RNA-missplicing diseases.

P1-827

#### **PITUITARY STALK INTERRUPTION SÍNDROME. CLINICAL, BIOCHEMICAL AND NEURORADIOLOGICAL RELATIONSHIPS**

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**Objectives:** Pituitary stalk interruption syndrome (PSIS) is characterized by the association of an interrupted or thin pituitary stalk, absent or ectopic posterior pituitary and anterior pituitary hypoplasia. It is manifested as isolated (IGHD) or combined pituitary hormone deficiencies (CPHD) of variable degree and timing of onset with a wide spectrum of clinical phenotypes. PSIS may constitute an isolated morphological abnormality or be part of a syndrome. To evaluate retrospectively clinical signs and symptoms present at early life stages and analyze their relationship with hormone laboratory tests and diagnostic imaging in children with Congenital Hypopituitarism (CPH) and PSIS.

**Methods:** This retrospective, single-center, case-cohort study was performed in 42 children out of a total of 80 patients with CPH in a pediatric hospital over 26 years. The CA range: 5d-9.5y.

**Results:** The patients analyzed were 26/42 (62%) with CPHD and 16/42 (38%) with IGHD. The perinatal histories showed hypoglycemia (61% CPHD vs 19% IGHD  $p: 0.01$ ) jaundice (38% CPHD vs 25% IGHD) micropenis (75% CPHD) hypoglycemic seizures (75% CPHD) and cholestasis (19% CPHD). The CPHD patients consulted at the average age of 2.1y, 30% in neonatal period, 70% before 2 y. MRI showed that CPHD patients had 81% absence and 19% thin pituitary stalk ( $p:0.0001$ ); IGHD patients presented 56% absence and 44% thin pituitary stalk ( $p:0.5067$ ). The 100% of the patients diagnosed in the neonatal stage had absent pituitary stalk.

**Conclusions:** Characterization of GH deficient patients by presence and type of hypothalamic-pituitary imaging abnormality provides valuable information as a predictor of

phenotypic severity, treatment response and the potential to develop additional hormonal deficiencies. Based on our data we conclude that MRI should be part of research protocols in early periods of life in patients with an evocative clinical spectrum of hypopituitarism. The early diagnosis of CPH can be performed with accuracy based on a high index of clinical suspicion, late recognition may increase morbidity and mortality with potential permanent deleterious effects.

P1-828

#### **COMPLICATIONS IDENTIFIED IN THE NATIONAL PROGRAM FOR HGH USE IN THE DOMINICAN REPUBLIC**

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**Objectives:** Human Growth Hormone (HGH) deficiency is the primary indication for the use of this hormone for treatment in children. Although the FDA and EMA have approved its use for entities such as Turner, SGA, Prader Willi, Gen Shox deficiency, CRI, Noonan and idiopathic short stature, the efficacy and safety of the application of HGH is a controversial issue due to its varied use in a number of pathologies where there is no deficit and as any medication is not complication-free.

**Methods:** A longitudinal, retrospective, descriptive study was performed in patients receiving rGH for 7 years (January 2010 - 2017) pertaining to the national GH program. From these we analyzed their age, sex, dose, etiology, time of therapy and complications

**Results:** 149 cases were included, from which: 82 female (55%) and 67 male (45%).

23 (15.4%) of these cases (10/23 Deficit GH, 13/23 others) presented complications [13 female (56.5%) and 10 male (43.5%)] . Details are as follow: Intracranial hypertension: 8 (34.7%); Scoliosis: 7 (30.4%); Hyperglycemia: 6 (26.0%); Edemas: 2 (8.6%), Allergy: 1 (4.3%), Thymoma: 1 (4.3%). Two patients presented both intracranial hypertension and scoliosis, and scoliosis and femoral epiphysiolisis.

When relating the dose of GH in mg / kg / day was observed: 0.025 mg / kg / day (34%); 0.035 mg/kg/day (17.3%); >0.05 mg/kg/day (47.8 %). The time of onset of complications among patients with GH treatment: 0-6 months (17.3%), 6-12 months (30.4%), 1-3 years (52.1%), > 3 years (8.6%)

**Conclusions:** Conclusions: Our observations are in accordance with the complications reported in the literature when using GH, except for the development of a patient with thymoma, and are more frequent at higher doses between 1-3 years of treatment and in non-deficient cases of GH where it is advisable to carefully evaluate its use as GH is being added where it already exists.

P1-829

#### **SMALL FOR GESTATIONAL AGE BABIES: GROWTH PROGNOSIS AT EARLY ADOLESCENCE.**

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**Objectives:** Small for gestational age babies are at increased risk of growth retardation. This topic lacks attention and deserves better guidance. The objective of this paper is to illustrate the importance of this critical issue and to outline growth prognosis at the beginning of adolescence of female and male babies born small for gestational age in comparison to controls born appropriate for gestational age. It is also a descriptive epidemiologic study of small for gestational age infants.

**Methods:** Our study is a case-control descriptive study of children born small for gestational age in 2002-2003 at Notre Dame Des Secours university hospital, Byblos. The weight, height and head circumference at birth have been retrieved from the medical charts and the diagnosis of intra-uterine growth retardation (IUGR) have been made based on the growth curves published by I. Oslen et al in 2010. The current height and weight are taken for the two groups and compared with each other using the 't test' for a better understanding of the prognosis of growth in children born SGA. Forty cases and forty controls were recruited with neonatal infection and chromosomal abnormalities being the criteria of exclusion. The prevalence of children born SGA is 4.9 % in this study. Maternal risk factors including smoking and eclampsia were noted in both groups.

**Results:** The majority of children with IUGR catch similar growth to that of their controls. No adverse consequences are observed in these children at the age of 11-12 years. No correlation observed between IUGR and current weight and height of the children except for the current weight of the girls born SGA which is less compared to that of the controls. None of those children born SGA needed a GH treatment for the achievement of their optimal growth.

**Conclusions:** Children born SGA have similar dimensions in early adolescence compared to those born with a size appropriate for gestational age (AGA) except for the weight of the girls born SGA. The awareness of physicians and parents is important for early referral to treatment with GH therapy if necessary.

P1-830

#### EASYPD™ CONNECT OBSERVATIONAL STUDY (ECOS) – FRENCH CASE HISTORIES AND GROWTH OUTCOMES

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**Objectives:** ECOS (a 5-year, open-label, observational study in 24 countries, started in 2010) assessed 'real-world' adherence and effects on growth outcomes of children treated for growth disorders with Saizen<sup>®</sup> recombinant human growth hormone (r-hGH, somatropin) administered

by the easypod™ electronic auto-injector device. We report an interim analysis of the final results from ECOS in France (NCT01291394).

**Methods:** Data from 202 children (mean [SD] age 9.56 [3.65] years; 54% male) were available for analysis (111 GHD, 71 SGA, 18 Turner syndrome and 2 with chronic renal failure). The majority (180 [90%]) were r-hGH naïve at baseline.

**Results:** Mean treatment adherence was 81% (95% CI 79-84 [81% GHD and SGA, 83.6% TS]). Adherence was ≥80% for 180 patients (89%) at 3 months, 175 (86%) at 6 months, 145 (72%) at 1 year, 93 (46%) at 2 years and 38 (19%) at 3 years. After 1 year, r-hGH-naïve children had a median (Q1:Q3) change in height SDS of +0.45 (0.24:0.69), height velocity of 7.98 cm/year (6.80:9.13) and change in height velocity SDS of 1.89 (0.38:3.79). The Spearman's product-moment correlation for adherence rate and change in height SDS was 0.035. Adherence rate was analysed by subgroups (e.g. age, gender, pubertal stage, self/non-self-injection and regimen): median adherence was ≥90% and was similar in all the subgroups. Median adherence was >90% for patients with injections 6 days/week vs. with 7 days/week.

**Conclusions:** The cohort above were not sufficiently granular to prove a strong relationship between adherence and patient growth. Study cases were solicited to evaluate the impact in monitoring and these show the benefits of patient monitoring using the easypod™ device to alert the physician to potential red flags (e.g. puberty and poor family support) for on-going compliance.

P1-831

#### ESTRADIOL AND TESTOSTERONE POTENTIATE THE EFFECT OF GH ON JAK2/STAT5 ACTIVATION AND IGF-I GENE EXPRESSION IN HEPG2 CELLS

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**Objectives:** To evaluate the effects of estradiol (E<sub>2</sub>) and testosterone (T) on the activation of JAK/STAT5 and IGF-I gene expression induced by GH in a human hepatic cell line (HEPG2).

**Methods:** HEPG2 cells were grown in a steroid free medium. At 80% confluence, cells were treated with or without a low concentration of E<sub>2</sub> (20 pg/mL), or a high concentration of T (10 ng/mL), and were subsequently stimulated with rhGH 40 ng/mL for 15 min. Cytoplasmic JAK2, STAT5 and nuclear STAT5 phosphorylation was analyzed by Western immunoblotting. IGF-I expression was studied by qRT-PCR after 24 h incubation with each sex hormone, which was followed by 24 h co-stimulation with each sex hormone and GH. The data were analyzed by Mann-Whitney Test and expressed as mean ± SEM. Results are shown in the Table, p < 0.05 was considered significant.

**Results:** GH significantly stimulated the phosphorylation and the expression of all the molecules studied in HEPG2 cells. In cells preincubated with E<sub>2</sub>, GH showed an increase in cytoplasmic JAK2 and STAT5 and in nuclear STAT5

phosphorylation when compared with GH stimulation alone. In preincubated cells with T, GH showed a significant increase in cytoplasmic JAK2, whereas cytoplasmic STAT5 phosphorylation showed a decrease compared to GH alone. Nuclear STAT5 phosphorylation however, was similar to that observed after stimulation with GH alone. The expression of *IGF-1* increased when E<sub>2</sub> and GH stimulation were combined, but this significant increase was not observed when T and GH were combined.

	Basal
pJAK2/JAK2	0.51 ± 0.05
C-pSTAT5/STAT5	0.39 ± 0.03
N-pSTAT5/STAT5	0.36 ± 0.05
IGF-1	0.05 ± 0.02

\*p<0.05 GH+E<sub>2</sub> vs GH; \*\*p<0.05 GH+T vs GH

**Conclusions:** Low concentrations of estradiol and high concentrations of testosterone, potentiate the JAK2/STAT5 signaling pathway induced by GH, suggesting that critical concentrations of steroids may modulate GH sensitivity in HEPG2 cells.

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P1-832

## THE EFFECTS OF GH TREATMENT IN EXTREMELY LOW BIRTH WEIGHT CHILDREN BORN SMALL FOR GESTATIONAL AGE

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**Objectives:** The effects of growth hormone (GH) treatment have not been sufficiently evaluated in extremely low birth weight (ELBW) children born small for gestational age (SGA). The expected effect of GH treatment is an increase in height SD score (SDS) without accelerating bone age to achieve normal adult height. We evaluated the effects of GH treatment in SGA short stature with ELBW on height and bone age.

**Methods:** Thirty-eight children, who were born SGA with ELBW were recruited in this study. SGA was defined as both birth weight and birth length being below the 10th percentile of gestational age, and either of which being less than -2.0 SD. They were divided into three groups based on the presence of catch-up growth within the first 3 years of life (CU) and GH treatment (GH); CU-/GH+ (n=22), CU+/GH- (n=9) and CU-/GH- (n=7). Height SDS and bone age in prepubertal periods was retrospectively determined based on their medical records and compared among three groups.

**Results:** At the initiation of GH treatment, the mean age was 4.5 years (range; 3.0 to 8.4 years), and the mean height SDS was -2.9 in CU-/GH+. The mean height SD scores at prepubertal age in CU-/GH+, CU+/GH- and CU-/GH- were -1.3, -1.4 and -2.2, respectively. The mean height SDS of CU-/GH+ was significantly greater than that of CU-/GH-. Importantly, GH treatment increased height SDS by 1.6 such that the height SDS at prepubertal age of CU-/GH+ was comparable to that of CU+/GH-. The mean ratios of bone age to

chronological age (BA/CA) at prepubertal period of CU-/GH+, CU+/GH- and CU-/GH- were 1.07, 1.06 and 1.07, respectively. There were no significant differences of BA/CA among three groups.

**Conclusions:** The current study revealed that the bone age was not accelerated by GH treatment in SGA children with ELBW. Moreover, GH treatment resulted in an increase in height SDS to the values comparable to SGA children with ELBW who showed catch-up growth. These findings indicate that GH treatment is an effective approach to normalize the adult height without accelerating bone age in SGA children with ELBW.

1.04 ± 0.  
0.19 ± 0. P1-833

## IMPACT OF RISK FACTORS FOR FETAL GROWTH RESTRICTION (FGR) ON INTRAUTERINE GROWTH AND BIRTHWEIGHT

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**Objectives:** Abnormal uterine artery Doppler at 23 weeks is considered to be a risk factor for FGR. However, the incidence of being born small for gestational age (SGA) in those with abnormal Doppler is not defined.

1. To determine the incidence of birthweight <2<sup>nd</sup> centile (BW<C2nd) in pregnancies at high risk of FGR

2. To determine the effect of specific antenatal FGR risk factors on fetal growth trajectory and birthweight

**Methods:** Data were obtained from women seen in a clinic for those at high risk of FGR. Entry criteria were low first trimester PAPP-a or second trimester raised inhibin +/- αFP, and abnormal uterine Doppler ultrasound at 23 weeks (defined by mean pulsatility index >1.3 or notching on one or both waveforms). Pregnancies were categorised according to FGR risk subgroup; small placenta (<10cm) and high resistance index (>0.7, sPhRI), small placenta & normal RI (sPnRI), normal placenta & high RI (nPhRI), normal placenta & normal RI (nPnRI).

**Results:** 599 pregnancies that resulted in full term livebirths were recruited (sPhRI; 29, sPnRI; 48, nPhRI; 65 and nPnRI; 457) of which, 67 (11%) were SGA births. The proportion of babies with BW< C2nd was highest in the sPhRI group (13/29, 49%), compared with the sPnRI (6/48,13%), nPhRI (12/65, 18%) and nPnRI (36/457, 8%) groups. ANOVA analysis of fetal growth trajectories between 23 weeks and term showed differences between FGR risk groups in Δ weight (sPhRI =1.97kg, sPnRI =2.50, nPhRI =2.41, nPnRI =2.61; p<0.001). Mean birthweight was also significantly different (sPhRI =2.59kg, sPnRI =3.13, nPhRI =3.02, nPnRI =3.23; p<0.001).

**Conclusions:** In pregnancies considered to be at higher risk of FGR, 11% were born SGA, rising to 49% for those with a small placenta and high RI. Serum markers combined with uterine artery RI and placental size can be used to identify adverse growth trajectory and small size at birth. The postnatal growth trajectories and cardio-metabolic development of this cohort are currently under investigation.

# ACAN GENE MUTATIONS WERE FOUND IN 22 % PATIENTS BORN SGA WITH FAMILIAR SHORT STATURE AND ACCELERATED BONE AGE

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**Objectives:** Heterozygous mutations in the *ACAN* encoding a proteoglykan aggrecan cause autosomal dominant familial short stature (FSS). The phenotypical spectrum ranges from proportionate short stature to a mild skeletal dysplasia. What makes people with the *ACAN* mutations strikingly different from the other patients with short stature is the accelerated bone age that causes premature growth cessation. The aim of the study is to search for the *ACAN* mutations in the patients treated for short stature in our center.

**Methods:** Among all children treated for primary growth failure in our center, we selected patients with growth hormone deficiency (GHD) and those born short for gestational age (SGA). From both groups, patients with FSS (height -2 SD or lower before growth hormone (GH) treatment and at least one parent with height -2 SD or lower) and accelerated bone age (bone age equals calendar age or higher) were investigated. Exons, exon-intron boundaries and promotor region of *ACAN* were analyzed using direct sequencing.

**Results:** Out of 432 patients with GHD and 178 with SGA, 72 have FSS. Of these, 21 patients have accelerated bone age (12 in GHD, 9 in SGA). Their median height was -2.84 SD (range -2.07 to -4.12 SD) and their median of bone age acceleration was +0.8 years (range 0.0 to +2.8 years). We identified heterozygous *ACAN* mutations in 2/21 patients and in all affected family members with short stature: a frameshift mutation c.1425delA (p.Val478Serfs) and a missense substitution c.916A>T (p.Ser306Cys). Both patients were born SGA. Their height before GH treatment was -3.5 SD, resp. -3.4 SD, the height of their affected parent was -2.9 SD, resp. -3.6 SD and bone age was accelerated by 2 years in both. We have found no apparent phenotypic differences in patients with *ACAN* mutation if compared to those with no mutation.

**Conclusions:** Whereas the proportion of subjects with *ACAN* mutation among patients with GHD and/or SGA was quite low (0.3 %), in a selected subgroup of children with FSS born SGA and having accelerated bone age was the frequency of *ACAN* mutation detection 2/9, i.e. 22 %. Targeted genetic testing is worth using in routine clinical praxis in this selected subgroup of patients.

The study was supported by Ministry of Health of the Czech Republic, grant no. 16-31211A.

# EFFECT OF COMMUNITY-BASED FOOD SUPPLEMENTATION IN IMPROVING GROWTH OF STUNTED UNDER-FIVE CHILDREN IN WEST NUSA TENGGARA

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**Objectives:** Stunted children have become a global health problem. Indonesia ranked fifth within countries with highest prevalence of stunting. Prevalence of underweight children in West Nusa Tenggara is as high as 30% and the province also ranked third in number of stunted children in Indonesia. Local government has tried to tackle this problem by giving supplementary food to underweight children. We aimed to assess whether community-based food supplementation was successfully improved children's growth

**Methods:** We conducted a prospective cohort study for 10 months. The children were given supplementary food according to Ministry of Health guidance which consist of formula milk, high calorie biscuit, and eggs until their weight was considered normal according to their current age and sex. Child's weight and height was measured every 3 months and the result was plotted in WHO growth charts for weight-for-age, height-for-age, and weight-for-height. Z score <-3 SD was classified as severely wasted, severely underweight, or severely stunted. Z score between -2 and -3 SD was classified as wasted, underweight, or stunted and -score >-2 SD was classified as normal.

**Results:** Twenty-five under-five children were participated in this study. Subjects' median age was 29 months old. None of the subjects had normal weight-for-age Z-score at the beginning of the study. Eighty four percent (N=21) of the subjects were severely underweight. Only 8% (N=2) subject had normal height-for-age z-score and 88% (N=22) of them were severely stunted. However, 80% (N=20) of the subjects had normal nutritional status. Changes of weight-for-age z-score throughout the study were varied. The highest median score was in the tenth month of follow up (-3.82). The highest median score of height-for-age score and weight-for-height score was also in the last month of follow up. At the end of the study, only one subject had normal weight-for-age score (4%) and none of the subjects had normal height-for-age score (N=0, 0%)

**Conclusions:** Supplementary food given by the government has not been successful in improving both body weight and height of under-five children in our study

# TREATMENT OUTCOMES IN CHILDREN WITH NOONAN SYNDROME – AN ANALYSIS FROM NORDINET® IOS AND ANSWER PROGRAM

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**Objectives:** To describe the characteristics of growth hormone (GH)-treated patients with Noonan syndrome who achieved near adult height.

**Methods:** Baseline characteristics and growth response to GH treatment to near adult height were evaluated for GH-naïve patients with Noonan syndrome enrolled in two complementary non-interventional, multicenter studies – NordiNet® International Outcome Study (IOS) (NCT00960128) and the ANSWER Program (NCT00615953) – which evaluated the long-term effectiveness and safety of Norditropin® ([somatropin] Novo Nordisk A/S, Denmark) as prescribed by treating physicians in a real-life clinical setting. Near adult height was defined as height achieved at age >18 years for boys and girls, or >17 years for boys and >15 years for girls with height velocity <2.5 cm/year. Height standard deviation score (SDS) was calculated using national and Noonan syndrome-specific (Ranke) references. Data are presented as median [Q1; Q3].

**Results:** Of 318 enrolled patients, 28 (32% girls) achieved near adult height: age at GH start was 11.1 [9.1–13.3] years for girls, 14.0 [11.8;15.4] years for boys; height SDS (national) at GH start was –2.6 [–2.9; –2.5] for girls, –2.9 [–4.0; –2.4] for boys; height SDS (Ranke) was 0.1 [0; 0.3] for girls, –0.9 [–1.5; –0.1] for boys; midparental height SDS was –0.4 [–0.8; 0] for girls, –0.7 [–1.3; 0.2] for boys. Age at near adult height was 15.5 [15.3; 16.6] years for girls, 18.1 [17.5; 19.3] years for boys. Duration of treatment to near adult height was 4.3 [2.7; 6.2] years for girls, 4.3 [3.4; 6.1] years for boys. Average GH dose during treatment was 43.1 [40.6; 49.8] µg/kg/day for girls, 44.6 [37.1; 51.7] µg/kg/day for boys. Near adult height SDS (national) was –1.5 [–2.0; –1.0] for girls, –1.7 [–2.4; –1.2] for boys. Near adult height SDS (Ranke) was 0.9 [0.8; 1.1] for girls, 0.8 [0.2; 1.7] for boys. At enrollment, 96% (n=27) of patients had height below the normal range. At near adult height, 67.9% (n=19) had height SDS (national) within the normal range (≥–2 SDS).

**Conclusions:** Approximately two-thirds of GH-naïve patients with Noonan syndrome achieved a near adult height SDS within the normal range after an average of 4 years of GH treatment.

P1-837

#### DEVELOPMENT OF A LONG-ACTING (LA) GROWTH HORMONE (GH): SIZE MATTERS

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**Objectives:** Multiple attempts have been made over 25 years to develop a LA-GH, to improve poor compliance associated with daily injections.<sup>1-3</sup> Initial depot formulations were compromised by poor skin tolerability (pain, nodule formation and lipoatrophy).<sup>3,4</sup> Protein fusion technologies have been developed to extend the half-life of hGH, leveraging increased molecular weight (MW) from ~60 kDa to >100 kDa<sup>3</sup> to reduce clearance.<sup>3</sup> To date only LA-GH based on the release of unmodified GH have gained regulatory approval.

**Methods:** N/A

**Results:** GH is highly conserved across species, with MW ranging from 19.4 kDa to 22 kDa.<sup>5</sup> It is likely that GH size has been under evolutionary control so that GH can interact with its receptor in various tissues, including both well-vascularized organs (eg, liver, muscle and heart) and poorly vascularized tissues (eg, the growth plate and fat). While IGF-1 from hGH binding in liver appears to account for 80-85% of long bone growth, hGH needs to diffuse into the growth plate to provide 15-20% of growth, via direct effects and induction of IGF-1 release within the growth plate.<sup>6</sup> Studies with labeled dextrans show a 40 kDa MW cut-off for diffusion into the growth plate of mice.<sup>7</sup> It is thus possible that large GH analogs might generate hepatic IGF-1, which diffuses into the growth plate and fat cells, but if the diffusion of GH is impeded suboptimal growth and increased fat mass/BMI may occur due to unopposed IGF-1.

TransCon hGH is a novel LA-GH prodrug in which rhGH is transiently linked to an inactive carrier, extending the half-life of the hormone. Unmodified 22 kDa hGH is sustainably released via physiological pH and temperature-induced linker hydrolysis. It is the only LA-GH based on unmodified hGH that is dosed at the same mg/kg dose and provides comparable exposure to daily hGH.<sup>8</sup>

**Conclusions:** A 6-month Phase 2 randomized study of TransCon hGH at 0.14, 0.21, or 0.30 mg/kg/week vs. daily Genotropin™ at 0.21 mg/kg/week demonstrated similar annualized HV of 11.9, 12.9, and 13.9 cm/year, respectively vs. 11.6 cm/year for daily Genotropin™, and stable BMI values, with mean change in BMI (kg/m<sup>2</sup>) of -0.04, 0.36, and -0.26 kg/m<sup>2</sup>, respectively<sup>8</sup>, strongly suggesting that the unmodified 22 kDa hGH reached GH receptors in all tissues.

P1-838

#### PEAK GROWTH HORMONE AFTER GLUCAGON STIMULATION TEST CORRELATES BETTER WITH IGF-I LEVELS IN SHORT CHILDREN

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**Objectives:** to investigate the diagnostic value of the glucagon test versus clonidine test in relation to IGF-I level in children and adolescents with short stature.

**Methods:** 100 children and adolescents with short stature (HtSDS = or < -2) underwent GH stimulation test using either Glucagon (n =22) or clonidine (n = 78) standard tests. Their

mean age was 10 +/- 2.9 years ; (30 females and 70 males). Apart from short stature, all had normal physical examination, normal renal and hepatic functions and normal hemogram. None had history of systemic disease, irradiation or head trauma. They had normal serum free T4 and TSH concentrations. IGF-I was measured in all children as a screening test. 22 children underwent Glucagon stimulation test while 78 children underwent clonidine stimulation test, without priming with sex steroids. Random selection is achieved because the ordering endocrinologists were blinded for the study.

**Results:** Mean GH peak response to glucagon was significantly lower than that observed after clonidine ( $P < 0.01$ ). GH peak after glucagon was less than 7 µg/l in 33% of subjects versus 20% of subjects after clonidine. The magnitude of the GH peak after glucagon was correlated significantly with IGF-I level ( $r = 0.31$ ,  $p = 0.04$ ) but not with the peak after clonidine stimulation ( $r = 0.14$ ,  $p > 0.05$ ). (table)

**Conclusions:** This study shows that glucagon has an effective GH-releasing activity and can be used to evaluate somatotroph function in young children with short stature. Peak GH secretion after glucagon stimulation correlate better with IGF-I levels compared to peak GH peak after clonidine. Data for this test in young children need to be established before its use in clinical practice. Normative data need to be established before use in clinical practice.

Clinical and lab data for short children tested by clonidine ver

	Age	Basal GH	peak GH	IGF1	FT4
	yr	ug/l	ug/l	Ug/l	Pmol/l
Clonidine	9.94*	1.85	10.67*	154.75	15.18
n = 78	3.01	3.22	6.31	82.81	1.96
Glucagon	7.36	1.01	6.32	99.00	15.32
n = 22	3.06	1.38	3.11	52.02	1.65

P1-839

SOMAPACITAN BINDS REVERSIBLY TO HUMAN ALBUMIN AT DOMAIN III

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**Objectives:** To identify binding sites for somapacitan on human albumin. Somapacitan is a human growth hormone (hGH) derivative. Somapacitan binds reversibly to albumin via a fatty acid moiety attached to a single mutated amino acid on the hGH backbone. Somapacitan is currently in clinical development for once weekly treatment of growth hormone disorders.

**Methods:** X-ray crystallography, small angle X-ray scattering (SAXS), size exclusion chromatography (SEC) and isothermal titration calorimetry (ITC) were used to identify somapacitan binding sites on human albumin. A ternary complex of

somapacitan, human albumin and the neonatal Fc receptor (FcRn) was crystallised. FcRn binds human albumin domains I and III potentially blocking binding sites on these domains. The binding stoichiometry of somapacitan to human albumin and albumin subunit preparations was examined. Human albumin subunits used were domains I+II and III. ITC was used to investigate the binding of somapacitan to human albumin and human albumin subunits.

**Results:** One somapacitan binding site on domain II was identified by X-ray crystallography. SEC suggested a possible binding site on domain III. ITC analysis revealed that somapacitan binds to high and low affinity binding sites on subunits I+II and III in a temperature-dependent manner. At 37°C somapacitan only binds to a high affinity binding site on domain III.

**Conclusions:** A model of human albumin with somapacitan binding at two sites was identified. One binding site on domain II determined by crystal structures, and one on domain III determined from SEC and ITC analysis. The somapacitan binding is temperature-dependent. At 37°C somapacitan only binds to the high affinity binding site on domain III.

P1-840

THE IMPACT OF GROWTH HORMONE TREATMENT ON HEIGHT GAIN OVER 3 YEARS AND FINAL HEIGHT OF CHILDHOOD CANCER SURVIVORS AFTER HEMATOPOIETIC SCT WITH CRANIOSPINAL IRRADIATION OR TOTAL BODY IRRADIATION

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**Objectives:** Childhood cancer survivors (CCS) who have been treated with cranial or total body irradiation (TBI) are at risk for growth hormone deficiency (GHD). We evaluated effect of GH on height in CCS who underwent hematopoietic stem cell transplantation (HSCT) with craniospinal irradiation (CSI) or TBI.

**Methods:** Retrospective cohort study (2004-2016) of 38 CCS (31 males) undergoing HSCT treated with GH for irradiation-induced GHD (23 CSI; 15 TBI). Diagnoses included: medulloblastoma (n = 23), neuroblastoma (n =10), acute leukemia (n = 5). We analyzed the following data: sex, age, BMI, IGF-1, puberty stage, other hormone deficiency and adverse effects including secondary neoplasms (SNs). Heights at specific time points were analyzed: diagnosis of primary cancer, HSCT, start of GHT, after 1 yr GHT, after 2 yrs GHT, after 3 yrs GHT and final height (FH) compared using height SDS (HSDS) and cumulative SDS change.

**Results:** The mean age at start of GH treatment was 9.4 yrs. Significant change was found in mean HSDS from cancer

diagnosis to after 3 yrs of GH therapy ( $-2.07 \pm 0.87$  at tumor diagnosis;  $-2.21 \pm 0.87$  at HSCT;  $-2.31 \pm 0.89$  at start of GHT;  $-1.99 \pm 0.79$  at after 1 yr;  $-1.85 \pm 0.77$  at after 2 yrs;  $-1.57 \pm 0.86$  at after 3 yrs of GHT, all mean HSDS,  $p < .001$ ). For the 18 patients for whom final height measurements were available, mean FH HSDS increased by  $-1.99 \pm 1.35$  SDS, but had no statistical significance ( $p = 0.281$ ). Height gain SDS over 3 yrs from start of GHT was positively correlated with female ( $p = 0.001$ ), younger age ( $p < .001$ ) and IGF-1 SDS increment during 3 yrs from start of GHT ( $p < .001$ ). Type of radiation, age at HSCT, age at TBI or CSI, duration of GHT, age at start of GHT and BMI did not correlate with height gain SDS and FH SDS. In multiple linear regression, only female was positively correlated with FH and total height gain ( $p = 0.002$ ). SN was diagnosed in 3 patients, meningioma, papillary renal cell carcinoma and papillary thyroid carcinoma.

**Conclusions:** In our CCS undergoing HSCT with CSI or TBI, GH therapy did not show significant increase in FH SDS. But when considering a positive impact of GH therapy on height gain and associated positive factors from this study, further study investigation and close long-term follow up of GH therapy are needed.

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Table 1. Baseline characteristics of the subjects

Characteristics	Total subjects (n=38)	P-value*
male/female, n	38 (31/7)	<.001
CSI/TBI, n (%)	23 (60.5)/ 15 (39.5)	0.089
Age at primary cancer diagnosis (yr), (range)	4.9 (0.3 – 11.6)	
Age at radiation therapy (yr), (range)	6.3 (1.2 – 11.8)	
Age at HSCT (yr), (range)	5.9 (1.2 – 12.6)	
Type of cancer (MBL/NBL/AL), n (%)	23 (60.5)/ 10 (26.3)/ 5 (13.2)	
Age at GH start (yr), (range)	9.3 (4.8 – 14.0)	
5 – 10, n (%)	22 (57.9)	0.001
≥ 10, n (%)	16 (42.1)	
Duration of GH therapy (yr), (range)	3.9 (3.1, 8.3)	
Time from cancer diagnosis to GHD diagnosis (yr)	3.3 (2.0, 9.1)	
Time from end of tumor therapy to GH start (yr)	2.3 (1.0, 8.1)	
Height SDS at GH start	-2.09 (-4.51, -0.65)	

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P1-841

# THE CORRELATION BETWEEN SERUM NT-PROCNP LEVELS AND GROWTH IN HEALTHY CHILDREN

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**Objectives:** C-type natriuretic peptide (CNP) has been shown to play a critical role in linear growth. Its bio-inactive aminoterminal propeptide (NT-proCNP) is easily measurable in plasma, and levels reflect the rate of CNP biosynthesis. Previous studies showed that serum NT-proCNP levels positive correlated with height velocity in healthy children, and increased after GH treatment in children with achondroplasia/hypochondroplasia. The aim of this study was to investigate the correlation of serum NT-proCNP levels with current growth status in healthy Korean children.

**Methods:** Our subjects included 115 boys and 91 girls aged 3-15years. All children with growth disorder (ex. short stature, precocious puberty and other endocrine or chromosomal disorder) were excluded. Serum NT-proCNP levels were measured by enzyme-linked immunosorbent assays (Biomedica, Austria). We analysed for relationship between NT-proCNP and other auxological factors (age, Height-SDS) by pearson correlation. A Mann-Whitney U test was performed between group A (Ht-SDS<25percentile) and group B (Ht-SDS>75percentile) for NT-proCNP levels.

**Results:** There were no significant difference in ages between boys and girls ( $8.7 \pm 2.8$ :  $8.8 \pm 2.7$ ,  $P = 0.648$ ). There were no significant difference in serum NT-proCNP levels between boys and girls ( $5.9 \pm 3.3$ :  $6.6 \pm 3.6$ ,  $P = 0.124$ ). For both gender, Serum NT-proCNP levels were higher in infants and declined with age until puberty. Serum NT-proCNP levels were negatively correlated with age in all subjects ( $r = -0.177$ ,  $P = 0.011$ ). During puberty, median NT-proCNP levels peaked at Bone age 12-13 years in boys and at 12 years in girls. Serum NT-proCNP levels were lower in subjects with group B compared with group A. however, that is not statistically significant.

**Conclusions:** In this studies, Serum NT-proCNP levels were not reflect the degree of the current height status. However, Serum NT-proCNP levels correlated with height velocity by age in healthy children.

P1-842

# SHORT STATURE DUE TO TWO NOVEL HETEROZYGOUS IGF1R MUTATIONS AND RESPONSE TO GH TREATMENT

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**Objectives:** Heterozygous mutations in the type I insulin-like growth factor receptor gene (*IGF1R*) cause pre- and postnatal growth failure and microcephaly.

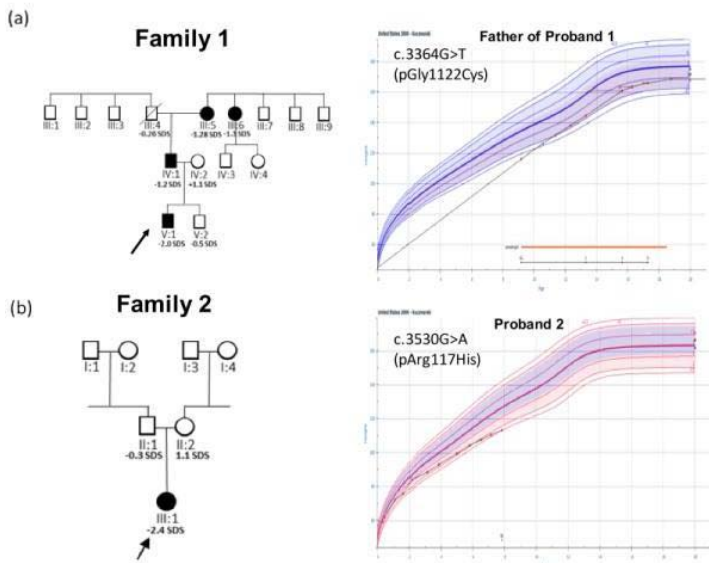
**Methods: Case presentations:** Proband of family 1, a 7.5-year-old male, presented with proportionate short stature (height -2.0 SDS). He was born SGA (birth weight SDS -2.1) and small head circumference (-2.0 SDS). Evaluation revealed a delayed bone age and elevated levels of IGF1 and IGFBP3. The father (38 yo) had also been born SGA (birth weight -3.8 SDS), had childhood short stature (height SDS -3.0) and had been treated with rhGH (0.46mg/kg/wk) from 9 to 18 years of age and had reached an adult height of 168.5cm (SDS -1.1; delta height SDS +1.9; Fig. 1). Paternal grandmother is also short (-1.6 SDS) and has a low head circumference. The mother's and younger brother's heights were normal (+1.5 and -0.5 SDS, respectively). Proband 2 is a healthy 8y10m old

girl with short stature (height SDS 2.4), born SGA (birth weight SDS -1.5) to healthy parents of normal height (father - 0.3; mother +1.1 SDS). The patient has IGF1 and IGFBP3 levels in the upper limit of normal and a normal GH profile (max peak 15microg/L), which taken together with the clinical picture raised the suspicion of mild IGF1 insensitivity.

**Results:** In each family, a novel heterozygous non-synonymous missense IGF1R variant were identified by Sanger sequencing. In family 1, c.3364G>T (pGly1122Cys) in the proband, his father and grandmother, but not in the unaffected brother. In family 2, a *de novo* missense variant c.3530G>A (pArg117His) was detected. Both variants were rare (not present in the ExAC or the 1000 genomes database) and predicted to be damaging by at least 4 of 5 in silico prediction tools. Interestingly, the father of proband 1 had been treated with GH for 9 years with a height gain of 1.9 SDS (Fig 1).

**Conclusions:** Our study presents two novel heterozygous IGF1R mutations causing short stature and microcephaly. One individual treated with GH for 9 years at relatively high dose suggest that individuals with heterozygous IGF1R mutations respond to GH treatment. However, further studies are needed to elucidate the efficacy of GH treatment in this condition.

**Fig 1.** Pedigree and growth charts for family 1(a) and family 2 (b).



P1-843

### TWO SISTERS WITH TURNER SYNDROME

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**Objectives:** Turner syndrome (TS) is a sporadic disease due to partial or total absence of the second X chromosome in a phenotypic female and has a prevalence of 1/2500 live female births. 45,X monosomy is found in approximately 50% of cases. Familial forms of TS have been documented rarely with <10 cases since the first report in 1963 of an aunt and niece this was followed in 1978 by seven affected women in

three generations of the same family.we report a familial case of TS.

**Methods:** Two sisters from non-consanguineous parents attended our unit with short stature. Clinical biological and morphological findings are summarized in the table below

### Results:

Parameters	Patient 1	Patient 2
Age (years)	6	9
Range in siblings	2/4	1/4
Height(cm)	100(-3SDS)	113(<-3SDS)
Dymorphism	Short neck, cubitus valgus, epicanthus, hypertelorism, high arched palate, wide-spaced nipples	Short neck, cubitus valgus, epicanthus, high-arched palate, wide-spaced nipples, shield chest.
Karyotype	45,X	45,X
Heart ultrasound	No congenital malformation	No congenital malformation
Kidney ultrasound	Horseshoe kidney	Normal size and position kidneys
Ear examination	normal	normal
Thyroid function	TSH:1,7-µUI/ml	TSH:2,18µUI/ml
Other abnormalities	None	Celiac disease

### Conclusions:

This family adds to the spectrum of reported cases of familial TS .It is possible that this malfunction arose as a mutation in one or the other parent's germ cell line. An alternative mechanism could be the presence of mosaicism in either parent's gonadal tissue. The chromosomal abnormalities including mosaicism and genetic defect can be transmitted to the descendants in familial cases and predispose to chromosomal fragility leading to chromosomal aneuploidy

P1-844

### NOVEL ACAN MUTATIONS IN FOUR CHILDREN WITH SHORT STATURE FROM TWO FAMILIES WITHOUT CONSISTENTLY ADVANCED BONE AGE

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**Objectives:** Heterozygous ACAN mutations have been reported to cause short stature associated with advanced bone age and various other clinical features. We used whole exome sequencing to identify the genetic cause of short stature observed in 4 children belonging to 2 families, and found two novel ACAN mutations. This enabled us to further expand the phenotype of patients with ACAN mutations.

**Methods:** The exome was sequenced in 2 siblings and both parents from one family (A), and in two siblings from another family (B). All children were born at term with normal birth weights. The children (age 2.6-7.6 yrs) presented with short stature (height -3.3 to -2.4 SDS), SH/H ratio ranging from +0.75 to +3.0 SDS, and armspan/H ratios ranging from 0.93 to 1.0. Bone ages varied from delayed (7 and 24 months) in two children to equal to chronological age and advanced (+1.1 yrs) in one child. At follow-up, bone age was still delayed in 1 patient, consistent with chronological age in 2 children, and advanced in 1. In both families 1 parent also had short stature, suggesting autosomal dominant inheritance. The exome sequences were analysed with a stringent post-sequencing annotation pipeline including a gene panel of 109 genes for filtering of the data.

**Results:** In all 4 children a heterozygous nonsense mutation in the *ACAN* gene was identified, inherited from the mother in family A (height -4.1 SDS), segregation analysis in family B is still ongoing. Several of their family members are known with short stature. The mutations were located in the G1 domain (c.706C>T,p.(Arg236\*)) in family A, and in the GAG attachment region (c.6673C>T,p.(Gln2225\*)) in family B. In three short relatives belonging to family B severe osteochondritis dissecans was observed as an extra clinical manifestation.

**Conclusions:** Two novel heterozygous nonsense mutations in *ACAN* were identified in two families with short stature, with osteochondritis dissecans segregating with short stature in one family. Remarkably, the bone age was only advanced in one of the four children, whereas in the other three children the bone age varied from delayed to consistent with chronological age. This indicates that the absence of advanced bone age should not be considered a contraindication for testing for *ACAN* mutations in children with short stature.

P1-845

#### IMPAIRED LINEAR GROWTH IN SIBLING BOYS WITH FAMILIAL HYPERKALEMIC PERIODIC PARALYSIS ASSOCIATED WITH THERAPY INDUCED RENAL TUBULAR ACIDOSIS

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**Objectives:** Hyperkalemic periodic paralysis (HyperPP) is a channelopathy characterized by episodic muscle weakness or paralysis with hyperkalemia. Recently, dichlorphenamide (Keveyis), a carbonic anhydrase inhibitor, was FDA approved for use in HyperPP. Since starting dichlorphenamide, siblings with HyperPP had significant decrease in frequency of episodes, but developed worsening impairment of linear growth velocity (GV) and renal tubular acidosis (RTA).

**Methods:** JS was evaluated for short stature (height 2.6<sup>th</sup> %ile, MPH between 25-50<sup>th</sup> %ile) at 6.5 yrs. IGF-1 level was 64 ng/mL (63-292 ng/mL) with delayed bone age (-2.4 SDs). GH stim testing was normal (peak GH 18.5 ng/mL). The working diagnosis was CDGP. He was re-referred at age 9 yrs with declining GV (height 0.8<sup>th</sup> %ile, GV 3.9cm/yr). He transitioned from acetazolamide to dichlorphenamide 5 months prior. His weight had increased from the 9<sup>th</sup> to 25<sup>th</sup> %ile since previous visit. Repeat IGF-1 was 79 ng/mL (81-255 ng/mL), with delayed bone age (-4SDs). Lab work revealed a normal anion gap acidosis, positive urine anion gap with normal renal function, consistent with RTA. He was prescribed sodium citrate.

His brother, SS, was evaluated for short stature (height 9<sup>th</sup> %ile) at 11 yrs. He had a gradual decrease in his height percentile with GV of 3.3cm/yr over 3 yrs with most significant decline in the past year. He had stable weight gain between the 50-75<sup>th</sup> %ile. He transitioned from acetazolamide to dichlorphenamide 6 months prior to evaluation. IGF-1 level was 139 (81-255 ng/mL) and bone age was congruent with chronological age. GH stim testing results are pending. Lab work revealed evidence of RTA, and he was prescribed sodium citrate.

**Results:** The etiology of the boys' deceleration in GV is multifactorial. Both are treated with low dose stimulants for ADHD, and JS also has CDGP. However, RTA is an important cause of growth failure that impairs the action of GH and IGF-1, and increases bone resorption.

**Conclusions:** We hypothesize that treatment of the acidosis caused by dichlorphenamide will improve their linear GV. It is important for providers to be aware of potential development of metabolic acidosis while on dichlorphenamide and how it can negatively impact linear growth.

P1-846

#### HETEROZYGOUS *IRS1* MUTATION CAUSES PRE- AND POSTNATAL GROWTH RETARDATION: A FAMILY WITH HETEROZYGOUS *IRS1* MUTATION AND *IGFALS* MUTATION.

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**Objectives:** *IRS1* is a key element for both insulin and IGF1 signaling. To date, there have been no reports of *IRS1* mutations in patients with growth failure. We report the first identified small for gestational age (SGA) familial

cases with short stature and heterozygous mutations in *IRS1* and/or *IGFALS*.

**Methods:** Case 1 was a 14-year-old Japanese girl born at full term, with a low birth weight (-1.9 SD) and height (-3.8 SD). Her father had a normal stature, and her mother had a short stature (-2.2 SD) with a low birth weight (-1.6 SD). At 6 years old, the height of patient 1 was -2.5 SD; therefore, GH treatment for SGA short stature was started. Case 2 was a 17-year-old Japanese girl who was also the elder sister of case 1. She was born at full term, with a low birth weight (-2.2 SD) and height (-2.5 SD). Although she was -2.0 SD for short stature before starting puberty, her final height was only 144 cm (-2.7 SD). Both patients were healthy except for the short stature, and mental development was normal. For the genetic analysis of these patients, we performed a targeted resequencing using the TruSight One sequencing panels. For the functional analysis of mutant *IRS1* and *IGFALS* proteins, we constructed FLAG-tagged *IRS1* or *IGFALS* vectors, and then performed immunoblotting of both *IRS1* and *IGFALS* by using HEK293 cells or L6 myoblasts transfected with wild type or mutant proteins.

**Results:** Case 1 and 2 and their mother were heterozygous for a p.Ser685\_686del mutation in *IRS1*. Furthermore, case 1 and her father were heterozygous for a p.Arg229His mutation in *IGFALS*. The HEK293 cells transfected with the mutated *IRS1* construct showed decreased *IRS1* expression levels, and the L6 myoblasts stably transfected with the same construct revealed increased degradation of *IRS1*. Furthermore, HEK293 cells transiently transfected with mutated *IGFALS* showed significantly lower expression of *IGFALS*.

**Conclusions:** Our findings suggest that the *IRS1* mutation led to a dysfunction of *IRS1* by increasing *IRS1* degradation, thus resulting in pre- and postnatal growth retardation. Additionally, the *IGFALS* mutation led to decreased production of *IGFALS* and result in more severe growth retardation in case 1. Thus, we speculate that mutations in *IRS1* can cause SGA short stature.

P1-847

#### ASSOCIATION OF HYPOCHONDROPLASIA WITH ACANTHOSIS NIGRICANS AND INSULIN RESISTANCE

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**Objectives:** We aimed to evaluate association of hypochondroplasia with acanthosis nigricans and insulin resistance.

**Methods:** Hypochondroplasia is associated with short limbs, short stature and lumbar lordosis, usually exhibiting a milder phenotype than achondroplasia. The occurrence of insulin resistance and acanthosis nigricans in patients with hypochondroplasia is rarely reported.

**Results:** A 14.5 years old female patient presented to our clinic with short stature. The patient was born with 2000 gr by caesarean section, followed with uncomplicated pregnancy. On physical examination; Height: 128 cm (2 SDS)],

brachydactyly, limitation of elbow extension, short legs [sitting height/height ratio: 0.6 (>2.5 SDS)], a short arm span (10 cm shorter than her total height) and acanthosis nigricans. Full blood count, biochemical analysis and thyroid function tests were normal. Since the clinical features were consistent with skeletal dysplasia, a heterozygous p.N540K (c.1620C>A) mutation was detected in *FGFR3* gene. Fasting blood glucose was 90 mg/dl (75-100), fasting insulin was 18,1 IU / mL (2-18) and HbA1c value was 5.8. The homeostasis assessment index for insulin resistance (HOMA-IR) was 4.04 (normal range 0.36–2.41) indicating insulin resistance. Postprandial glucose was 121 mg/dl and postprandial insulin was 42.7 IU / mL, which suggested insulin resistance.

**Conclusions:** This finding demonstrates insulin insensitivity and acanthosis nigricans associated with hypochondroplasia. Long-term follow-up for patients with hypochondroplasia is required to clarify the risk of long-term metabolic complications.

P1-848

#### INTELLECTUAL DISABILITY AND OVER-GROWTH --A CASE CAUSED BY NOVEL MUTATION OF *NFIX* GENE BASED ON WHOLE-EXON SEQUENCING

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**Objectives:** Intellectual disability and overgrowth can be seen in some genetic disorders. Here we report a patient showing moderate Intellectual disability with overgrowth (height > 3SD), who diagnosed with Marshall-Smith syndrome caused by a novel mutation of *NFIX* gene identified by whole-exon sequencing (WES).

**Methods:** Genomic DNA from the proband was extracted from peripheral blood leukocyte. Karyotype analysis was performed on metaphase cells. Array-based comparative genomic hybridization of DNA from the patient's peripheral blood lymphocytes and WES were performed respectively.

**Results:** The proband, a 4yr2mon old girl, is the first child of healthy nonconsanguineous Chinese parents. She was born by uterine-incision delivery after 41 weeks of gestation. Her birth weight was 3.5 kg. She showed a distinctive face including prominent forehead, high anterior hairline, downslanting palpebral fissures, prominent chin and blue sclera. During further development, delay in language and motor skills as well as poor coordination were noted. She presents poor wound healing, bruising susceptibility, accelerated skeletal maturation (+2.5 years) and constipation. Her height was 122cm (> 3SD) and her fingers were long. Brain MRI performed less white matter. Karyotyping was 46, XX and array CGH analysis was normal. Then we performed WES for this patient and identified a novel frameshift mutation of *NFIX* gene.

**Conclusions:** *NFIX* analysis should be considered in patients presenting with overgrowth, macrocephaly and

developmental delay including those in whom Sotos syndrome has been considered clinically but are negative for pathogenic *NSD1* variants or chromosome microdeletion.

P1-849

#### **MECASERMIN TREATMENT OF A CHILD WITH CONGENITAL HYPERINSULINISM LINKED TO INS-R MUTATION**

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**Objectives:** Mecasermin is recombinant human insulin-like growth factor 1 (IGF1) which is approved for the treatment of short stature in children with documented primary IGF1 deficiency.

Leprechaunism, also known as Donohue syndrome, is a severe disease, secondary to a severe congenital insulin resistance, with prenatal and neonatal growth retardation, typical dysmorphic features, glycaemic dysregulation characterized by hyperinsulinemia and hyperandrogenism. These patients have a poor prognosis with death in the first year of life.

**Methods:** We describe the case of a 3.5 years child, born at 35,4 weeks, with severe fetal growth restriction (weight 1149 gr; length: 38 cm; cranial circumference: 28 cm), typical facial features with low implant ears, low implant hairs, hypertrichosis, hypertrophic external genitalia, postnatal growth failure, and severe hyperglycaemia (327 mg/dl) alternated with hypoglycaemia (10 mg/dl) also during i.v. infusion of glucose; significant hyperinsulinism (1000 mcU/dl) with elevated C peptide levels (43,41 ng/ml), persistent hypertension (113/74 mmHg). He has consanguineous parents (cousins) and the mother underwent abortions before the baby was born.

**Results:** A treatment with diazoxide (5 mg/kg/day) was tried with limited efficacy. He was treated with ACE-inhibitor (Captopril) at the dose of 0,02 mg/kg/day with a low response. The Captopril dose was increased at 0,04 mg/kg/day with a regulation of the blood pressure (76/54mmHg). The genetic study of INS-R was showed a homozygote mutation in the insulin receptor (INS-R) gene. The mutation reported was c.3289C>T (CAG->TAG) p.Gln1097Stop (Q1097X). For the growth delay and the hypotrophic muscular masses he started a off-label treatment with mecasermin at increasing doses. He had no adverse events linked to the treatment. Otherwise, he improved growth and muscular strength.

**Conclusions:** The singular case is of relieve for the rarity of the disease and for the good response to the treatment with mecasermin, the real opportunity for these children with a severe disease otherwise with a poor prognosis.

P1-850

#### **FIRST REPORT OF AN IGFALS MUTATION IN A CHILEAN PATIENT WITH GROWTH HORMONE INSENSITIVITY AND LOW LEVELS OF IGF1 AND IGFBP3**

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**Objectives:** The main role of the acid-labile subunit (ALS) is to stabilize the IGFBP3/IGF complexes in the vascular compartment, extending thereby the otherwise very short half-life of circulating IGFs. Inactivating mutations in the gene coding for ALS (*IGFALS*) results in IGF1 deficiency, short stature and delay puberty. The aim of these study was to identify the genetic cause in a patient with suspected ALS deficiency.

**Results:** The proband is the third son of non-consanguineous parents (mother 150 cm, father 162 cm), evaluated for the first time at the age of 17<sup>4/12</sup> years because of his short stature (154.4 cm, -2.84 SD), with a bone age of 16 years and a body mass index in the 61<sup>th</sup> percentile. He was born with a normal birth weight and length (3,150 g and 49 cm). Sexual development and pubic hair correspond to Tanner stage 2, both testes showing a 10 mL volume. Hepatic and renal function, lipid and thyroid profile were normal, as well as his fasting glycaemia (88 mg/dL) and insulin level (16.3 uIU/mL). FSH, LH and total testosterone were concordant with his pubertal stage: 2.7 mIU/mL, 1.9 mIU/mL, and 139.2 ng/dL, respectively. Further studies showed low levels of IGF1 (45 ng/mL) and IGFBP3 (*IGFALS* gene coding regions was performed. The patient was found to be homozygous for a missense variant, c.1871C>T, p.Pro624Leu (rs756451070; NM\_001146006.1, NP\_001139478.1), reported as very rare by the Exome Aggregation Consortium (1 allele among 44.672 individuals) but not in a clinical context. According to ACMG recommendations, this is a likely pathogenic variant.

**Conclusions:** Identification of *IGFALS* mutations is a useful tool to confirm the diagnosis of ALS deficiency since it is a probable cause of growth retardation in children with low IGF1 levels, and contributes to clinical decision making about growth hormone replacement.

P1-851

#### **GROWTH HORMONE DEFICIENCY IN A BOY WITH NEPHROGENIC DIABETES INSIPIDUS**

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**Objectives: Background** Diabetes insipidus (DI) is a rare disorder of urinary concentrating ability caused by arginine vasopressin (AVP) insufficiency (central diabetes insipidus) or impairment of renal tubular response to AVP (nephrogenic diabetes insipidus). X-linked nephrogenic diabetes insipidus (AVPR2 gene mutations) has an estimated prevalence of 4 in 1,000,000 while CNDI caused by AQP2 mutation is rarer and estimated to occur in 1 in 20 million births. Growth hormone deficiency in association with cranial DI is well described. This is the first reported case of isolated GH deficiency in a child presenting with CNDI.

**Results: Case**

A 4 year old boy presented to the emergency department with a short history of vomiting and diarrhoea. He was dehydrated and laboratory studies confirmed hypernatremia (serum sodium 155mmol/L). His parents reported chronic polyuria and polydipsia with longstanding daily intake of approximately 4-5 litres of water. He was short ( height 94cm, G p.Ser318Arg). Insulin tolerance testing revealed a suboptimal peak growth hormone of 3.8ug/L, consistent with isolated growth hormone deficiency. Bone age was consistent with chronological age. He was commenced on growth hormone 0.025mg/kg/day with good growth response.

**Conclusions:** This is the first reported case of GH deficiency and CNDI. This case describes an interesting combination of two rare conditions, not previously described in association.

P1-852

**GH THERAPY IN A NON-GHD SHORT CHILD WITH SYRINGOMYELIA AND CHIARI I MALFORMATION**

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**Objectives:** Syringomyelia is a dilatation of the central canal of the cord frequently associated with congenital malformation of the cranial-cervical junction and Chiari I malformation. GH deficiency is also reported in these subjects and replacement therapy with GH seems not only to increase growth velocity but also to improve Chiari I malformation and syringomyelia.

**Methods:** We report the case of a 4 year old child who undertook a RMN for a venous facial angioma which showed incidentally Chiari I malformation and cervical syringomyelia. Following neurosurgical decompression, he required surgical revision for cerebral spinal fluid fistula and recurrence of syringomyelia. He was then referred to our clinic for short stature (Height-3SDS; Growth velocity -1.83SDS). The main organic causes of short stature, such as coeliac disease, hypothyroidism and GH deficiency were excluded (GH arginine stimulation test peak value 12.7 ng/ml). GH therapy (0.5 mg/day) was started on the basis of previous studies reported in the literature showing an improvement of the syrinxes during GH treatment in absence of significant side effects. Since the response to treatment was unpredictable, we performed a close clinical follow-up with quarterly auxological examinations and annually RMN imaging.

**Results:** The child showed during 3 years of GH treatment a significant increase of stature (from -3 to -1,7SDS) and Growth Velocity (from -1.83SDS to 3.67SDS). Furthermore the RMN showed a stabilization of the cranial-cervical junction and partial reduction of the syrinx cavity.

**Conclusions:** Our case suggests the possible efficacy of GH therapy in children with short stature and syringomyelia regardless of the presence of GH deficiency.

P1-853

**GROWTH HORMONE THERAPY FOR SHORT STATURE ASSOCIATED WITH WOLFRAM (DIDMOAD) SYNDROME**

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**Objectives:** We report an interesting case of Wolfram syndrome (WFS) treated with growth hormone for poor growth. Limited data exist concerning growth hormone therapy in WFS.

**Methods:** Case report.

**Results:** A 10 year-old female presented for endocrinologic evaluation following diagnosis of bilateral optic nerve atrophy after ophthalmology evaluation for progressive visual impairment. She had onset of polyuria, polydipsia since age 1 year. She had bilateral sensorineural hearing loss diagnosed at age 3 years, requiring cochlear implants. She was diagnosed with type I diabetes mellitus (DM) at age 5 years with initial HbA1c of 10.5%. She received insulin therapy at a total daily dose of 0.3-0.4 unit/kg/day, with HbA1c of 6.6%-8.9%. Upon diagnosis of optic atrophy, in the setting of DM and deafness, WFS was diagnosed and subsequently confirmed by WFS1 gene mutation. Diabetes insipidus (DI) was also diagnosed based on her continued polyuria, polydipsia, and enuresis despite insulin therapy, mild hypernatremia (148 mmol/L) and low urine specific gravity and osmolality. Her DI symptoms resolved after oral desmopressin. She had slow growth with decreasing height percentile from the 5<sup>th</sup>% (Z score -1.7) at age 5 years to <1<sup>st</sup> percentile (Z score -2.4) at age 10 years. Her mid-parental height was at the 75th%. She had normal TSH obtained annually after her DM diagnosis and her celiac screen was negative. Further pituitary studies showed low IGF-1 (84 ng/mL, normal 96-537), normal IGF-BP3 (3.2 ug/mL, normal 1.8-7.1). A growth hormone stimulation test showed peak growth hormone of 11.9 ng/mL. She had normal cortisol on ACTH stimulation test. Because of her poor growth, growth hormone was initiated at 0.22 mg/kg/week. Her growth velocity improved from 3.7 cm/year pretreatment to 9.6 cm/year after a year of treatment.

**Conclusions:** WFS with DI should be suspected in any patient with DM who continues to have polyuria and polydipsia after insulin therapy, especially in the setting of known hearing loss and vision changes. Early recognition of WFS allows timely pituitary workup and early treatment with desmopressin to alleviate DI symptoms. This case highlights benefit of growth hormone therapy for poor growth in WFS as growth hormone

neurosecretory dysfunction may be present as a result of the neurodegenerative process.

P1-854

#### DE NOVO IGF2 MUTATION ON THE PATERNAL ALLELE IN A PATIENT WITH SILVER-RUSSELL SYNDROME AND ECTRODACTYL

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**Objectives:** Although paternally expressed *IGF2* gene is known to play a critical role in placental and body growth, only a single mutation has been found in *IGF2*. Here, we report a *de novo* *IGF2* mutation that occurred on the paternal allele in a patient with Silver-Russell syndrome (SRS) and ectrodactyly.

**Methods: Case report:** This Japanese male infant was delivered by a cesarean section at 31 weeks of gestation because of intrauterine growth arrest and fetal distress. At birth, his length was 34.0 cm (−3.7 SD for gestational age), his weight 764 g (−4.1 SD), and his occipitofrontal circumference (OFC) 27.0 cm (−1.0 SD). Placenta weighed 176 g. Physical examination revealed SRS-compatible craniofacial features, undermasculinized genitalia, and bilateral hand and left foot ectrodactyly. On the latest examination at 18 months of age, his length was 65.4 cm (−4.2 SD), his weight 7,100 g (−2.9 SD), and his OFC 45.0 cm (−1.6 SD). Serum IGF-1 was 37.4 nmol/L (age- and sex-matched normal range, 1.8–19.3), IGF-2 46.9 nmol/L (44.5–85.5), LH <0.5 IU/L (<0.5), FSH 1.0 IU/L (<1.5), and testosterone <0.35 nmol/L (<0.35).

**Results: Molecular studies:** Whole exome sequencing followed by Sanger sequencing revealed a *de novo* *IGF2* indel mutation leading to frameshift (c.110\_117delinsAGGTAA, p.(Leu37Glnfs\*31)) that satisfied the condition for the occurrence of nonsense mediated mRNA decay. Furthermore, the mutation was shown to reside on the paternal allele by sequencing the long-PCR product harboring the mutation and methylation sensitive *Sma*I and *Sall*I sites before and after *Sma*I/*Sall*I digestion.

**Conclusions:** We identified a *de novo* *IGF2* indel mutation that occurred on the paternal allele in a patient with SRS and ectrodactyly. The results, together with the previous findings in four familial cases with a paternally inherited *IGF2* nonsense mutation and those in patients with variable *H19*-DMR epimutations leading to compromised but not abolished *IGF2* expression, suggest that the whole phenotype of this patient including SRS and ectrodactyly is explainable by the *IGF2* mutation, and that phenotypic

severity is primarily determined by the *IGF2* expression level in target tissues.

P1-855

#### REDUCED THYMIC ACTIVITY AND TREC LEVELS IN CHILDREN WITH GROWTH HORMONE DEFICIENCY

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**Objectives:** The thymus is the primary locus for development and maturation of T cells. T cell receptor (TCR) excision circles (TREC), are DNA fragments which serve as a sensitive tool for the assessment of T cell production and thymic maturity.

Previous studies have shown that hormones produced in the hypothalamic-pituitary axis can affect thymic degradation.

Growth hormone (GH) has a positive effect on thymic activity as observed in mouse models, where GH deficiency led to disturbances in T cell production. Mouse models show that supplementary GH improves thymic cellularity, divergence of TCR and recovery of the hematopoietic system in immunocompromised patients and elderly. One proposed mechanism is through the JAK2/STAT pathway. The aim of our study was to show correlation between GH levels and thymic activity using TREC measurements as a marker.

**Methods:** In a case-control study, serum samples of GH deficient (GHD) and sufficient (GHS) children with short stature, were analyzed. Real Time PCR was performed and number of copies of TREC were quantified. Clinical data was collected from the medical charts.

**Results:** A total of 32 patients were recruited. 15 patients (47%) with GH deficiency (study group) and 17 patients (53%) with GH sufficiency (control group). Both groups were similar in age and height. TREC quantification was 1513 and 2309 in the study and control groups respectively (p=0.07). A linear correlation was found between the peak GH level and TREC quantification (p<0.01).

**Conclusions:** TREC levels were lower in GHD patients compared to GHS with a tendency towards significance. A strong correlation was seen between peak GH levels during a stimulation test, and TREC levels. These results support the role that GH may play in thymic activity. A larger cohort of patients is needed to establish these correlations significantly.

P1-856

#### SILVER RUSSELL SYNDROME CAUSED BY MUTATION IN THE ONCOGENIC PATHWAY HMGA2-PLAG1-IGF2

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**Objectives:** *IGF2* is an imprinted gene known to have a major role in the control of fetal growth. Silver Russell syndrome (SRS) is characterised by severe fetal and post-natal growth retardation, and is mainly caused by epigenetic defects within the 11p15 region (which includes *IGF2*). Indeed, loss of methylation at the paternal *H19/IGF2*:IG-DMR and chromosome 7 maternal uniparental disomy (upd(7)mat) are the main molecular mechanisms of SRS. However, despite a clinical diagnosis of SRS, about 40% of the patients do not have a molecular defect identified. Therefore, we aimed to look for new molecular defects in patients with suspected SRS and no methylation defect at chromosome 11 or upd(7)mat.

**Methods:** Whole exome sequencing (WES) was performed on DNA from a familial case of SRS. Targeted high throughput sequencing was then carried out on DNA from 192 sporadic patients referred for suspected SRS.

**Results:** From a familial case of SRS, we identified by WES a heterozygous mutation in the *PLAG1* gene. As *PLAG1* has been linked to *HMGA2* and *IGF2*, targeted sequencing of these three genes allowed the identification of five new mutations within the *HMGA2-PLAG1-IGF2* pathway in five sporadic cases of SRS. *In vitro* studies with si-RNA mediated *HMGA2* and *PLAG1* silencing demonstrated the upstream regulation of *IGF2* expression by this pathway through a specific P3-*IGF2* promoter interaction, therefore confirming the implication of these mutations in the SRS phenotype.

**Conclusions:** Genetic disruption of the oncogenic *HMGA2-PLAG1-IGF2* pathway represents a new molecular mechanism of foetal and post-natal growth restriction and cause of SRS. This confirms the role of this pathway in the regulation of physiological growth.

P1-857

#### SHORT STATURE IN PRETERM BORN CHILDREN

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**Objectives:** Identify short stature in preterm born children.

**Methods:** Measurements at birth, 6, 12 and 24 months corrected age and at recall [6.4±0.5 years (5.2-8.0)]. Weight and length/height SDS were calculated (Fenton & Kim until 50 weeks; WHO 2006-2007, after). Short stature was defined as height SDS ≤ -2, and extrauterine growth restriction (EUGR) as difference ≥ 2SD between birthweight and/or length to 40 weeks post-conception.

**Results:** 170 children (97 boys), gestational age (GA) 32.5±2.9 weeks (24.0-36.7), median birth weight 1772.5g (range, 580-3135), length 41.3±4.6cm (30-49). Fifteen children were extremely preterm (GA<28 weeks), 20 were small for GA

(SGA). 32.7% of preterm children born appropriate for GA (AGA) had EUGR. Median weight SDS at 6, 12 and 24 months corrected age and at recall were -0.6, -0.2, -0.5 and -0.3, respectively. Correspondent values for length/height SDS were -0.4, -0.3, -0.3 and -0.3. Children born with GA<32 weeks and children born preterm SGA were leaner and shorter compared with those born after 32 weeks ( $p<0.01$ ) and those born AGA ( $p<0.05$ ). Twelve (7.1%) were underweight and 8 (4.7%) had short stature, which 4 were also underweight. Significant difference was observed only in height SDS of children whose mothers had eclampsia or severe preeclampsia (-1.0 vs. -0.3 SD,  $p=0.03$ ). Nine children (5.9%) were short stature at 2 yrs. corrected age and remained significantly lower in weight and height at recall ( $p=0.02$  and  $p<0.001$ , respectively) compared to normal height children at 2 yrs. Girls and boys height SDS was higher than their mothers' height (-0.3 vs. -0.8,  $p=0.03$  and -0.3 vs. -0.9,  $p<0.001$ , respectively), but excluding from this analysis overweighted and obese children, the differences were not maintained. The main determinants of short stature were length SDS at 12 month corrected age (OR=0.29,  $p=0.02$ ) and maternal height SDS (OR=0.13,  $p=0.01$ ). Weight SDS at recall and length SDS at 24 months explained 87% of the height variation at recall ( $R=0.87$ ,  $p<0.001$ ).

**Conclusions:** Most preterm children recovered weight and length until 6 months of life. SGA birth, GA<32 weeks, lower maternal height, maternal eclampsia or preeclampsia and EUGR are risk factors for growth disorders in preterm born children.

P1-858

#### GH THERAPY EFFICIENCY IN FETAL ALCOHOL SYNDROME

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**Objectives:** Fetal alcohol spectrum disorders describe a range of marked by impaired neurological and physical development, secondary to fetal alcohol exposure. Fetal Alcohol Syndrome (FAS) represents the most commonly recognized part of the spectrum with neurological and functional deficits. It associates characteristic clinical features such as smooth philtrum, thin upper lip, low nasal bridge, epicanthal folds, short nose and micrognathia, as well as intellectual impairment. Growth delay secondary to growth hormone deficiency (GHD) represents one aspect.

To evaluate growth pattern in FAS children compared to GH deficient children. We present 5 clinical cases (1 girl and 4 boys- mean height 107.1±19.7cm, mean weight 14kg ±

2.65kg with mean age of 7.64 ±3.18 years) diagnosed with FAS by suggestive phenotype in association with growth hormone deficiency (GHD) treated with rhGH.

**Methods:** They were evaluated at initiation and 12 months after GH treatment. The clinical (height, weight, BMI) and biological response to treatment was compared with age-matched children (3 girls and 11 boys).

**Results:** GH treatment (mean 0.04 ±0.013 mg/kg/day) was introduced after confirmation of GH deficiency, with low IGF1 levels (mean 75.9 ± SD: 49.6ng/dl) at introduction.

Comparisons were made between FAS and 14 sex and aged matched children with short stature in treatment with growth hormone.

There was no difference in growth rate between FAS children and the reference group (t test= 0.793, p=0.439). There was also no difference in growth gain in standard deviations between FAS children and the reference group (t test= 0.202, p=0.843). On the other hand, in order to obtain a growth rate comparable to children with hypopituitarism a higher dose of rhGH was needed (mean 0.040±0.013ui/kgc/day) compared to reference group (mean 0.0322±0.004ui/kg/day).

**Conclusions:** Fetal alcohol syndrome is a complex, non-curable entity without a specific treatment. Growth deficit represents one aspect of the disease, manageable by growth hormone treatment with similar results to children deficient in GH, without FAS. However, higher rhGH doses might be needed in order to attain the same growth rate and final height.

P1-859

#### MEIER-GORLIN SYNDROME: COULD IGF1 DEFICIENCY PLAY A ROLE IN THE PATHOGENESIS OF SHORT STATURE IN THESE PATIENTS?

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**Objectives:** We investigate the role of GH-IGF1 axis in Meier-Gorlin syndrome (MGS).

**Methods:** We performed clinical and endocrinological evaluation of a 3.9 years old male child from Senegal, referred to our hospital for dwarfism and microcephaly, reduced appetite and vomit.

**Results:** At the admission the weight was 4.860 g (-10.1 DS), height 64 cm (-9.3 DS) and OFC 45.5 cm (-3.0 DS). There was no data on prenatal growth. At clinical examination, he showed a triangular face, retro/micrognathia, microstomia, full lips, frontal bossing, clinodactyly of forth and fifth finger of both hands. Ears were underdeveloped, low set and rotated backwards. He also showed bilateral cryptorchidism and micropenis. Motor and speech development was

delayed. Endocrine work-up evidenced a delayed bone age (9 months), unremarkable thyroid function tests, ACTH, cortisol, basal GH (6.37 ng/ml), while low levels of IGF1 (GMNN, encoding geminin, a DNA replication inhibitor; interestingly, so far other 3 cases of MGS with heterozygous *GMNN* gain-of-function mutations have been described. Considering the very low level of IGF1 and basal value of GH, we performed an IGF1 generation test: daily subcutaneous administration of GH at a dose of 0,03 mg/kg for ten days. IGF1 levels remained persistently low after stimulation (

**Conclusions:** In MGS, the variable results of GH stimulation tests and variable efficacy of GH therapy reported in literature suggest a wide range of GH sensitivity as possible contribute to the severity of phenotype in this syndrome. Nevertheless, the scarcity of data in literature about GH-IGF1 axis in MGS allows us only to speculate about the possible role of GH resistance in these patients, thus further studies are needed. Considering our data, we wonder if IGF1 replacement therapy might be useful to improve linear growth in these patients.

P1-860

#### THE EVALUATION OF PATIENTS RECEIVING GROWTH HORMONE THERAPY

*Ayca Torel Ergur, MD; Sevinc Odabasi Gunes, MD; Ugur Can Kara, MD, Kirikkale University Faculty of Medicine, Kirikkale, Turkey*

**Objectives:** Growth is a complicated process, which is affected by genetic, environmental factors, hormones and growth factors. One of the most important factors is growth hormone deficiency (GHD), which causes many serious problems in not only growth but also many other systems. In this study growth velocity (GV) and effect growth hormone therapy (GHT) on organs systems of patients who were diagnosed GHD and received (GHT) were discussed.

**Methods:** Forty-four patients who had low GV and diagnosed pathological short stature were involved in the study. Growth hormone stimulation tests were done in order to evaluate GHD. Peak growth hormone <5 ng/ml was diagnosed total GHD, 5-10 ng/ml was diagnosed partial GHD. GHT was started in adjusted dosages according to the etiology of GHD and patients were called for follow-up for every 3 months in order to investigate anthropometric measurements and effect of GHT on other systems by evaluating fasting blood glucose, fasting insulin, HbA1c, thyroid functions, total blood count, IGF1, IGFBP3. At the end of every year, GHT was discontinued for 6 weeks and insulin tolerance test was done in order to evaluate GHD.

**Results:** 22 girls and 22 boys, whose age was 10.36 ± 2.72 years and bone age was 8.04 ± 2.8 were involved in the study. Diagnoses of the patients were as follows: 19 total GHD, 20 partial GHD, 4 syndromic short stature (SSS) (2 Turner syndrome, 1 cleidocranial dysostosis, 1 idiopathic), 1 neurosecretory dysfunction. GV of 29 patients who completed first year treatment was 9.46 ± 2.23 cm/year, 8 patients who completed second year treatment 7.03 ± 1.52

cm/year, 4 patients who completed third year treatment  $6.67 \pm 1.86$  cm/year. 3 patients dropped out of treatment. HbA1c levels of the patients did not elevate during therapy and IGF1-IGFBP3 levels were within the secure limits.

**Conclusions:** We suggest that it's important to close follow-up of patients receiving GHT for clinical and laboratory parameters in order to reach optimal predicted height. We believe that close follow-up of titration and application of dosage of growth hormone contributes to high GV results of our patients.

## POSTER SESSION 1

Thursday, September 14, 2017, 5:45-6:45pm

### P1 - Multisystem endocrine disorders

#### P1-900 – P1-915

P1-900

#### COEXISTENCE OF ENDOCRINOPATHIES IN CHILDHOOD RHEUMATIC DISEASES

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**Objectives:** \* To screen the endocrine dysfunction in SLE and JIA patients.

\* To identify the pubertal delay in these patients.

**Methods:** \* A cross-sectional study was conducted on Saudi children with SLE and JIA who are followed at King Faisal Specialist Hospital and Research Center, Riyadh between September 2013 and April 2015.

\* All patients were reviewed for demographic data, disease duration. Patients have completed the clinical assessment including family history of autoimmune diseases, growth parameters and tanner stage as well as the following investigations: parathyroid hormone, 25-OH vitamin D levels, TSH, FT4, thyroglobulin antibodies, thyroperoxidase antibodies, random blood sugar, HbA1C, IGF1, IGFBPIII, LH, FSH.

\* For SLE patients, complement (C3, C4) levels, anti-double-stranded DNA antibody and anti-nuclear antibody were included.

\* Furthermore, we calculated the disease activity score using Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).

\* The proposal approved by the Research Affairs Council at KFSHRC.

**Results:** \* A total of 42 (30 female) of consecutive Saudi children, 22 with JIA and 20 with SLE were included.

\* All SLE patients had multiple organs involvement.

\* JIA patients comprised 13 patients with polyarticular subtype, 4 patients with oligoarticular subtype and 5 patients with systemic onset subtype.

\* The most common autoimmune disease among family members was hypothyroidism.

\* The most frequent endocrinopathies were vitamin D insufficiency (35%) and thyroid disease (31%).

\* Nineteen patients (11 SLE, 8 JIA) were short for their age and gender; 7 patients (4 SLE and 3 JIA) had growth hormone insufficiency as confirmed by low IGF1, IGFBPIII.

\* Sixteen SLE patients found to have active disease with a mean of SLEDAI score 6. The levels of 25-OH vitamin D correlated inversely with SLEDAI scores but not statistically significant.

**Conclusions:** \* Our findings showed that coexistence of endocrinopathies are not uncommon in children JIA and SLE.

\* Abnormal thyroid function occurs frequently and similar in SLE and JIA.

\* Screening for possible endocrinopathies namely thyroid disease during assessment of SLE and JIA children is worth to consider.

P1-901

#### HORMONAL PROFILE OF CHILDREN AND ADOLESCENTS WITH PRADER-WILLI SYNDROME

*Iuliana Gherlan, MD, "C.I.Pahon" National Institute of Endocrinology, Bucharest, Romania; Cristina Patricia Dumitrescu, PhD; Andra Caragherogheopol, MS/MA; Florin Alexiu, Physicist, "C.I.Pahon" National Institute of Endocrinology, Bucharest, Romania; Camelia Procopiuc, MD, "CI Parhon" National Institute of Endocrinology, Bucharest, Romania*

**Objectives:** Prader-Willi syndrome (PWS) is a genetic disorder characterized by severe infantile hypotonia and failure to thrive in infancy, hyperphagia with early-childhood onset obesity, central hypogonadism, characteristic dysmorphic features and developmental delay. Growth hormone insufficiency is frequent, but a complete description of the entire hormonal profile of those patients is rare.

**Methods:** We retrospectively reviewed the medical records of PW patients admitted to paediatric endocrinology department between 2010 and 2016.

**Results:** 15 PW patients (11 boys, 4 girls, mean age at diagnosis 5.6 years), were investigated in a 6 year period. 12/15 patients had height below mean, 3/15 (20%) patients were 2 SD below mean at first admission.

93.33% of patients had a BMI above 2 SD at first evaluation. IGF1 had values below mean in 84.6 % cases, in average  $-1.2 \text{ SD} \pm 1.24 \text{ SD}$  compared to age and sex.

freeT4 was persistently in normal range in all patients, only one patients had repeatedly increased values of TSH indicating subclinical hypothyroidism.

Low values of morning plasmatic cortisol were described in 4/15 (26.67%) patients; in all cases central adrenal insufficiency was excluded by performing  $1\mu\text{g}$  Synacthen stimulation test – interestingly, all these patients had high normal values of plasmatic cortisol at 6 A.M., indicating a dysregulation of circadian rhythm of hormonal secretion. 60% patients had serum levels of DHEAS above normal range, 1 female patient had clinical evident precocious adrenarche. 81.8% boys had uni/bilateral cryptorchidism, 75% boys at pubertal age had no signs of pubertal onset.

**Conclusions:** PW syndrome in children and adolescents is associated with a pleomorphic hormonal profile (aside GH deficiency); an extended protocol of endocrine evaluation needs to be applied.

P1-902

#### CLINICAL AND ENDOCRINOLOGIC MANIFESTATIONS OF ANOREXIA NERVOSA IN ADOLESCENT AND YOUNG ADULT MALES VERSUS NORMAL WEIGHT CONTROLS

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**Objectives:** Current literature suggests a female predominance for anorexia nervosa (AN). The reason for this gender bias could be under reporting in males or a true biological bias in females. Enhanced provider awareness and higher index of suspicion could prevent the delay in the diagnosis in males. Clinical and endocrinologic features associated with AN are well characterized in females, but not in males with the disorder. We aimed to delineate the clinical and endocrinologic features at presentation in males with AN.

**Methods:** A retrospective chart review was conducted between 2000 and 2016 of 53 males-36 with AN and 17 normal-weight healthy controls (HC), aged 10-23 years. AN was diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV or V (depending on the year of diagnosis). Data were extracted from electronic medical records.

**Results:** AN and HC did not differ for age or height. As expected, AN had lower BMI ( $17.8 \pm 1.7$  vs.  $21.3 \pm 2.6$  kg/m<sup>2</sup>;  $P < 0.0001$ ) and BMI%ile [8.38 (2.81–19.49) vs. 57.1 (44.46–77.14)] than HC. The mean age at AN diagnosis was  $15.9 \pm 3.0$  years. A sizeable proportion of males with AN had low random plasma glucose (17%) and polycythemia (29%). There was no difference between groups in serum sodium or potassium levels. 16.7% patients had a previous history of obesity. The most prevalent mode of weight loss (after calorie restriction) was over exercising, which was seen in 38.9% of the group.

55% of AN males were hypogonadal. For the subset in whom testosterone levels were available (AN n=14; HC n=8), at Tanner 5 by exam, AN had significantly lower total testosterone levels compared to HC ( $P < 0.0001$ ). Total testosterone levels were positively associated with %median BMI for age ( $r = 0.52$ ,  $P = 0.0015$ ), BMI%ile for age ( $r = 0.55$ ,  $P = 0.0006$ ), red cell count ( $r = 0.48$ ,  $P = 0.014$ ), hemoglobin levels ( $r = 0.47$ ,  $P = 0.016$ ), and fasting plasma glucose levels ( $r = 0.42$ ,  $P = 0.014$ ).

**Conclusions:** Over exercising is the second most prevalent mode of weight loss in males with anorexia nervosa. Anorexia nervosa should be considered in a post pubertal male with

hypogonadism. Low testosterone levels are common in this condition and may contribute to clinical features such as anemia.

P1-903

#### INSULIN SENSITIVITY REGULATING MIRNAS SHOW CHANGES IN GRANULOSA CELLS (GC) FROM POLYCYSTIC OVARY SYNDROME (PCOS) OVARIES

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**Objectives:** Changes in miRNA levels are associated with insulin resistance and inflammation, that are features of PCOS. FOXO1, a key factor in insulin signaling, is also cystic fibrosis transmembrane conductance regulator (CFTR)-dependent. We showed that CFTR and FOXO1 genes are downregulated in PCOS ovaries (unpublished data). MiR155 was reported as an HMGB1-induced inflammation suppressor in the liver. We aimed to assess differences in miR146a, miR155, miR320, and miR370 in GC of women with or without PCOS undergoing IVF, all FOXO1 and insulin sensitivity regulators.

**Methods:** We enrolled 20 women (CA:  $31.1 \pm 1.2$  yr; BMI:  $25.2 \pm 1.2$  kg/m<sup>2</sup>; hirsute N.4; with amenorrhoea N.2; oligomenorrhoea N.9; regular cycles N.9) with PCOS according to the Rotterdam Criteria, undergoing ovarian stimulation for IVF, and 30 healthy women (CA:  $36.2 \pm 0.7$  yr; BMI:  $23.9 \pm 0.9$  kg/m<sup>2</sup>), fertile oocyte donors, with tubarian or unknown infertility causes, normal endocrine exams and menstrual cycles (CTRL). RNA from GC, isolated from follicular fluid (FF), was extracted using the MirVana kit. MiRNAs of interest were assessed using TaqMan qPCR and normalized with respect to U6 snRNA and RNU48. Relative gene expression was calculated as dCTs and fold change. HMGB1 was assayed in FF using a specific ELISA kit. The N. of dominant follicles (>17mm) after stimulation was also considered for statistical analyses.

**Results:** miR155 was lower in PCOS compared with CTRL ( $6.1 \pm 0.2$  vs  $7.1 \pm 0.1$  dCT,  $p < 0.05$ ). In the entire group, miR155 correlated with both HMGB1 ( $r = -0.28$ ;  $p = 0.05$ ) and miR146a ( $r = 0.49$ ;  $p = 0.001$ ), and miR155 with CA ( $r = 0.29$ ;  $p = 0.04$ ) and with N. of follicles ( $r = -0.43$ ;  $p = 0.003$ ). MiR320 correlated with both miR370 ( $r = 0.60$ ;  $p = 0.001$ ) and CA ( $r = -0.29$ ;  $p = 0.04$ ). In PCOS, miR146a correlated with miR155 ( $r = 0.75$ ;  $p = 0.001$ ) and miR320 correlated with both miR370 ( $r = 0.65$ ;  $p = 0.005$ ) and CA ( $r = -0.61$ ;  $p = 0.009$ ). MiR370 correlated with CA ( $r = 0.5$ ;  $p = 0.042$ ). In CTRL, miR146a correlated with both miR320 ( $r = 0.48$ ;  $p = 0.008$ ) and miR370 ( $r = 0.38$ ;  $p = 0.039$ ). MiR155 correlated with both

miR320(r:0.53;p:0.003) and CA(r:-0.38;p:0.04). Finally, miR320 correlated with miR370(r:0.54;p:0.002).

**Conclusions:** These miRNAs showed relationships with HMGB1, reflecting glucose metabolism and inflammation, CA, and N. of dominant follicles. In PCOS GC, miR155 was lower.

P1-904

#### **HIGH MOBILITY GROUP BOX 1 (HMGB1) IS INCREASED AND CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR (CFTR) AND WINGED HELIX FORKHEAD (FOXO1) ARE REDUCED IN OVARIES FROM POLYCYSTIC OVARY SYNDROME (PCOS)**

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**Objectives:** We described in cystic fibrosis related diabetes, reduced FOXO1 and increased HMGB1 both dependent on CFTR loss of function. HMGB1 was related with insulin-resistance, glucose tolerance state and inflammation. Inflammation is a feature also of PCOS. Therefore, we hypothesized that CFTR and FOXO1 could be reduced in granulosa cells(GC) and HMGB1 increased in follicular fluid (FF) in PCOS.

**Methods:** We enrolled, 30 women(CA:33.2±1.0yr;BMI:25.6±0.9kg/m<sup>2</sup>; hirsute N.12; with amenorrhoea N.5; oligomonorrhoea N.14; regular cycles N.11) with PCOS according to the Rotterdam Criteria, undergoing ovarian stimulation for IVF, and 50 women (CA:36.8±3.7yr; BMI:24.3±0.4kg/m<sup>2</sup>), fertile oocyte donors, with tubarian or unknown infertility causes, with normal endocrine exams, regular menstrual cycles, no hyperandrogenism, as controls(CTRL). Subjects with genetic diseases, chronic diseases, coeliac disease, tumors and endometriosis were excluded.

RNA was extracted from GC isolated from FF using Ficoll in 8 PCOS and 8 CTRL using the MirVana kit. CFTR and FOXO1 were evaluated using TaqMan qPCR, normalized with respect to  $\beta$ -Actin, as housekeeping gene. PCOS dCts were differentially expressed with respect to the pool of CTRL dCts. Relative gene expression was calculated as fold change. HMGB1 was assayed in FF using a specific ELISA kit. Statistical analyses were performed and stratified regression models used separately for PCOS and CTRL to test the effect of E2, N. of dominant follicles(>17mm at pickup), CA, BMI, hirsutism and features of menstrual cycles (only in PCOS) on HMGB1. All models were adjusted for CA and BMI. Estradiol (E2) was assayed in serum at pickup.

**Results:** CFTR and FOXO1 gene expression were downregulated in PCOS(-0.4±0.008 and -0.1±0.003, respectively).

HMGB1 was higher in PCOS than in CTRL, independent of CA and BMI(42.4±4.4 vs 30.9±3.2ng/ml p<0.05). E2 was also

higher in PCOS than in CTRL (2013.6±268.9 vs 1348.1±127.4pg/ml, p<0.05).

Both in PCOS and CTRL, CA, BMI, and N. of follicles were not associated with HMGB1. In CTRL, HMGB1 was significantly associated with E2 (p:0.02;[CI 0.001-0.014]).

**Conclusions:** CFTR and FOXO1 gene expression are reduced in the ovaries of PCOS women and this is associated with an increase in HMGB1. This increase is independent of CA and BMI.

P1-905

#### **OCCULT INSULINOMA, GLUCAGONOMA AND ENDOCRINE PANCREATIC PSEUDOTUMOUR IN A PATIENT WITH MULTIPLE ENDOCRINE NEOPLASIA TYPE 1.**

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**Objectives:** To describe exceptional pancreatic features of Multiple Endocrine Neoplasia type 1 (MEN1) in an adolescent. **Methods:** Prospective patient evaluation.

**Results:** A 14 year old adolescent MEN1 patient with a novel *MEN1* mutation, c.1391dupC, p.Ala465GlyfsTer66, presented with severe hyperinsulinemic hypoglycemia, but repeated imaging with endoscopy, MRI, 68Ga-DOTA-NOC PET/CT, 18F-DOPA PET/CT and 111-Indium-exendin SPECT failed to identify the occult insulinoma. An identified pancreatic tumor was resected, but revealed to be a glucagonoma. Resection of the pancreatic head failed to cure the patient despite increased caput labelling. By the third surgery, a lesion that we termed a pancreatic endocrine pseudotumor was resected, representing increased pancreatic islet tracer DOPA PET labelling due to severe aggregation of islets of Langerhans after inflammatory destruction of exocrine pancreatic tissue as the result of the previous surgery. The insulinoma was only detectable and removed after eight months of search despite extensive diagnostic imaging including several different PET/CT scans.

**Conclusions:** A pancreatic endocrine pseudotumour occurred as a novel manifestation of MEN1 after repeat pancreatic surgery. Prolonged conservative treatment instead of surgery in MEN1 without clearly visible pancreatic tumors at imaging should be balanced against the risk of development of metastases, side effects, and quality of life.

P1-906

#### **A CASE OF CONGENITAL GENERALIZED LIPODYSTROPHY TYPE 2 WITH NOVEL BSCL2 GENE MUTATION**

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**Objectives:** Congenital generalized lipodystrophy (CGL), or Berardinelli-Seip syndrome [OMIM 269700], is a rare autosomal recessive disorder characterized by the generalized absence of adipose tissue, extreme insulin resistance, hypertriglyceridemia, hepatomegaly, hepatic steatosis and early onset of diabetes mellitus. Four unrelated genes have been identified as causative genes for CGL; *AGPAT2* gene cause type 1 (CGL1), *BSCL2* gene cause type 2 (CGL2), *CAV1* gene cause type 3 (CGL3) and, *PTRF* gene cause type 4 (CGL4). Herein, we described a case with CGL2 due to novel homozygous *BSCL2* gene mutation.

**Methods: Case:** Three years-seven months old girl presented with a general lack of subcutaneous fat, prominent muscular hypertrophy, hollow cheeks, triangular face, acanthosis nigricans nigricans in fold areas; especially in the neck and bilateral axilla and hypertrichosis in arms and legs, abdominal swelling due to hepatomegaly, which are all of characteristic physical findings of CGL. Her parents were first degree cousins. She was born as a term neonate weighing 2500 g with no perinatal complications. In laboratory findings (reference ranges) were as follows: glucose 75 mg/dL (70-105), C-peptide 6.8 ng/mL (0.9-4.3), insulin 47.4  $\mu$ U/mL (1.9-23), HbA1c 5.2% (4.8-6.0), total cholesterol 132 mg/dl (<200), triglyceride 134 mg/dl (<200), AST 39 U/L, ALT 55 U/L. Hypertriglyceridemia was first detected at 5 years of age in patients with metformin therapy for insulin resistance. Despite taking metformin treatment, the patient's insulin levels increased steadily, and serum AST levels were also elevated. At the age of nine years, grade-2 hepatic steatosis with hepatomegaly was detected in abdominal ultrasonography.

**Results:** During follow-up, her HbA1c level elevated to 6.5% at the age of eleven year and three months. The fasting and 2-hour post-OGTT glucose-insulin levels of patient were 152 mg/dL-158.3  $\mu$ U/mL and 209 mg/dL-95.8  $\mu$ U/mL, respectively. Insulin detemir was started in addition to metformin treatment because of diagnosis diabetes. A clinical diagnosis of CGL was corrected by the identification of a novel homozygous mutation (IVS2+2 T>C) of the *BSCL2* gene.

**Conclusions:** Analyzes with GenSplicer and HumanSplicingFinder modeling programs show that this mutation can cause this disease.

P1-907

#### **CENTRAL PRECOCIOUS PUBERTY, GROWTH HORMONE DEFICIENCY AND SEVERE PROGRESSIVE SCOLIOSIS IN NON-CLASSIC CONGENITAL ADRENAL HYPERPLASIA (NCAH) WITH PRESERVATION OF FINAL ADULT HEIGHT: A CASE STUDY**

Irena Hozjan, MN; Denis Daneman, MD; Irena Hozjan, MN, University of Toronto, Toronto, ON, Canada

##### **Objectives: Background:**

Treatment of NCAH presents a challenge as interventional therapies are often required to manage the hormonal effects of the diagnosis. Occasionally, there are additional challenges.

##### **Methods: Case presentation:**

Young male, first seen at 5.5 years of age with a two year history of virilising changes ( $\uparrow$  Pubic hair,  $\uparrow$  phallus size) and tall stature. No family history of precocious puberty or other health conditions. Mid-parental height 170 cm. Height 128cm ( $++>97$  centile), weight 29.8 kg, mild facial acne, mild facial hair, skin pigmentation normal, T3 PH, testes 3 mls. Bone age 10 years, 17OHP 144, De-oxy cortisol 171, Renin 0.83 (0-1.7). Homozygous for intron 2 mutation in 21 OH gene, NCAH. Glucocorticoid therapy initiated.

At 6.4 years, poor treatment adherence and pubertal progression noted, testes 4 mls, BA 12-13 years. LHRH stimulation test noted a pubertal response, and GnRH agonist initiated.

At 10.9 years poor growth velocity noted and subsequent provocative GH stimulation testing indicated growth hormone deficiency (GHD) and GH therapy initiated.

At 13 years, a moderate S-shaped thoraco-lumbar scoliosis was noted. Over time, worsening scoliosis with unbalanced curves developed. MRI brain/spine noted no cause of scoliosis. Spinal fusion surgery ultimately required. Final adult height (FAH) 171.4cm.

**Results:** N/A

**Conclusions:** The diagnosis of central precocious puberty was anticipated in the management of NCAH; however, GHD was novel as was the development of a severe progressive S-shaped scoliosis while on GH therapy. GHD and scoliosis are not known risk factors in NCAH. Scoliosis is reported in less than 1% of the patients in post marketing GH surveillance databases. Spinal curvature progression may occur during growth acceleration in adolescence, and a causal association with GH treatment has not been substantiated. Progression of scoliosis is associated with double major curves and GH may increase the risk of progression, as in this patient scenario, and requires vigilance by the treating practitioner.

P1-908

#### **ADRENOCORTICOTROPIC HORMONE DEFICIENCY AS PRESENTATION FORM OF MULTIPLE HORMONE RESISTANCE IN PSEUDOHYPOPARATHYROIDISM TYPE 1A: DESCRIPTION OF 2 CASES.**

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**Objectives:** Pseudohypoparathyroidism type 1a (PHP1a) is caused by mutations in the *GNAS* gene (coding for the Gs-alpha protein), and may be associated with multiple hormone resistance, most frequently thyroid-stimulating hormone (TSH) and parathyroid hormone (PTH).

Methods: CASE 1

A 6-year-old boy had a history of desmoplastic medulloblastoma (currently stable), spastic tetraparesis and developmental delay. In the neonatal period, hypothyroidism was detected together with asymptomatic hypoglycaemia with hyperinsulinaemia and hypocortisolism. (Table 1) No other hypothalamic-pituitary alterations were detected in blood tests or by MRI. Throughout evolution, he was reevaluated on 3 occasions with fasting cortisol values <3µg/dL and ACTH <25pg/mL. At 6 months of age, he presented asymptomatic hypocalcaemia with hyperphosphoraemia, elevated serum PTH and low vitamin D3 levels. Renal function is normal. The patient presents round facies, obesity and generalised brachydactyly of hands and feet.

CASE 2

A 5-year-old girl had a history of neonatal sepsis, spastic tetraparesis, epilepsy and overall developmental delay. In the context of neonatal sepsis, she presented hypoglycaemia with low cortisol and hypothyroidism. (Table 1). Thyroid ultrasonography was normal and MRI showed no alterations in the hypothalamic–pituitary axis. On several occasions, she presented low values of ACTH and cortisol and fasting hypoglycaemia coinciding with the withdrawal of hydrocortisone. From 4 years of age, she presented high serum PTH levels and calcium, phosphorus and 25 OH vitamin D levels were normal. She presented short stature, obesity, round facies and brachydactyly (shortening of the fourth and fifth metacarpal bones).

**Results:** Owing to the clinical history and analytical reports in association with the features of Albright’s hereditary osteodystrophy (AHO), it was decided to study the *GNAS* gene which showed the same change in heterozygosity in exon 9, a substitution of arginine for cysteine in position 232. (p.R232C; c.697C>T).

**Conclusions:** ACTH deficiency, though rarely described, may be an early manifestation of PHP1a, perhaps a specific mutation. The association of peripheral hypothyroidism and ACTH deficiency raises the suspicion of multiple hormone resistance syndrome.

TABLE 1					
Adrenal pituitary axis			Phospho-Calcium Metabolism		
	CASE 1	CASE 2		CASE 1	CASE 2
Cortisol (5.27-22.45 µg/dL)	2.16	1.92	Calcium (8.8-10.8 mg/dL)	6.5	8.5-9.3
ACTH (4.7-48.8 pg/mL)	16	74.7	Phosphorus (4-7 mg/dL)	7.5	6.3-5.9
Insuline (3-25 mU/L)	17	NC	PTH (14.5-87.1 pg/mL)	529	400-500
TSH (6.27-0.64 mU/L)	22.1	20.5	25-OH-D3 (20-80 ng/mL)	7.6	24
T4L (0.8-1.76 mg/dL)	0.86	1.07	/	/	/

P1-909

GROWTH HORMONE DEFICIENCY, HYPERGONADOTROPIC HYPOGONADISM AND COHEN SYNDROME FEATURES IN TWO SISTERS-A NEW SYNDROME?

Mirjana Kocova, PhD; Elena Sukarova-Angelovska, PhD, University Pediatric Clinic, Medical faculty, Skopje, Macedonia, The Former Yugoslav Republic Of; Jurgen Klammt, PhD, University of Leipzig, Leipzig, Germany; Bernard Aral, PhD, Univeristy of Dijon, Dijon, France; Mehul Dattani, Professor, UCL Great Ormond Street Institute of Child Health, London, United Kingdom

**Background:** Rare diseases have become a new field in medicine. However, overlapping and various symptoms frequently make the clinical diagnosis cumbersome.

**Objective and hypotheses:**To present two sisters with unusual association of clinical symptoms with a complex diagnostic approach. It might be a new syndrome.

**Methods** GH deficiency was diagnosed through L-dopa test. LH, FSH and estrogens were analyzed. Internal genitalia were assessed using ultrasonound and pelvic MRI. Genetic testing for GH and GHRH gene, as well as COH1 gene were performed in collaboration with different laboratories.

**Results:** Both girls had severe dwarfism starting early in infancy. They had some of the features of Cohen syndrome (obesity, short philtrum, severe myopia and ambliopia but without chorioretinal dystrophy, thick hair and leucopenia). Testing for GH confirmed complete isolated GH deficiency and therapy with GH was carried for 14 and 12 years respectively with excellent response (reaching final height at 25%o). Puberty did not occur and FSH and LH values were high (FSH=60.2 IU/ml, GH-37.3 IU/ml, and FSH= 56 IU/ml,LH=33 IU/ml respectively).Estrogenes were not detectable. Ultrasound and MRI showed absence of the ovaries and severe hypoplasia of the uterus. There were no mutations of Prop or Pit 1 gene, and only one splicing mutation in the COH1 gene was detected, rejecting the autosome recessive Cohen syndrome. No patient with Cohen syndrome has been reported with GH deficiency, nor with hypergonadotrophic hypogonadism. The older syster was with normal development and graduated from university, whereas the younger had moderate mental retardation requiring special schooling. Exon sequencing of the candidate gene is underway for a possible detection of a new syndrome.

**Conclusions:** This is a complex syndrome involving dysmorphic features, eye involvement, GH deficiency and hypergonadotropic hypogonadism. Molecular analyses performed so far suggest that it might be a rare variant of Cohen syndrome or a new syndrome.

P1-910

A CASE OF GENETICALLY CONFIRMED 29-MONTH-OLD BOY WITH FAMILIAL MULTIPLE ENDOCRINE NEOPLASIA TYPE 1(MEN1)

Jun Hui Lee, MD, Catholic university of Korea, Seoul, Korea, Republic Of; Moon Bae Ahn, MD, College of medicine, The Catholic University of Korea, Seoul, Korea, Republic Of; Min Ji Son, MD; Shin Hee Kim, MD; Su Yeon Kim, MS/MA, Catholic University of Korea, Seoul, Korea, Republic Of; Won Kyoung Cho, PhD, College of medicine, The Catholic University of Korea, Seoul, Korea, Republic Of; Kyoung Soon Cho, MD; Sung-Dae Moon, PhD; Kyoung Soon Cho, MD, Catholic university of Korea, Seoul, Korea, Republic Of; Min Ho Jung , PhD, College of medicine, The Catholic University of Korea, Seoul, Korea, Republic Of

**Objectives:** Multiple endocrine neoplasia type 1 (MEN1) is an inherited disorder recognized as tumors within 2 or more

endocrine glands in a single patient. MEN1 is caused by mutations inactivating tumor suppressor gene *MEN1* and follows an autosomal dominant inheritance with 50 % chance of passing the affected gene onto the subsequent offspring.

**Methods:** A 29-month-old boy was referred with familial history of MEN1. The index patient was his father who underwent tumor resection of multiple organ sites including parathyroid gland, pancreas, duodenum, and thyroglossal duct. Other relatives in the pedigree, except for the patient's aunt who was also affected by the disorder, had never been screened. The patient showed no clinical signs or symptoms without any evidence of abnormal findings on physical examination and biochemical studies.

**Results:** Genetic testing revealed a heterozygous nonsense mutation, which was identical to his father's, caused by conversion of tryptophan into stop on codon 471 of exon 10 of *MEN1* (W471X). According to the disease characteristics, tumor progression can occur as early as the age of 5 (i.e. insulinoma or anterior pituitary tumor), therefore, identification of a germline *MEN1* mutation should soon be preceded especially for a first degree with family history. Afterwards, timely mannered biochemical and radiological approaches are suggested for systematic evaluation and effective long term management.

**Conclusions:** A child suspicious of MEN1 should be referred to pediatric endocrinologist to undergo accredited genetic testing and counselling and confirm the diagnosis in prior to any particular biochemical and radiological screening is proposed.

P1-911

#### PROHORMONE CONVERTASE 1/3 DEFICIENCY DUE TO A HOMOZYGOUS PCSK1 MUTATION AS CAUSE OF CONGENITAL MALABSORPTIVE DIARRHEA IN ASSOCIATION WITH BLUE-DIAPER SYNDROME

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**Objectives:** To identify the origin of clinical symptoms in a neonate of healthy consanguineous parents from northern Syria who presented with severe malabsorptive diarrhea. In addition, a bluish discoloration of the diaper was noted at several occasions, leading to the suspicion of Blue-diaper syndrome (BDS), an enigmatic disease entity characterized by urinary excretion of indigo derivatives.

**Methods:** The underlying genetic cause of the disease was analyzed by whole-exome sequencing. To further support the idea of BDS, we analyzed urine samples of the child at

different time intervals using a triple quadrupole mass spectrometer Xevo TQ-S coupled with an UPLC-I-class system.

**Results:** Extensive diagnostic work-up including intestinal and liver biopsies could not clarify the underlying pathology. Whole exome sequencing revealed a homozygous frameshift mutation in *PCSK1* (NM\_000439.4: c.679del, p.Val227Leufs\*12) while the parents were identified as heterozygous carriers. Mutations in *PCSK1* have been reported as a rare cause of early-onset malabsorptive diarrhea and multiple endocrine dysfunctions. *PCSK1* encodes prohormone convertase 1/3, which is a calcium-dependent serine endoprotease that is essential for peptide hormone processing and activation. Laboratory work-up confirmed the diagnosis of prohormone convertase 1/3 deficiency (e.g. by detection of massively increased serum proinsulin levels). Further investigations demonstrated the presence of indigo derivatives in urine samples with highest concentrations during the first week of life. Of note, bluish discoloration of diapers was variable and not constantly visible, especially during later disease course.

**Conclusions:** The association of BDS and congenital malabsorptive diarrhea might be indicative of prohormone convertase 1/3 deficiency. The formation of indigo blue has been linked to unabsorbed tryptophan, leading to bacterial degradation of tryptophan to indole, which is absorbed and metabolized to 3-hydroxyindol. Urinary 3-hydroxyindol dimerizes under slightly basic pH conditions to indigo blue. Further studies measuring urinary indigo concentrations of patients with *PCSK1* defects and/or of infants with malabsorptive diarrhea might help to determine the specificity and prevalence of this phenomenon.

P1-912

#### PARATHYROID ADENOMA FIRST SIGN OF ENDOCRINE NEOPLASIA (MEN1)FAMILIAL TYPE

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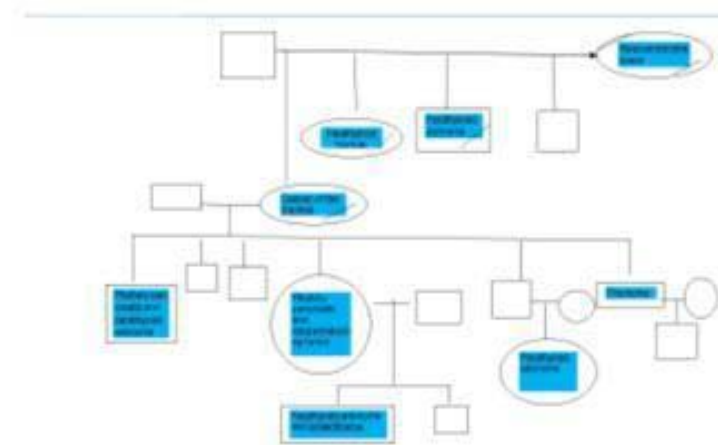
**Objectives:** To describe the importance of the presence of PARATHYROID ADENOMA as the first sign of ENDOCRINE NEOPLASIA (MEN1)FAMILIAL TYPE

We would like to describe four generations of a Colombian family in which predominates presence to parathyroid adenoma as the first sign of the MEN type 1

**Results:** VIEW PDF

**Conclusions:** Concerning the frequency of endocrine adenomas in endocrine neoplasia Multiple, our findings agree with the literature in that parathyroid tumors are more common followed by pituitary and pancreatic. The presence of parathyroid adenomas often in the first sign of the disease. Early diagnosis prevents morbidity and mortality. Molecular test is in process in this family.

PLEASE SEE TABLE ON FOLLOWING PAGE



P1-913

### SHORT STATURE IN A CHILD WITH MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 B

*Marielis Rincon-Subtirelu, MD; Lina Huerta-Saenz, MD, Children's Mercy Hospital, Wichita, KS, United States*

**Objectives:** Multiple Endocrine Neoplasia type 2 B (MEN2B) is an autosomal dominant syndrome characterized by medullary thyroid carcinoma (MTC), pheochromocytoma, mucosal neuromas, and thickened corneal nerves. Clinical features include full lips, thickened eyelids, high-arched palate, and marfanoid habitus. Short stature has not been described as part of the phenotype.

**Methods:** Case report.

**Results: Case presentation:** A 4-year-old Hispanic male was evaluated for failure to thrive. His past medical history was significant for low birth weight of 4 lbs 3oz at 39 week, and global developmental delays. The family history was negative, with midparental target height at 25-50<sup>th</sup> percentile. Review of systems was positive for gastroesophageal reflux and sleep disturbances. His height was at the 0.19<sup>th</sup> percentile, and weight at 1.14<sup>th</sup> percentile. Physical exam showed prominent abdomen and torso, but no obvious skeletal dysmorphologies. The skull was normal, with tall forehead and coarse facial features, epicanthal folds, prominent eyelashes, wide and depressed nasal bridge, full everted thick lips, wide spaced teeth, and thick gums. The rest of his exam was normal, including thyroid gland and skin. He was diagnosed with short stature and dysmorphic features. Initial laboratory evaluation was normal. He was referred to Genetics.

Follow up evaluation showed growth failure. He was found to have growth hormone (GH) deficiency after stimulation. GH therapy was never started due to pending evaluation for suspected sleep apnea. Exome Sequencing demonstrated a heterozygous likely pathogenic de novo variant in HECW2 gene, c.4436G>A (p.R1479Q), consistent with the diagnosis of HECW2-related disease, and he also had a heterozygous pathogenic variant in the RET gene, c.2753T>C (p.M918T), consistent with MEN2B syndrome. Subsequent thyroid ultrasound showed a small mass, and calcitonin level was elevated. He underwent a total thyroidectomy for MTC.

**Conclusions:** This is the first report of short stature and GH deficiency associated to MEN2B syndrome. It illustrates the need to consider extensive genetic testing in children with short stature and dysmorphic features. GH therapy for this patient is contraindicated due to tumor risk predisposition.

P1-914

### ALLGROVE SYNDROME: 3 CASES REPORT

*Nihad Selim Abdelaziz, MD, University Hospital of Annaba, Annaba, Algeria; Foued Abdelaziz, MD, El Hadjar Medical Practice, ANNABA, Algeria; Amina Talbi, MD; Anissa Hammani, MD; Rym Bediar, MD; Nadira Bouchair, PhD, University Hospital of Annaba, ANNABA, Algeria*

**Objectives:** Allgrove syndrome (triple A syndrome) is an autosomal recessive disorder characterized by achalasia, alacrimia and adrenal insufficiency with isolated glucocorticoid deficiency, it is a multisystem disease and in addition to cardinal manifestations there are associated features especially neurologic problems. the aim of this report is to present different level of expression of the disease.

**Methods:** This report concerns three cases of Allgrove's syndrome

**Results:** The two first cases are brother and sister from consanguineous marriage aged 9 and 19 years with long-standing dysphagia and vomiting that started at age of 1 month. They had been diagnosed as achalasia and treated accordingly. The association with alacrimia and hypoglycemic seizures as a sign of glucocorticoid deficiency were consistent with Allgrove's syndrome. Additional features consisted of reduced visual acuity because of amblyopia, muscle atrophy, nasal speech and neurologic abnormalities with mental retardation more severe with the sister. The third case was diagnosed at the age of 4 years with glucocorticoid deficiency as he was presenting hyperpigmentation of his skin, hypoglycemic seizures and asthenia, at the age of 9 years further investigations including barium swallow along with the clinical evaluations showed the association with achalasia and alacrimia. the three patients are under glucocorticoids replacement and artificial tears eye drop.

**Conclusions:** Alacrimia is considered to be the earliest clinical manifestation of Triple A syndrome however achalasia is often the initial sign that causes the parent to consult. Early recognition of glucocorticoid deficiency would prevent hypoglycemic convulsions and neurological sequelae.

P1-915

### PERSISTENT DIABETES MELLITUS POST-ADRENALECTOMY IN NEONATAL MCCUNE-ALBRIGHT SYNDROME

*Mustafa Tosur, MD; George S Jeha, MD, Texas Children's Hospital / Baylor College of Medicine, Houston, TX, United States*

**Objectives:** Neonatal McCune-Albright Syndrome (MAS) is a rare disease with severe clinical manifestations, including

hyperglycemia associated with Cushing syndrome. However, there is no report on persistent diabetes mellitus following neonatal MAS.

**Methods:** We report the first case of persistent diabetes mellitus post-adrenalectomy in neonatal MAS.

**Results: Case Presentation:**

A Hispanic female was born at 33 weeks of gestation with microcephaly, café-au-lait patches and small for gestational age (birth weight 1162 gram). In the first week of life, she developed hypertension, electrolyte abnormalities and neonatal diabetes mellitus (insulin 14 mIU/mL, blood glucose [BG] 206 mg/dL) requiring insulin. She was diagnosed with hyperthyroidism and put on propylthiouracil at 11 days of age. Hypercortisolism was noted at 3 weeks of age (random cortisol 128 mg/dL). She was transferred to our facility for suspected neonatal MAS. MRI of the adrenal glands showed homogeneously enlarged glands. She developed malignant hypertension requiring multiple anti-hypertensives. She underwent to bilateral adrenalectomy at 2 months of age. Despite the improvement in blood pressure and glycemic control, anti-hypertensive and insulin needs persisted. Ultrasound of pancreas was normal and diabetes autoantibodies were negative. Hypoinsulinemic hyperglycemia (insulin 1.2 mIU/mL, C-peptide 1.2 ng/dL, BG 196 mg/dL) was confirmed. She underwent total thyroidectomy at 6 months of age. R201H (Arginine to Histidine) mutation was confirmed in *GNAS1* gene on a serum sample. Peripheral precocious puberty, multi-focal bony involvement with osteopenia and multiple fractures, neonatal cholestasis, nephrocalcinosis and poor growth were among other findings. She died from multi-organ failure at 8 months of age.

**Conclusions:** We report the first case of persistent diabetes mellitus post-adrenalectomy in neonatal MAS. High disease burden affecting multi-organ system is suggestive of a somatic mutation very early in the development. We postulate that the constitutive activation of a G-protein coupled receptor (i.e., GPRC5B) in pancreas with or without beta cell toxicity effect of steroids could have led to a persistent hypoinsulinemic diabetes mellitus.

## POSTER SESSION 1

Thursday, September 14, 2017, 5:45-6:45pm

### P1 - Neuroendocrinology including hypothalamic pituitary

#### P1-1000 – P1-1016

P1-1000

#### NGS (NEXT GENERATION SEQUENCING) IN CONGENITAL HYPOPHYSECTOMY AND MIDLINE DEFECTS

Anna E M Allegri, MD, GENOVA, GENOVA, Italy; Massimo Acquaviva, biologist, Gaslini Children's Hospital, Genova, Italy; Natascia Di Iorgi, MD, University of Genova, Giannina Gaslini Institute, Genova, Italy; Flavia Napoli, MD, Istituto Giannina Gaslini, Genova, Italy; Annalisa Calcagno, MD, University of Genova, Giannina Gaslini Institute, Genova, Italy; Giuseppe

Patti, MD, PhD student, GENOVA, Genova, Italy; Annalisa Gallizia, MD, Istituto Giannina Gaslini, Genova, Italy; Sara Notarnicola, MD, University of Genova, Giannina Gaslini Institute, Genova, Italy; Angela E Covone, biologist, Gaslini Children's Hospital, Genova, Italy; Mohamad Maghnie, MD, Giannina Gaslini Institute, Genova, Italy; Paola Diana, MD, University of Genova, Giannina Gaslini Institute, Genova, Italy

**Objectives:** Congenital hypopituitarism (CH) with midline brain and pituitary defects (MD-P) is often due to mutations of pituitary transcription factors. Most patients with CH/MD-P are not inherited and only few familial cases have been reported suggesting that mutations in others genes may be related to these rare conditions. The objectives were to improve molecular diagnosis and to detect new genes/variants involved in the development of midline structures and pituitary gland by using Whole Exome Sequencing (WES).

**Methods:** CH/MD-P patients were selected after clinical, visual and endocrine assessments; brain magnetic resonance investigation, cardiac and renal ultrasound; Karyotype, CGH-array and DNA extraction of "Trios" (proband and parents). WES was performed in "Trios". Ion Proton equipment and AmpliSeq technology for exome library preparation was used (Life Technology). Suitable bio-informatic tools were used as filtering strategy of exome sequencing data. The identified candidate causative variants will undergo Sanger validation and functional studies

**Results:** We conducted WES on 26 individuals belonging to 8 families. Our preliminary data showed a high-impact novel mutation/variant with high suspicion to be responsible of the condition observed in the proband in one family

**Conclusions:** We believe that identifying potential new mutations/variants will make it feasible to predict both clinical outcomes from genetic data and for assessing the risk of future affected individuals

P1-1001

#### CLINICAL CHARACTERISTICS AND THERAPEUTIC OUTCOMES IN 30 CHILDREN AND ADOLESCENTS WITH PROLACTINOMAS FOLLOWED IN A SINGLE TERTIARY REFERRAL CENTER.

Maria Isabel Di Palma, MD; Cinthia Chareca, MD; Carlos Rugilo, MD; Celeste Mansilla, MD; Fabiana Lubieniecki, MD; Javier Gonzalez Ramos, MD; Daniel Alderete, MD; Laura Fernandez Fatsuca, MD; Juan Manuel Lazzati, Biochemist; Diana Monica Warman, MD, Hospital Nacional de Pediatría "Juan P. Garrahan", Buenos Aires, Argentina; Mercedes Maceiras, Biochemist, Hospital de Pediatría JP Garrahan, Buenos Aires, Argentina; Alicia Belgorosky, MD, PhD; Marta Ciaccio, MD, Hospital de Pediatría Prof. Dr. Juan P. Garrahan, Buenos Aires, Argentina

**Objectives:**

Prolactinomas are rare in children. It has been described immunological dysfunction and autoimmune thyroid disease (AITD) in adult patients with prolactinomas. The aim is to report clinical presentation, response to treatment, and long-

term follow-up of children and adolescents with prolactinoma followed in a single tertiary referral center.

#### Methods:

We retrospectively analyzed clinical data of 30 (15F/15M) young patients with prolactinoma seen in a tertiary referral center between 1988 and 2016. Chronological age was (mean±SD) 14.4±1.91 y (r 8,5-18). Mean duration of follow up was 3,9 years (r 0,16-10). 9 patients were referred after surgery, all received dopamine agonist (DA) and 1 radiotherapy. 1 patient received surgery and radiotherapy after failure of DA. 20 patients were only treated with bromocriptine (BC) at doses ranging from 2.5 to 25 mg/day or cabergoline (CB) at doses ranging from 0.5 to 8 mg/week orally. Resistant patients received BC 15 to 25 mg or CB 3.5 to 8 mg.

#### Results:

We found equal prevalence of both sexes.

Macroprolactinomas were more prevalent 86%, F80% M93%. There were 26% invasive and 23% giant adenomas. PROL levels were higher in boys (M 7259±7732 F 2285±4059 ng/ml p 0.02). Symptoms at diagnosis were: headache 73.3%, pubertal disorder 70%, visual field defect 56.6%, over weight/obesity 40% and galactorrhea 33%. AITD was negative in all patients except one. 1 patient had clinical and molecular diagnosis of MEN1. 80% of the group was sensitive to DA (100% Microprolactinomas 77% of Macroprolactinomas and 42% of Giant). Resistance to DA was associated to higher PROL levels (11235±8477 vs 2345±3635 ng/ml p 0.04).

#### Conclusions:

As in other series DA is the first line treatment in pediatric population. In our cohort macroprolactinomas have a higher prevalence and no sex difference is found, probably due that microprolactinomas are not referred to a tertiary center. DA resistance is associated with higher PROL levels. AITD is not present in this pediatric cohort but future studies are needed to clarify this point. DA resistance represents a challenge to find a new drug treatment in pediatric prolactinoma.

P1-1002

#### CLINICAL AND ENDOCRINOLOGICAL CHARACTERISTICS OF PATIENTS WITH SEPTO-OPTIC DYSPLASIA AT THE CHILDREN'S HOSPITAL OF MICHIGAN.

Noelle Andrea V Fabie, MD; Lina Saadeh, MD; Doris R Taha, MD, Children's Hospital of Michigan/Wayne State University, Detroit, MI, United States

**Objectives:** Septo-optic dysplasia (SOD) is a disorder of brain development characterized by a combination of optic nerve hypoplasia, midline brain defects, and pituitary gland/hormone abnormalities. The purpose of this study is to review records of SOD patients and identify clinical features that are unique to this group of patients.

**Methods:** A retrospective study was performed and records of SOD patients younger than 18 years of age were reviewed. Data including demographic information, hormone levels, imaging results, growth parameters and results of genetic testing were obtained. Descriptive analysis was used.

Qualitative data is presented as frequencies and percentages while quantitative data is presented as means+/- SD.

**Results:** Thirty-nine patients were diagnosed with SOD between the years 2000 and 2017; 67% (n=26) of them were males. Eleven (28%) of the patients had all three features of the disease. The average time of diagnosis was 0.9 years. Levels of cortisol, thyroid stimulating hormone, Free T4, Insulin-like growth factor 1, and Insulin-like growth factor-binding protein 3 were obtained. Eleven patients (28%) had undetectable IGF-1 levels at diagnosis; mean IGF-1 level was 64.27+/-54.64 ng/mL for those with measurable levels. Mean TSH and FT4 levels were 3.26+/-2.92 uIU/mL and 1.01+/- 0.32 ng/dL, respectively. A total of 27 patients (69%) developed some form of hormone deficiency and were started on hormone replacement therapy. Fifteen patients (38%) had central hypothyroidism (50% diagnosed at presentation). Adrenal insufficiency was seen in 16 patients (41%), growth hormone deficiency in 18 patients (46%). Seven patients (18%) had diabetes insipidus. Eleven patients had some genetic testing done and two (18%) had chromosomal deletions - deletion of 5p15.33-5p13.3 and deletion of 1p31.1-p31.3.

**Conclusions:** Our findings suggest that SOD remains a disease with clinical variability. It is usually diagnosed within the first year of life and is slightly more predominant in males. Variable degree of hypopituitarism is common in these patients; growth hormone deficiency being the most common. Severe growth hormone deficiency is common with 28% of the patients having undetectable IGF-1 levels at diagnosis. Genetic studies may be helpful in elucidating a genetic abnormality in some patients.

P1-1003

#### INCIDENCE OF PITUITARY HORMONE DEFICIENCIES IN CHILDREN RECEIVING PROTON BEAM RADIATION FOR BRAIN TUMORS.

Erika Zevin, MD, Indiana University School of Medicine, Indianapolis, IN, United States; Erica A. Eugster, MD; Nadine G Haddad, MD, Indiana University School of Medicine and Riley Hospital for Children, Indianapolis, IN, United States

**Objectives:** Children with a history of brain tumor who receive cranial radiation are at risk for pituitary hormone deficiencies (PHD). Compared to photon beam radiation therapy (RT), proton beam RT (PBRT) is a newer modality that allows the delivery of higher doses to the tumor while sparing normal tissue. There is minimal information regarding the frequency and type of PHD in children receiving PBRT. Our objective was to characterize endocrine abnormalities in children with a history of non-pituitary CNS tumors who received PBRT. We also sought to determine if certain tumor types incurred a higher risk of PHD than others.

**Methods:** Medical records of children with CNS tumors treated at Indiana University Health Proton Therapy Center in Bloomington, Indiana between 2000 and 2015 were reviewed. Only charts of patients who had undergone endocrine evaluation were included. Children with

craniopharyngiomas were excluded due to high risk for PHD in these patients.

**Results:** Eighty three patients (48 boys) were identified. Average age at PBRT was  $8.33 \pm 4.67$  years (range 1.2-17.5 years). Average duration of follow up was  $4.85 \pm 2.70$  years (range 0.6-15 years). All patients also received treatment with surgery, chemo or both.

The most common CNS tumors were medulloblastomas (MB) (30%), gliomas (19%), ependymomas (16%), juvenile pilomyxoid astrocytomas (8%) and germinomas (7%). Growth hormone deficiency was the most common PHD occurring in 40% of patients, followed by central hypothyroidism (20%), hypogonadotropic hypogonadism (18%) and ACTH deficiency (12%). One patient had precocious puberty.

The frequency of PHD was highest in patients with MB (56%), all of whom were diagnosed with endocrinopathies within 5 years following completion of PBRT.

**Conclusions:** PHD are common in children who receive PBRT. Prospective studies are needed in order to define the time course and specific risk factors for the development of hypopituitarism in children who receive PBRT for CNS neoplasms.

P1-1004

#### **PERI-OPERATIVE MANAGEMENT OF DIABETES INSIPIDUS FOLLOWING BARIATRIC SURGERY FOR HYPOTHALAMIC OBESITY: EFFECTS ON DESMOPRESSIN**

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**Objectives:** Hypothalamic obesity (HyOb) causes rapid weight gain and early metabolic co-morbidities, typically in survivors of intracranial tumors. Tumor survivors with HyOb often develop panhypopituitarism. Bariatric surgery has been used for treatment of HyOb to cause weight reduction. Peri-operatively, management of diabetes insipidus (DI) may be complicated by surgical effects on fluid intake and medication absorption. We aim to determine effects of desmopressin dosing following surgery.

**Methods:** Retrospective review of patients with HyOb and panhypopituitarism including DI who completed bariatric surgery at our center was completed from 2004 until present. Patient demographics, timing of surgery, and desmopressin dosing used pre-operatively, at hospital discharge, and at follow up were collected. Comparative statistics were performed for analysis.

**Results:** Six patients (4 female, median age 18.3 years; inter-quartile range 25<sup>th</sup>-75<sup>th</sup>% [IQR], 15.6-18.8 years) were identified. Seven surgical events were identified (Roux-en-Y gastric bypass or RYGB, n=5, sleeve gastrectomy, n=2). One patient received 2 bariatric procedures, having sleeve gastrectomy initially and later undergoing RYGB. Oral

desmopressin was used with 4 patients (5 of 7 procedures), 1 patient used subcutaneous and 1 used intranasal desmopressin formulations. Pre-operatively, median total oral desmopressin dose was 700mcg daily (IQR, 600-1600 mcg). Post-surgical dosing decreased by 50% with median total dose 350mcg daily (IQR, 300-400 mcg). At median follow up of 5 months (IQR, 2-10 months), median total dose increased to 700mcg daily (IQR, 300-1400 mcg). Total intranasal (20 mcg daily) and subcutaneous desmopressin (5.2 mcg daily) doses did not change post-operatively.

**Conclusions:** For patients with HyOb and DI, bariatric surgery causes a temporary reduction in oral desmopressin requirements by a median of 50% in the immediate post-operative period. Dosing later returns near pre-operative requirements. Providers should be cautious with oral desmopressin use following bariatric surgery, and should plan for temporary reduction in dosing or use of intranasal or subcutaneous administrative routes to avoid desmopressin overtreatment.

P1-1005

#### **RELATIONSHIP BETWEEN LOWER HEART RATE VARIABILITY AND RISK FOR THE METABOLIC SYNDROME IN PATIENTS WITH CHILDHOOD-ONSET CRANIOPHARYNGIOMA**

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**Objectives:** Autonomic nervous system (ANS) dysfunction is implicated in the development of hypothalamic obesity and metabolic disturbances. We evaluated changes in ANS activity by measuring heart rate variability (HRV) in patients with childhood-onset craniopharyngioma and analyzed for relationships between HRV changes and obesity, hypothalamic involvement (HI) and the metabolic syndrome.

**Methods:** Fifty-three patients (31 males, 10-30 years old) with childhood-onset craniopharyngioma were enrolled between March 2014 and January 2016. The extent of HI was graded using magnetic resonance imaging. HRV indices of overall variability, parasympathetic and sympathetic modulation were measured. Anthropometric measurements, fasting glucose, insulin, lipid panel, and blood pressure were determined to assess for components of the metabolic syndrome.

**Results:** Patients with extensive HI showed increased body mass index (BMI) z-scores and waist circumference than those with mild HI ( $P < 0.05$  for both). Measures of HRV did not differ between obese and non-obese subjects, while subjects with extensive HI had significantly lower overall HRV than those with mild HI ( $P < 0.05$ ). Lower overall HRV was associated with increased insulin resistance, triglycerides, and



systolic blood pressure, respectively ( $P < 0.05$  for all). Lower overall HRV was independently associated with the metabolic syndrome after adjusting for sex, age, obesity and family history of metabolic and cardiovascular disease ( $P < 0.05$ ).

**Conclusions:** Extensive HI is associated with obesity and decreases in overall HRV. Lower overall HRV is an independent risk factor for the metabolic syndrome in patients treated for childhood-onset craniopharyngioma.

P1-1006

#### **ENHANCED AT PUBERTY1 (EAP1) GENE EXPRESSION KNOCKDOWN DELAYS PUBERTY, BUT DOES NOT CHANGE HYPOTHALAMIC KISS1 GENE EXPRESSION IN VIVO.**

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**Objectives:** An intronless gene, enhance at puberty1 (EAP1) was recently reported to be an up-stream gene in the hypothalamus reproductive gene network. However, the mechanism underlying the regulation of puberty by EAP1 has not been elucidated. EAP1 is postulated to act on puberty by promoting the hypothalamic kiss1 metastasis-suppressor (kiss1) gene which is essential for initiating of puberty. The aim of this study was to test this hypothesis.

**Methods:** By using intraventricular microinjections of lentiviral-mediated RNA interference to knockdown EAP1 expression in 21-day-old rats, rats were divided into three experimental groups (lentivirus [LV]-EAP1-short hairpin RNA [shRNA], LV(-) control, and saline groups).

**Results:** Puberty was delayed and hypothalamic gonadotropin-releasing hormone (GnRH) mRNA was decreased. However, surprisingly, after blocking EAP1 gene, both Kiss1 mRNA and protein level were unchanged with respect to the control group.

**Conclusions:** These results indicate that EAP1 may act through other pathway rather than kiss1/G protein-coupled receptor (GPR54) signaling in vivo.

P1-1007

#### **PITUITARY IMAGING IN 189 PATIENTS WITH CONGENITAL GROWTH HORMONE DEFICIENCY.**

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**Objectives:** Congenital Growth Hormone Deficiency (GHD) is often associated with specific pituitary anomalies. Brain MRI is therefore useful in both diagnosis and prognosis. Evaluate the frequency of MRI anomalies in congenital GHD and correlate these findings with pituitary deficiency.

**Methods:** Retrospective study including all children seen in our clinic for Congenital Growth Hormone Deficiency (GHD) which was defined as peak GH of EITHER  $<20\mu\text{U/l}$  associated with abnormal pituitary OR peak GH less than  $20\mu\text{U/l}$  in two stimulation tests (glucagon and insulin) when pituitary imaging was normal. Abnormal imaging included the presence of one to three of the following anomalies: Hypoplastic Anterior Pituitary (HAP), Missing/Interrupted Pituitary Stalk (IPS) and Ectopic Posterior Pituitary (EPH). Patients were divided in two groups: group 1 with Isolated GHD (IGHD); group 2 with Multiple Pituitary Hormone Deficiency (MPHD). Imaging findings were then compared between the two groups.

**Results:** Of 222 patients followed for GHD, 189 were included in the study (63 F/126M). Group 1 comprised 144 patients (76.1%), mean $\pm$ SDS age at diagnosis being  $7.15\pm3.75$  years. Mean (SD) height at diagnosis in Group 1 was  $-3.08\pm0.8$  SDS. Group 2 comprised 45 patients (23.8%), age at diagnosis  $7.88\pm6.08$  years, height  $-3.93\pm1.46$  SDS. GHD deficiency was most severe in group 2 with a peak GH of  $3.37\pm5.04\mu\text{U/l}$  versus  $10.16\pm6.24\mu\text{U/l}$  in group 1  $p<0.001$ . Brain MRI was abnormal in 61 (42.4%) patients in group 1 versus 35 (77.7%) patients in group 2  $p<0.001$ . HAP was found in 39 patients: 33 (22.9%) in group 1 versus 6 (13.3%) in group 2. EPH was present in 26 (57.8%) cases from group 2 versus 24 (16.7%) cases in group 1  $p<0.001$ . EPH was associated with a risk of MPHD with RR of 2.15 IC95% [1,5-3,1] and with severe GHD with RR of 4,4 IC 95% [2,3-8,5]. MRI triad was more frequent in MPHD 16(35.6%) versus 16(11.1%) in IGHD, Isolated IPS was presents in 4 cases (3 IGHD, 1 MPHD).

**Conclusions:** Pituitary imaging remains an important tool in the diagnosis of congenital GHD. Patients with EPH run a higher risk of developing MPHD and a more severe GHD. Genetic aetiology is suspected in some cases of IGHD in which genetic testing needs to be performed.

P1-1008

#### **PEDIATRIC CUSHING'S DISEASE IN AN OBESE GIRL WITH DEVELOPMENTAL DELAY: A DIAGNOSTIC CHALLENGE**

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**Objectives:** Cushing's syndrome is rare, with an incidence of 2-5 cases in a million people per year, 10% are children. After pre-school years, Cushing disease (CD) is the most common etiology. We present a case of CD. The diagnosis was

challenging as initially the patient was considered to have obesity and developmental delay due to a genetic syndrome.

**Methods:** Case Report

**Results:** A 10 year old girl was referred to our Pediatric Endocrine clinic for obesity. She has history of developmental delay, head bobbing and frequent laughter for which she was evaluated by Neurology, with negative workup. Angelman syndrome/Prader Willi syndrome were rule out by genetic testing. She had significant rapid weight gain of 80lbs in the last 2 years. Her growth velocity was 4 cm/yr (decreased height from 95% to 65%), Ht 142.8cm(65%), Wt 72.5kg(>99%), BMI 31 kg/m<sup>2</sup>(>99%) and normal BP. Physical exam was significant for happy demeanor, moon face with plethora, acne, central obesity, buffalo hump, acanthosis nigricans, striae on abdomen, hyperpigmented face, fingernails and knuckles. Breast was Tanner stage II and Tanner IV pubic hair. Bloodwork revealed a random pm cortisol of 24.38ug/dl, ACTH 95pg/ml, insulin level 37.75 mU/L and HbA1c 6.4%. Eleven pm salivary cortisol levels were elevated at 487ng/dl, 480ng/dl and 166ng/dl (norm <130ng/dl). Twenty four-hour urine free cortisol level was elevated at 86mcg/24 hr (norm < 70mcg/24hr). Post-1mg dexamethasone suppression test resulted in 8am cortisol of 10.64ug/dl (norm <1.8ug/dl) and post-8mg dexamethasone suppression test resulted in 8am cortisol of 1.13ug/dl, suppressed level, consistent with CD. Rest of the pituitary hormones were normal. MRI brain revealed a 1cm pituitary adenoma and MRI abdomen reported normal adrenal glands. She was then referred to Neurosurgery for tumor resection.

**Conclusions:** Pediatric patients with CD may not have all the typical features for the disease for which high index of suspicion is needed. Moreover, the presentation could be misleading for more common conditions, as in our case. However, physicians should consider CD when obesity, decreased growth velocity or emotional lability are present. Early diagnosis is imperative for treatment outcomes.

P1-1009

**RADIOTHERAPY AS FIRST-LINE TREATMENT FOR PEDIATRIC CUSHING'S DISEASE:TWO CASES FROM THE 1990'S**

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**Objectives:** Nowadays, recommended first line therapy for pediatric Cushing's disease(PCD) is transsphenoidal surgery(TSS). Pituitary radiotherapy(RT) was suggested as primary therapy before the development of TSS but is now preferred as second-line treatment after unsuccessful TSS. In this report, we aimed to evaluate the outcome of RT as first line therapy in PCD in two patients.

**Methods:** Medical records and present situation of two boys with PCD, now in their thirties, who had been treated with RT as first line therapy back in the 1990's were investigated.

**Results: Cases 1 and 2:**Two boys, thirteen and twelve years old, had presented with typical signs and symptoms of

Cushing syndrome. The findings of high and detectable ACTH respectively and decrease of cortisol only during high dose dexamethasone suppression test in both were compatible with CD. However, no lesions were visible in pituitary MRI's. Inferior petrosal sinus sampling was not performed. External beam RT delivering 45 Gy in 25 fractions was given to both. Cortisol levels were reduced at the end of first month and retained so at the end of the sixth month. Cushingoid appearance had disappeared at the end of the third month. Long term follow-up was not optimal and their final heights were well below their target heights. However, in 2017, they are perfectly healthy with no recurrence. One patient is married and is a father.

**Conclusions:** The outcomes of the two patients suggest that RT might be used as first line of treatment in PCD in special circumstances when TSS can not be performed optimally. However close follow-up, especially for growth, is necessary.

P1-1010

**PSEUDOTUMOR CEREBRI RESULTING IN EMPTY SELLA SYNDROME AND MULTIPLE PITUITARY HORMONE DEFICIENCIES**

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**Objectives:** Pseudotumor cerebri (PTC) is frequently associated with an empty sella turcica in neurologic literature. This radiologic abnormality is commonly asymptomatic, but it may present with non-specific neurological symptoms or more rarely with pituitary dysfunction. This case highlights a patient with PTC and secondary empty sella syndrome whose symptoms of hypopituitarism were attributed to the PTC, chronic pain, and medication side effects and resulted in delayed diagnosis and management.

**Methods:** A 17 year old male presented with concerns for delayed puberty and hypogonadism in the setting of known PTC. The patient was diagnosed with PTC seven years prior and had received medical and surgical management including a ventriculoperitoneal (VP) shunt requiring multiple revisions. The patient continued to suffer from chronic headaches and back pain despite prolonged opiate and lidocaine patch use. In addition to chronic pain, he had decreased energy, poor stamina, and frequent nausea and vomiting that was attributed to his underlying PTC, surgical interventions, and chronic narcotic use. This resulted in withdrawal from school and bedridden status for four years. Upon evaluation by pediatric endocrinology, previous CT and MRI images of the brain demonstrated a partially empty sella. Testing of the pituitary revealed multiple pituitary dysfunctions including hypogonadotropic hypogonadism, secondary adrenal insufficiency, and central hypothyroidism. He had a rapid increase in energy level following treatment with testosterone, hydrocortisone, and levothyroxine and was subsequently able to wean off his narcotic pain management and graduate from high school.

**Results:** N/A

**Conclusions:** PTC may cause secondary empty sella syndrome and thus potential for pituitary dysfunction. Serial pituitary function screening is necessary, especially in the setting of abnormal growth and development or poor energy. This patient had symptoms of hypopituitarism for several years, which were attributed to other factors. Early recognition and management of pituitary dysfunction is essential for normal growth and development. Avoidance of anchoring in a diagnostic evaluation may prevent unnecessary treatments and significantly increase quality of life.

P1-1011

#### **MACROPROLACTINOMAS AND ANTERIOR PITUITARY DYSFUNCTION IN ADOLESCENT MALES**

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**Objectives:** Prolactinomas are relatively uncommon in children and adolescents. Microprolactinomas are the most common prolactin-secreting tumors, and generally present with menstrual irregularities or galactorrhea in post-menarchal girls. We report three cases of adolescent boys presenting with macroprolactinomas associated with varying degrees of anterior pituitary dysfunction.

**Methods:** Three cases were reviewed and summarized from chart review.

**Results:** Two prepubescent boys presented with mild visual complaints, and one pubescent boy presented with new-onset psychosis. All three patients had prolactin levels >200 ng/mL, and all responded to cabergoline therapy. The two prepubescent boys showed progression of puberty, but continued to require cortisol and thyroid hormone replacement despite prolactin suppression. The third patient had ongoing psychiatric symptoms and slightly decreased testosterone levels at follow-up.

**Conclusions:** Pituitary adenomas are uncommon in the pediatric population, and the majority of cases are microprolactinomas in adolescent girls. The occurrence of macroprolactinomas associated with hypopituitarism in three boys with non-specific presenting symptoms suggests a need for increased clinical suspicion for prolactinomas in adolescent males with non-specific symptoms, and close monitoring of anterior pituitary function in children with prolactinomas.

P1-1013

#### **CRANIOPHARYNGIOMA IN CHILDHOOD AND ADOLESCENCE: ENDOCRINE-METABOLIC REPERCUSSIONS**

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**Objectives:** To evaluate and correlate clinical and anthropometric characteristics, adiposity indexes, growth hormone deficiency, treatment with recombinant human growth hormone (rhGH) among craniopharyngioma patients.

**Methods:** 57 patients treated for craniopharyngioma were evaluated according to: clinical characteristics, hypothalamic involvement, tumor treatment, anthropometric variables [Z score of weight, height and body mass index (BMI), at diagnosis and post-treatment], adiposity indexes [category of BMI at diagnosis and post treatment - overweight or obesity, percentage of body fat (%BF) by dual-energy x-ray absorptiometry, waist circumference, subcutaneous and visceral adipose tissue by abdominal tomography] and criteria for metabolic syndrome. Correlations among these parameters were analyzed by multiple regression and logistic models. The sample was divided according to growth hormone deficiency and rhGH treatment therapy as follows: growth without growth hormone, current use of rhGH, prior use of rhGH, patients who did not use rhGH so far and non growth hormone deficient.

**Results:** Mean age at diagnosis was 9.6 year-old and 16.6 at study evaluation. 54/57 (94.7%) received at least two hormone replacements and 43/57 (75.4%) had hypothalamic involvement. 24/57 patients (42.1%) were treated with surgery and radiotherapy. At diagnosis, 12/57 (21%) were obese and 33/57 (57.9%) at study evaluation. There was no decrease of Z height, meaning that patients presented with real weight gain. BMI category worsened at a median of 3.2 year after first treatment. Z BMI at diagnosis influenced Z BMI ( $p=0.005$ ) post-treatment, %BF ( $p<0.001$ ), waist circumference ( $p<0.05$ ) and the occurrence of metabolic syndrome ( $p<0.05$ ). Visceral adipose tissue and %BF were decreased in patients using rhGH ( $p<0.05$ ). 55/57 patients were growth hormone deficient and 26/57 (45.6%) presented growth without growth hormone.

**Conclusions:** Patients with craniopharyngioma worsened BMI category at a median of 3.2 year after the first treatment. The higher Z BMI at diagnosis, the higher Z BMI, %BF, waist circumference and the occurrence of metabolic syndrome post-treatment. Replacement of rhGH had a beneficial effect on adiposity, decreasing %BF and visceral adipose tissue.

P1-1014

#### **NOVEL LZTR1 GENE VARIANTS ASSOCIATED TO NOONAN SYNDROME AND GROWTH HORMONE DEFICIENCY**

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**Objectives:** Noonan syndrome is an autosomal dominant, multisystemic disorder caused by germline mutations that encode components of the RAS/MAPK signaling pathway. Pathogenic *LZTR1* variants have been associated with RASopathies and Schwannomatosis. Short stature is a frequent finding but its pathophysiology poorly defined. Recently, transgenic mice with pituitary-specific overexpression of B-Raf presented dwarfism and abnormal pituitary development suggesting a role for B-Raf in hypopituitarism. The aim of this study is to describe a novel mutation of *LZTR1* gene associated to Noonan Syndrome and GH deficiency (GHD).

**Methods:** A 12.5 year-old boy presented with short stature (Ht 123.6 cm, SDS -3.5) and typical Noonan Syndrome characteristics: triangular face, high-arched palate, low-set ears, micrognathia, pectus excavatum and transposition of the great vessels and pulmonary stenosis. Hormonal investigation revealed isolated GHD (basal IGF1 46 ng/mL < -2SDS, peak GH after clonidine and glucagon tests 1.4 ng/ml). Somatropin was provided from 12.5 to 22 years. Pituitary MRI revealed thickening of the left optic nerve and chiasm suggestive of glioma and no other abnormalities. Patient's DNA was submitted to a customized target gene panel (Agilent Sure Select Technology) containing 28 genes associated with hypopituitarism and 60 other genes associated with short stature.

**Results:** Compound heterozygosity [c.2212C>T:p.Q738];[c.494G>T:p.R165L] in *LZTR1* was identified. The patient was negative for the 17 other genes previously associated with Noonan Syndrome and for the GHD genes. Segregation in the family demonstrated that he received each variant from one of his progenitors with normal phenotype.

**Conclusions:** *LZTR1*, leucine-zipper-like transcription regulator 1, encodes a protein member of the BTB-kelch superfamily, highly expressed in the pituitary. This gene was recently identified in six non-related families with Noonan Syndrome phenotype with an autosomal dominant model, but still, its function is poorly known and possibly may be involved in the RAS MAPK pathway. We describe the first association between *LZTR1* gene variants with NS associated to GHD. Further studies are required to demonstrate the relation of this gene with the RAS/MAPK signaling pathway and the etiology of hypopituitarism.

P1-1015

#### FLUCTUATING THYROID FUNCTION, INCONSISTENT SPONTANEOUS AND STIMULATED GH SECRETION, AND PITUITARY HYPOPLASIA IN A BOY WITH A NOVEL *IGSF1* MUTATION

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**Objectives:** The most frequent genetic cause of congenital central hypothyroidism (CeH) is the recently discovered X-linked *IGSF1* deficiency. We describe the clinical and biochemical data of a patient carrying a novel *IGSF1* mutation and thereby further extend the astonishing phenotypic variability of patients with this syndrome.

**Methods:** GH secretion was assessed by a 4x/hour night profile and an insulin tolerance test (ITT, 0.1U/kg). Serum hormones were measured with standard tests. After negative findings on Sanger sequencing for *PROP1* and *POU1F1*, we sequenced *IGSF1*.

**Results:** A 7.5 year old boy, born at term with a weight of 3.3 kg and length of 51 cm, was referred for slow linear growth and delayed second dentition. Cognitive and psychomotor development were normal. His height SDS was -1.7, target height SDS +0.6 and bone age (BA) was delayed by 2.5y. A borderline low FT4 of 9.5 ng/l (reference 9.3-17 ng/l) and normal TSH (2.2 mU/L) suggested a mild CeH. Prolactin was low (66 mU/l). Treatment with 25 µg/d L-T4 was started and a GH night profile at 8y revealed sufficient peaks (up to 41 mU/l). No catch-up growth and BA advancement was observed in spite of increasing L-T4 doses up to 75 µg/d. After discontinuing L-T4 at age 11, serum FT4 remained normal (11.7 ng/l). At 12y an ITT showed partial GHD (GH<sub>max</sub> 7.8 mU/L) and a normal cortisol response. The 3<sup>rd</sup> MRI showed a hypoplastic anterior pituitary. rhGH was started, followed by a substantial catch-up in growth and BA, but a decrease in FT4 (6.1 ng/l) for which L-T4 was reinstituted. Adrenarche was delayed. In contrast to a normally timed but fast progressive testicular growth (17ml by US at 15y), pubic and axillary hair appeared late (13.5y), and serum testosterone remained prepubertal until 15y while FSH and LH were normal. *IGSF1* sequencing revealed a novel pathogenic mutation (c.2989C>T, p.Arg997\*).

**Conclusions:** In addition to characteristic features (CeH, disharmonious pubertal development, macroorchidism, hypoprolactinemia, delayed adrenarche) our patient showed three novel clinical features: 1) thyroid function fluctuating between low and normal; 2) discrepancy between a normal spontaneous GH peak and low GH response to ITT later in life; 3) pituitary hypoplasia. In boys with CeH, *IGSF1* is the first candidate gene to be tested.

P1-1016

#### LATENT HYPOPITUITARISM IN AN INFANT WITH AN ABERRANT KARYOTYPE: 46 XY (9QH+)- IS THERE A CONNECTION?

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**Objectives:** Simultaneous alteration of several hormonal axes in congenital hypopituitarism can be caused by intrinsic pituitary disease, hypothalamic disorder or extrinsic extrasellar dysplasia. The phenotype can vary and the goal is the early diagnosis and precocious substitutive therapy implementation. The association of bilateral congenital undescended testis and micropallus in male neonate is presumptive evidence of congenital hypopituitarism.

**Methods:** CASE REPORT: 3 years old boy, born by caesarian section (presence of the nuchal cord), only child of a normal, healthy couple, born at term (40W), birth weight: 4000g, length: 51cm. At birth it was raised the suspicion of intersexuality presenting bilateral undescended testis and micropenis (negative Barr test; karyotype: 46XY 9qh+ considered normal human polymorphism). At 8 months, the laboratory results revealed the diagnosis of partial hypopituitarism: central hypothyroidism, low levels of growth hormone, IGF1 and hypogonadotropism (stimulation tests revealed a subnormal response of follicle stimulating hormone and luteinizing hormone to gonadotropin releasing hormone stimulation, normal response of thyroid stimulating hormone to thyrotropin releasing hormone stimulation). Thyroid supplementation was immediately implemented with little or no effects on the growth velocity. Growth hormone deficiency became obvious around the age of 3, height: 92cm (-1.35SD), growth velocity: 0.28cm/month, delayed bone age ~1 year 6 months. MRI showed hypoplastic tuber cinereum, lack of visualizing of the pituitary stalk, atrophic anterior pituitary gland.

**Results:** The patient presents bilateral undescended testis and micropenis, secondary hypopituitarism due to hypothalamic deafferentation; genetic analysis found a chromosome 9 anomaly (9qh+)- which is considered to be a normal polymorphism, but this association has never yet been cited.

**Conclusions:** Cryptorchidism and especially micropallus can be a precocious sign of pituitary insufficiency. The early diagnosis preempts further complications and constant monitoring helps implement substitutive treatment without delay.

## POSTER SESSION 1

Thursday, September 14, 2017, 5:45-6:45pm

### P1 - Obesity, lipids, and co-morbidities

P1-1100 – P1-1136

P1-1100

#### FISH OIL SUPPLEMENTATION DURING INSULIN RESISTANT PREGNANCY PREVENTS THE DEVELOPMENT OF INSULIN RESISTANCE IN THE ADULT OFFSPRING

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**Objectives:** This study aimed to determine in a rat model, whether supplementation with fish oil (rich in omega-3 fats), during the pregnancy of insulin resistant mothers, could prevent the development of insulin resistance and other aspects of metabolic dysfunction in the offspring.

**Methods:** Virgin female rats were time-mated and randomised into four treatment groups: Con-Con, dams fed a control diet (15% calories from fat) and administered water by gavage; Con-FO, control diet with 1ml of fish oil by gavage; HF-Con, high-fat diet (45% calories from fat) and water by gavage; and HF-FO, high-fat diet and fish oil by gavage. The fish oil was independently verified to be unoxidised (peroxide value 2.7meq/kg). Dams were fed *ad libitum* during pregnancy and lactation, but daily gavage occurred only during pregnancy. After weaning, male offspring consumed a chow diet *ad libitum* until adulthood, when they underwent detailed assessments of body composition and metabolism, including dual-xray absorptiometry and an oral glucose tolerance test with calculation of the Matsuda index of insulin sensitivity.

**Results:** Maternal high-fat diet led to increased food consumption (+89 g;  $p=0.044$ ), adiposity (+6.4% body fat;  $p=0.008$ ), systolic blood pressure (+12 mmHg;  $p<0.0001$ ), and plasma triglyceride (+0.55mmol/l;  $p=0.014$ ) and leptin (+4.1 ng/ml;  $p=0.002$ ) concentrations in adult HF-Con offspring. HF-Con offspring also exhibited lower insulin sensitivity than Con-Con rats (Matsuda index 38% lower;  $p=0.036$ ). Male offspring from HF-FO group were similar to HF-Con regarding food consumption, adiposity, and most metabolic parameters. However, insulin sensitivity in the HF-FO group was improved relative to the HF-Con offspring (Matsuda index 85% higher;  $p=0.014$ ) and similar to the Con-Con offspring.

**Conclusions:** Supplementation of dams consuming a maternal high fat diet (an established insulin resistant model) with unoxidised n-3 PUFA rich oils prevented the development of insulin resistance, but had no impact on body composition or other metabolic parameters in adult male offspring. Future

studies should assess whether this effect translates to obese human pregnancy.

Study outcomes among adult male offspring according to the maternal diet (control or high-fat), at gavaged treatment during pregnancy [fish oil or control (water)]. Data are means ± standard error †p<0.05, ‡p<0.01, and †††p<0.0001 for a maternal diet effect among the offspring of dams th received control gavage; \*p<0.05, and \*\*p<0.01 for an effect of the gavage treatment between group exposed to the same maternal diet.

	Maternal control diet		Maternal high-fat diet	
	Control	Fish oil	Control	Fish oil
n	12	12	12	12
<b>Insulin Sensitivity</b>				
Matsuda index	1.35 ± 0.17	1.27 ± 0.25	0.84 ± 0.09†	1.55 ± 0.26*
HOMA-IR	3.02 ± 0.41	3.89 ± 0.63	4.57 ± 0.54†	2.66 ± 0.42*
<b>Body Composition</b>				
Adult body weight (Day 108) (g)	495 ± 19	541 ± 15	593 ± 22†	593 ± 19
Body fat (%)	22.9 ± 1.1	24.2 ± 1.2	29.3 ± 1.0††	27.0 ± 1.4
<b>Other metabolic parameters</b>				
Triglycerides (mmol/l)	0.68 ± 0.07	0.94 ± 0.09	1.23 ± 0.15†	0.87 ± 0.11
Fasting leptin (ng/ml)	1.6 ± 0.3	4.2 ± 1.3*	5.7 ± 1.3††	4.0 ± 0.9
Systolic blood pressure (mmHg)	124 ± 1	125 ± 1	136 ± 1††††	135 ± 1
Lifetime food consumption (g)	705 ± 22	751 ± 13	794 ± 17†	795 ± 31

P1-1101

CIRCULATING FIBROBLAST GROWTH FACOTR-21 (FGF-21): A BIOMARKER OF SUBCLINICAL ATHEROSCLEROSIS IN OBESE YOUTH WITH NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)?

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**Objectives:** FGF-21 is highly expressed in the liver and is involved in glucose and lipid metabolism. Elevated FGF-21 concentrations are associated with obesity, atherogenic lipid profile, and NAFLD. It is not clear if FGF-21 may constitute a biomarker for subclinical atherosclerosis (SCA) in youth with NAFLD at high risk for the metabolic syndrome. We investigated the relationship of FGF-21 to endothelial function biomarkers of SCA in obese Hispanic youth with NAFLD (MRS hepatic fat fraction >5.5%) vs. without NAFLD across the spectrum of glucose regulation.

**Methods:** Obese Hispanic adolescents (mean age: 15.4±0.3 years), 13 with normal glucose tolerance,19 with prediabetes (PreD) and 16 with type 2 diabetes (T2D) underwent evaluation of reactive hyperemia index (RHI) and augmentation index (Alx) by peripheral arterial tonometry, blood pressure (BP), lipids, peripheral (IS) and hepatic insulin sensitivity (HIS) by hyperinsulinemic-euglycemic clamp with [6,6, <sup>2</sup>H<sub>2</sub>] glucose, body composition by DXA, visceral (VAT) and hepatic fat (HF) by MRI/MRS.

**Results:** The NAFLD vs. no-NAFLD groups did not differ in age, sex, glycemic status, HbA1c (5.6±0.1 vs. 5.8±0.1%), BP, % body fat or VAT. The NAFLD group had higher HF, ALT, FGF-21, LDL-cholesterol (98.0±4.5 vs. 79.0±4.9 mg/dl), lower IS, lower RHI (vascular reactivity) and higher Alx-75 (vascular stiffness) measures (Table). FGF-21 concentrations were related to VAT, HFF (r=0.45, p=0.002), HIS (r=-0.39, p=0.009), RHI (r=-0.33,p=0.03), and Alx

(r=0.45, p=0.02). In a multiple regression analysis, FGF-21 (β=-0.31) and HFF (β=-0.44) contributed to the variance in RHI independent of %BF, VAT, and age (R<sup>2</sup>=0.35, p=0.01). With Alx as the depednent variable in the regression model, FGF-21(β=0.4) was the significant determinant of Alx (R<sup>2</sup>=0.44, p=0.004). This relationship was independent of HIS (as a variable in the regression model) for Alx but not for RHI.

**Conclusions:** Circulating FGF-21 levels are elevated in obese youth with NAFLD and are associated with measures of insulin sensitivity and endothelial dysfunction. FGF-21 may constitute a biomarker of higher risk for vascular dysfunction in these youth.

	No-NAFLD	NAFLD	P-value
	11M/14F 10 NGT/8 PreD/ 7 T2D	11M/12F 3 NGT/11 PreD/ 9 T2D	
BMI z-score	2.1 ± 0.09	2.3 ± 0.07	0.1
% Body Fat	37.2 ± 1.3	40.5 ± 1.4	0.1
Visceral adipose tissue (VAT) (cm <sup>2</sup> )	88.6 ± 6.6	99.7 ± 6.5	0.2
Intrahepatic Fat (%)	3.2 ± 0.3	11.1 ± 1.1	<0.001
ALT (IU/L)	31.4 ± 5.0	74.0 ± 11.03	0.001
FGF-21(pg/ml)	203.8 ± 31.3	343.2 ± 34.9	0.005
Insulin Sensitivity (mg/kg <sub>FFM</sub> .min per μU/ml)	4.0 ± 0.4	2.8 ± 0.3	0.01
HIS (mg/kg.min. μU/ml) <sup>-1</sup>	24.6 ± 3.6	14.1 ± 1.3	0.01
RHI	1.7 ± 0.08	1.4 ± 0.05	0.004
Augmentation Index (%)	-11.1 ± 1.3	-5.7 ± 1.6	0.013

Results: Mean ± SEM.

P1-1102

PREDICTIVE FACTORS FOR CHANGE IN LEAN AND FAT MASS IN OBESE ADOLESCENTS AFTER A 3 MONTH INTENSIVE WEIGHT LOSS PROGRAM

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**Objectives:** In France, 3 to 4% of adolescents are obese. Lifestyle interventions aim at loss of fat mass. However, the loss of lean mass is usually an unintended consequence of weight loss. The main objective of this study was to evaluate the changes in body composition of obese adolescents attending a 3 month inpatient intensive weight loss program and to analyze the predictive factors for these changes.

**Methods:** Retrospective, single-center study including 80 adolescents (11-18 y) with common obesity attending a 3 month inpatient intensive weight loss program at the Capucins' medical center, Angers (France) between January 2012 and March 2015. Body composition (assessed by dual energy X-ray absorptiometry), anthropometric, metabolic and hormonal data were compared before and after the stay.

**Results:** Total weight (- 7.8 ± 4.3 Kg), BMI (- 3.3 ± 1.44 Kg/m<sup>2</sup>), total (- 6.7 ± 3.2 kg) and truncal (- 3.3 ± 1.8 kg) fat mass, lean body mass (-1.6 ± 2.6 kg), fasting glycaemia (-0.13 ± 0.4 mmol / L), fasting insulinemia [- 2.7 (-6.5 - 0.3) μU / ml],

and HOMA [-0.43 (-1.4-0.05)] decreased significantly after the intervention ( $p < 0.05$  for all paired comparisons). In univariate analysis, total and truncal fat loss were negatively correlated with baseline HOMA ( $r = -0.28$ ;  $r = -0.27$ ) and DHEAS ( $r = -0.39$ ;  $r = -0.45$ ) values ( $p < 0.05$  for all comparisons). The loss of truncal fat mass was negatively correlated with baseline free T3 ( $r = -0.29$ ;  $p = 0.04$ ). Loss of total fat, truncal fat and lean mass were negatively correlated with baseline BMD ( $r = -0.433$ ,  $r = -0.405$ ,  $r = -0.549$ ) ( $p < 0.05$  for all comparisons). After multiple linear regression analysis, variables independently related to total fat mass loss were baseline free T3 ( $B = -5065$ ;  $p = 0.008$ ) and DHEAS levels ( $B = -602$ ;  $p = 0.015$ ). Variables independently related to total lean mass loss were baseline BMD ( $B = -5676$  and  $p = 0.006$ ) and triglycerides ( $B = -1900$  and  $p < 0.01$ ).

**Conclusions:** Our 3 month inpatient intensive weight loss program allows adolescent to decrease their BMI and to improve metabolic syndrome. High baseline T3 and / or DHEAS levels seem to predict greater fat loss during the program. High baseline BMD seems to predict greater lean loss.

P1-1103

#### POOR INITIAL WEIGHT LOSS AND WEIGHT REGAIN DURING THE SECOND YEAR AFTER GASTRIC BYPASS IN ADOLESCENTS: EFFECTS ON CARDIO-METABOLIC RISK MARKERS AND ASSOCIATION WITH LONG-TERM SURGICAL FAILURE

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**Objectives:** To investigate the incidence of poor weight loss during the first year and weight regain during the second year in adolescents after Roux-en-Y gastric bypass (RYGB) and to examine how this affects risk markers for obesity related comorbidities and finally to study if poor initial weight development affects surgical failure five years after surgery.

**Methods:** The prospective controlled Swedish multicenter study, Adolescent Morbid Obesity Surgery study (AMOS) have followed 85 participants whom were between 13-18 years old at time of surgery. Anthropometrics, body composition, blood chemistry were assessed at baseline, one, two and five years after surgery. For patients recruited from the Stockholm area ( $n=16$ ), a frequently sampling intravenous glucose tolerance test was performed. Group comparison between those who had weight regain (WR) and none WR or fat% regain (FR) and none FR during the second year as well as an exploration of predictors for surgical failure, defined as weight loss 35 or excess weight loss  $<50\%$ , five years after surgery was undertaken.

**Results:** Weight regain occurred in 41% and FR occurred in 39% of participants during the second year with an overlap of 68%. FR had a more pronounced impact on cardio-metabolic risk markers than WR. Differences of 0.3mmol/L in  $\Delta$ low-density lipoprotein and 2.2  $\mu$ u/L-1.min in  $\Delta$ insulin sensitivity was observed between FR and none FR ( $p=0.011$  and  $p=0.012$  respectively) controlling for baseline BMI and respective baseline values. The relative risk of surgical failure was 8.7 times higher for participants with poor initial excess weight loss ( $<60\%$ EWL in the first year) combined with WR during the second year, controlling for neuropsychiatric disorder. Poor weight loss did not affect metabolic parameters.

**Conclusions:** Two years after surgery WR was common and comprised of both fat-free and fat mass. FR had a marked negative impact on obesity related risk markers. Patients with the combination of poor initial weight loss and WR during the second year are at high risk for long-term failure and they should get increased support to optimize the effect of surgery. Also, intensified support during the first years after surgery might be of importance for long-term results.

P1-1104

#### ASSOCIATION BETWEEN PARENTS' METABOLIC SYNDROME AND 12-18 YEARS-OLD OFFSPRING'S OVERWEIGHT: RESULTS FROM THE KOREA NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEYS (K-NHANES) 2008-2013.

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**Objectives:** The association between parental obesity and offspring's obesity has been reported. However, little information is available on the correlations of parents' metabolic syndrome and offspring's obesity in Korean adolescents.

**Methods:** Data were obtained from the Korean National Health and Nutrition Examination Survey conducted during 2008-2013. In the present study, 2275 adolescents aged 12-18 years-old and their parental pairs (father=1589, mother=2127) were analyzed. Of these 2275 adolescents, 1798 were normal weight (under age and sex specific BMI 85<sup>th</sup> percentile) and 477 (more than age and sex specific BMI 85<sup>th</sup> percentile) were overweight.

**Results:** In overweight adolescents, their parents' data of metabolic risk factors including BMI {father (F),  $24.0 \pm 0.1$  vs.  $25.5 \pm 0.2$ ,  $P < 0.0001$ ; mother (M),  $23.0 \pm 0.1$  vs.  $24.5 \pm 0.2$ ,  $P < 0.0001$ }, Fat (%) (F,  $21.8 \pm 0.3$  vs.  $23.6 \pm 0.4$ ,  $P < 0.0001$ ; M,  $32.3 \pm 0.2$  vs.  $33.7 \pm 0.4$ ,  $P < 0.0001$ ), Waist circumference (WC) (F,  $84.1 \pm 0.4$  vs.  $88.0 \pm 0.6$  cm,  $P < 0.0001$ ; M,  $76.5 \pm 0.3$  vs.  $80.3 \pm 0.7$ ,  $P < 0.0001$ ), systolic blood pressure (SBP) (M,  $111.6 \pm$



0.4 vs.  $113.7 \pm 0.8$  mmHg,  $P < 0.008$ ), diastolic blood pressure (DBP) (F,  $81.2 \pm 0.5$  vs.  $82.9 \pm 0.8$ ,  $P < 0.04$ ; M,  $73.8 \pm 0.3$  vs.  $75.4 \pm 0.6$  mmHg,  $P < 0.01$ ), fasting glucose (F,  $100.1 \pm 1.2$  vs.  $106.6 \pm 2.2$ ,  $P < 0.007$ ; M,  $93.3 \pm 0.5$  vs.  $98.8 \pm 1.4$  mg/l,  $P < 0.0003$ ) were higher than that of normal weight adolescents' parental data. BMI of offspring showed positive correlations with parental metabolic risk factors including WC (F,  $r=0.3$ ,  $P<.0001$ ; M,  $r=0.2$ ,  $P<.0001$ ), SBP (F,  $r=0.06$ ,  $P<0.004$ ; M,  $r=0.09$ ,  $P<.001$ ), DBP (F,  $r=0.07$ ,  $P<0.02$ ; M,  $r=0.09$ ,  $P<.0006$ ), fasting glucose (F,  $r=0.1$ ,  $P<0.0006$ ; M,  $r=0.2$ ,  $P<.0007$ ), TG (M,  $r=0.07$ ,  $P<0.01$ ), LDL (M,  $r=0.09$ ,  $P<0.0009$ ) and TC (M,  $r=0.1$ ,  $P<0.0001$ ). When their parents are classified as metabolic syndrome, the odds ratio for being offspring overweight at adolescent was significantly increased after adjusting for age, sex {F, 95% confidential index (CI), 1.5 (1.1-2.0); M, 95% CI, 1.9 (1.4 - 2.7)} and age, sex, drink, smoke, exercise, income, daily average sleep time (F, 95% CI, 1.5 (1.1 - 1.9); M, 95% CI, 1.96 (1.4 - 2.7)).

**Conclusions:** parental metabolic syndrome might be associated with offspring overweight in 12-18 year-old Korean adolescents.

P1-1105

#### **BONE HEALTH RISK EVALUATION IN EIGHT YEAR OLD BORN SMALL FOR GESTATIONAL AGE GIRLS**

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**Objectives:** Reduced bone mineral density (BMD) and bone mineral content (BMC) were reported in SGA infants. The risk of diseases such as obesity and metabolic syndrome, coronary heart disease in children born small for gestational age (SGA) were reported to be high. The aim of this study was to examine the impact of SGA on bone mineralization during prepubertal period compared with appropriate for gestational age (AGA) group and how to interpret pediatric body composition analysis reports in monitoring and management for children who have potential to develop osteoporosis in adulthood.

**Methods:** We reviewed hospital records of 85 girls who had anthropometric parameters and body composition analysis data with pediatric dual energy X-ray absorptiometry (DXA) at 7 or 8 years. All were full term and 38 girls were born with SGA and 47 were born with AGA. They visited at KUMC pediatric clinic for general examination including growth and pubertal development assessment between 2007 and 2016.

**Results:** Height, weight, body mass index (BMI) were not significantly different between the two groups. All SGAs were successful in the catch up growth. There was no significant difference between the two groups in body composition profiles; lean mass (LM), bone mineral content (BMC), fat mass (FM) and fat free mass (FFM). Biochemical and hormonal profiles were not significantly different. BMC showed a positive correlation with age and growth parameters; height, weight, BMI and their Z-scores. BMC showed a positive correlation with lean mass and fat mass.

The positive correlation of BMC increase with FM increase was greater in SGA group than AGA group. In the relationship between FFMI and FMI, the FMI tends to increase further in the SGA group.

**Conclusions:** Catch-up growth in children born with SGA may reduce risk of osteoporosis later life, but excessive catch-up growth may contribute to the development of metabolic syndrome. Therefore, more attention for growth monitoring and life style education in early life should be stressed in children born SGA.

P1-1106

#### **NOVEL ROLE FOR STORE-OPERATED CALCIUM ENTRY IN REGULATION OF THE LIPID METABOLISM**

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**Objectives:** Calcium signaling is fundamental to many cellular processes. An important pathway for increasing intracellular  $Ca^{2+}$  levels is store-operated  $Ca^{2+}$  entry (SOCE) regulated by stromal interaction molecule 1 (STIM1), STIM2, and  $Ca^{2+}$  channel ORA1. Alterations in cellular  $Ca^{2+}$  homeostasis have been reported in obesity and diabetes but the pathways involved are unclear. SOCE-deficient patients suffers from inherited disease: Calcium Release-Activated Calcium (CRAC) channelopathy characterized by immunodeficiency, autoimmunity, myopathy, and anhidrotic ectodermal dysplasia. We showed substantial evidence for a cell-intrinsic role of SOCE in the regulation of lipid metabolism both in mice and humans (*Maus M et al. Store-Operated  $Ca^{2+}$  Entry Controls Induction of Lipolysis and the Transcriptional Reprogramming to Lipid Metabolism. Cell Metab. 2017 Jan 21.pii:S1550-4131(16)30654-4.doi:10.1016/j.cmet.2016.12.021*).

**Methods:** Histologically, SOCE-deficient transgenic mice accumulate pathological amounts of lipid droplets in the liver, heart, and skeletal muscle. SOCE-deficient patients showed lipid droplets in their skeletal muscle. Following starvation, SOCE-deficient patient fibroblasts showed severe defect in lipid droplets mobilization on BODIPY stain as well as significantly reduced levels of free fatty acids and glycerol in medium and cyclic adenosine monophosphate (cAMP) in cytosol, respectively.

**Results:** mRNA and protein levels of hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) were reduced. SOCE-deficient patient fibroblasts and NIH3T3-L1 mice cells expressed significantly lower basal and fasting mRNA levels of peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1a) and peroxisome proliferator-activated receptor alpha (PPARα), transcriptional regulators of lipid metabolism. Thapsigargin-induced SOCE in wild type fibroblasts led to increased mRNA expression of PGC-1a and PPARα. That effect was reversed by adenylyl cyclase inhibitor. SOCE-deficient cells had impaired cAMP response element-binding protein (CREB) phosphorylation. That effect was rescued by elevating cAMP levels.

**Conclusions:** SOCE controls cAMP-dependent induction of PGC-1α/PPARα expression and lipolysis. Our data provide evidence for an important role of SOCE in lipid metabolism.

P1-1107

#### **NORMALIZATION OF TESTOSTERONE LEVELS IN SERUM IN ADOLESCENT BOYS AFTER UNDERGOING ROUX-EN-Y GASTRIC BYPASS FOR SEVERE OBESITY**

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**Objectives:** Males with severe obesity have low androgen levels owing to increased visceral adiposity and elevated aromatase activity. Laparoscopic Roux-en-Y gastric bypass (RYGB) is effective in achieving weight loss and causes changes in body composition. Little is known about its effects on sex steroid hormones in adolescents, although testosterone levels have been reported to normalize in males after surgery.

The objective was to evaluate possible changes in serum levels of sex steroids in adolescents undergoing bariatric surgery in the Adolescent Morbid Obesity Surgery (AMOS) study. The hypothesis was that testosterone levels increase to normal levels in young males.

**Methods:** Inclusion criteria were: age 3 and BMI >35 kg/m<sup>2</sup>. A total of 29 boys with median (range) age 16.9 (13.6-18.8) years; BMI 47.3 (35.1-58.3) kg/m<sup>2</sup> were included. Nineteen of these underwent dual-energy X-ray absorptiometry (DXA, Lunar prodigyO, pediatric mode, v.11.4, GE Medical Systems, Madison, WI) and serum sampling for analysis of sex steroids before performing RYGB. Patients had follow-up at one, two and five years after surgery. A group of BMI- and gender-matched control males was prospectively identified in the national Swedish child obesity registry and assessed at five-

year follow-up. Serum testosterone concentrations were determined with liquid chromatography-tandem mass spectrometry. Statistical analyses were performed with Wilcoxon Signed Rank Test.

**Results:** Median (range) BMI reduction was 14.2 (10.1-18.9) kg/m<sup>2</sup> after one year and 13.5 (1.9-27.1) kg/m<sup>2</sup> after five years. DXA revealed a substantial reduction in fat mass (p<0.001). Testosterone levels increased significantly, from 6.6 (2.1-18.6) to 14.6 (2.1-27.6) nmol/L at one year and 19.4 (7.4-30.9) nmol/L five years after surgery (p=0.001 for both). There were significant different testosterone levels between controls (20.0 nmol/L) and RYGB males 5 years later (p=0.021).

**Conclusions:** Testosterone levels increase to normal after RYGB in male adolescents with severe obesity, while low levels persist in controls over 5 years. Normalization may prevent feminization of habitus during this vulnerable developmental phase.

P1-1108

#### **LONGITUDINAL CHANGES AND DETERMINANTS OF FAT MASS PERCENTAGE IN EARLY LIFE**

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**Objectives:** Determining longitudinal body composition in infants is of great importance. Changes in fat mass percentage (FM%) predominantly occur in the first three months after birth, the critical window for adiposity development. Accelerated gain in FM% during this critical window increases the risk for adult diseases. The objective of this study is to investigate longitudinal changes and determinants of FM% in infants from birth until the age of 2 years.

**Methods:** Of 168 term born infants (110 males), obstetrical data were obtained from medical records. Fat mass percentage was determined by PEA POD (COSMED, Italy) during visits at the age of 1, 3 and 6 months, and by DXA (Lunar Prodigy, GE Healthcare, UK) at the age of 2 years. To prevent movement during DXA, a vacuum cushion (465 75100, Schmidt, Germany) was used. All DXA scans were analyzed using enCORE software version 14.10.

**Results:** Median (IQR) FM% was 16.4 (14.1-19.3) at 1 month, 23.3 (19.8-25.9) at 3 months, 23.8 (20.1-27.4) at 6 months and 14.8 (12.8-17.7) at the age of 2 years. Fat mass percentage at 1 month correlated with FM% at 3 months (r=0.411, p<0.001) and 6 months (r=0.409, p<0.001), but not at 2 years (p=0.13). FM% at 6 months correlated significantly with FM% at the age of 2 years (r=0.363, p<0.001).

Delta FM%<sub>1-3mo</sub> tended to correlate (r=0.149, p=0.078) and delta FM%<sub>1-6mo</sub> correlated with FM% at 2 years (r=0.271, p=0.002). Contribution of other variables to FM% at 2 years was assessed by multiple regression analyses. Birthweight

and delta FM%<sub>1-3mo</sub> were positively associated with FM% at 2 years ( $p=0.013$  and  $p=0.023$ , resp.) after adjustment for the non-significant variables for FM% at 2 years; gender, parity, pre-pregnancy BMI, mother's weight gain during pregnancy and exclusive breast- or bottle feeding during 3 months.

**Conclusions:** This study shows longitudinal changes in FM% in infants until the age of 2 years, with highest increase between 1 and 3 months. Birthweight and delta FM%<sub>1-3mo</sub> correlated positively with FM% at the age of 2 years after adjustment for gender, type of feeding and maternal factors.

P1-1109

#### VITAMIN D DEFICIENCY PREDICTS IMPAIRED FASTING GLUCOSE IN CHILDREN WITH OBESITY: A PROSPECTIVE FOLLOW-UP STUDY

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**Objectives:** We have previously shown, in a cross-sectional study, that VD deficiency (VDD) was associated with impaired fasting glycemia (IFG) in obese children. The aim of the present study was to investigate if VDD increases the risk for (IFG) 1-2 years later.

**Methods:** This study is a prospective follow-up study of 147 children with obesity according to IOTF criteria (51 % male, 49 % female, mean age 12 years, range 5-17. Children with IFG at baseline ( $n=18$ ) were excluded.

Fasting blood samples for VD and metabolic parameters were obtained at start and at the end of the study. Prescription of VD supplementation was documented. VDD was defined as  $25(\text{OH})\text{D} < 30 \text{ nmol/L}$ . The mean follow-up time was 17.6 months, range 10-28.

**Results:** Eighteen children (12 %) developed VDD during the study period and 43 (29%) had VDD at baseline. Twenty-one (14.3%) had VDD both at baseline and follow-up. Eighteen children (12.5%) developed IFG during the study period with a higher risk for IFG in children who had VDD at baseline and follow-up compared with children without VDD at baseline and/or follow-up, independently of age, ethnicity, seasons, VD supplementation, onset of obesity and BMI z-score. No differences in metabolic risk markers were found when comparing VDD children with children being non-VDD at baseline and/or at follow-up.

**Conclusions:** VDD was associated with an increased risk for the development of IFG approximately one to two years later. However, the association between VDD and later IFG was not affected by VD supplementation, which may indicate that there are no directly causal link between VD and IFG. Thus, VDD predicts IFG but it is unclear whether differences in food intake or underlying metabolic factors affect both VD and fasting glucose levels.

P1-1110

#### IMPACT OF FITBITS ON PHYSICAL ACTIVITY IN OBESE CHILDREN ENROLLED IN A WEIGHT MANAGEMENT PROGRAM

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**Objectives:** To determine if activity trackers combined with weekly telephone review of physical activity with families participating in the Healthy Kids program augment activity goals

**Methods:** This randomized, prospective study enrolled obese kids 7-18 years from the University Hospitals Healthy Kids (HK) program from May to October, 2015. Subjects were randomized either to receive a Fitbit Charge HR versus standard HK program. Subjects had baseline bloodwork, resting energy expenditure (REE), and recovery heart rate (RHR) following a 3 minute step test. Subjects also wore an Actigraph accelerometer for 7 days to measure intensity of physical activity. Patients underwent the 12 week HK program, and data from their Fitbit account was reviewed by telephone weekly. Subjects without Fitbits also received weekly calls to review subjective activity. Both groups were given goals to improve activity levels as tolerated. After 12 weeks, subjects had reassessment of REE, RHR, bloodwork, and Actigraph. Groups were compared for differences.

**Results:** 60 subjects were recruited; 35 (17 controls, 18 Fitbit) subjects returned for follow-up after the HK program. The remaining subjects never started the HK program, withdrew from our study, and/or became unreachable. 32/35 subjects completed at least 7 HK classes and completed at least 5 telephone calls.

There were no statistically significant differences in baseline demographics, BMI z-score, RHR, REE, or activity intensity. Compared to baseline Actigraph activity intensity, children wearing Fitbits trended to higher activity intensity by the end of 12 weeks, while children without Fitbits trended towards lower activity intensity from baseline. There were no statistical differences in other measured outcomes between the two groups.

**Conclusions:** We were unable to demonstrate that the use of Fitbits with remote monitoring of physical activity resulted in changes in cardiovascular fitness, resting energy expenditure, or BMI z-scores. However, children wearing Fitbits increased their overall activity level from baseline, while kids without Fitbits actually had a drop in activity intensity compared to baseline. Further studies evaluating the effectiveness of Fitbits in obese pediatric subjects are necessary.

# **THYROID STIMULATING HORMONE DOES NOT CORRELATE WITH WAIST CIRCUMFERENCE, BMI OR TESTOSTERONE IN ADOLESCENTS WITH POLYCYSTIC OVARY SYNDROME**

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**Objectives:** Thyroid Stimulating Hormone (TSH) levels in hypothyroid adolescents correlate with waist circumference. There is evidence that TSH levels are increased in obese adolescents compared to normal weight adolescents and that those with hyperandrogenism have a higher rate of autoimmune thyroiditis. What is unclear is if the thyroid axis perturbation is more due to 1) visceral fat distribution than BMI and 2) the degree of hyperandrogenemia when present and occurring before clinical hypothyroidism. The hypothesis is that TSH levels correlate with increased visceral adiposity measured by waist circumference in adolescents with hyperandrogenism.

**Methods:** Retrospective chart review of adolescents in a multidisciplinary PCOS clinic. Inclusion criteria: female sex, age 13-20 years, waist circumference and BMI measured, laboratory studies performed at the University Hospital laboratory, meeting the Androgen-Excess Society diagnostic criteria for PCOS. Exclusion criteria: use of oral contraceptives or metformin at first visit. Data analysis included linear and multivariate regression comparing TSH versus testosterone, WC and BMI z-scores.

**Results:** 46 females met inclusion criteria. Mean and SD of TSH was 2.4 +/- 1.8 uIU/mL. No significant correlation was found between TSH and waist circumference ( $p=0.79$ ), BMI ( $p=0.37$ ), or free testosterone level ( $p=0.56$ ). Multivariate analysis found no significant association for each combination of variables (Figure 1).

**Conclusions:** In a group of adolescent females with androgen excess, TSH levels were not significantly associated with waist circumference, BMI, or androgen levels. TSH levels can be elevated with increased adiposity due to leptin feedback on TRH secretion. Previous studies in both adults and prepubertal children have shown influences of fat distribution on serum leptin levels. The lack of association of TSH with WC in this study does not support that finding. Therefore, there may be another factor in fat distribution in euthyroid girls with hyperandrogenism and rising TSH. Evolving androgen levels from puberty to adulthood may be responsible for differences in visceral fat distribution between adults and adolescents.

This research is supported by a T32 grant DK077586.

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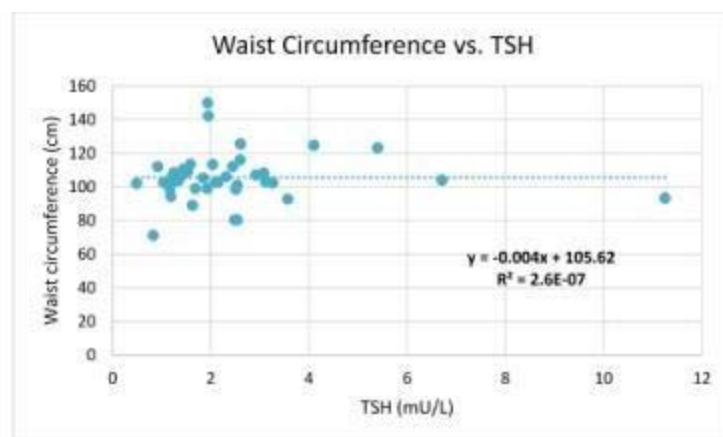


Figure 1A.

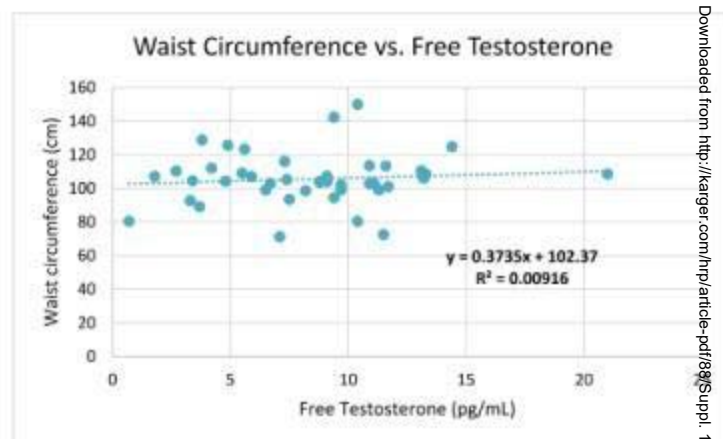


Figure 1B.

P1-1112

# **RELATIONSHIP OF INSULIN RESISTANCE TO LIPIDS AND LIPOPROTEINS IN YOUTH WITH DOWN SYNDROME**

Kannan Kasturi, MD, NIH, Bethesda, MD, United States; Stephanie T Chung, MBBS, National Institutes of Health, Bethesda, MD, United States; Sheela Magge, MD; Andrea Kelly, MD; Cochrane Claire, MD; Melissa Xanthopoulos, MD, CNMC, Washington, DC, United States; Rachel Walega, MS/MA, Children's National Health System, Washington, DC, United States

## **Objectives: Abstract (2,005 characters, including spaces)**

Youth with Down Syndrome (DS) are at increased risk for obesity that may predispose them to a more atherogenic lipid profile. However, it is unknown whether the same level of obesity confers a similar degree of risk for cardiometabolic disease in youth with and without DS. Therefore, we compared the relationship of insulin resistance with fasting lipids and lipoprotein profile in 236 youth (148 with DS and 88 age and BMI-matched controls), age  $14.8 \pm 6$  (mean  $\pm$  SD), BMI ( $92 \pm 7$  kg/m<sup>2</sup>, 56% female and Tanner Stage I-V). Using fasting indices, insulin resistance was measured by homeostatic model assessment – insulin resistance (HOMA-IR) and lipoprotein profile assessed with nuclear magnetic resonance (NMR) spectroscopy. The log-transformed values were used

for Pearson correlations and multiple regression analyses. In youth with DS compared to controls, there were no differences in waist circumference ( $P>0.05$ ), prior history of dyslipidemia ( $P>0.05$ ), or HOMA-IR (1.8 (0.6-6.2) vs. 2 (0.6-6.9), median (IQR)). Youth with DS, compared to controls, had higher triglycerides (88 (50-242) vs. 72 (38-175) mg/dl), total cholesterol (170 (115-239) vs. 151 (116-198) mg/dl, LDL cholesterol (107 (56-162) vs. 89 (57-129) mg/dl, large VLDL (3.9 (0.5-17.5) vs. 2.4 (0.6-9.8) nmol/L), and small LDL (518.5 (63-1067) vs. 417 (62-815) nmol/L, all  $P<0.001$ ). HOMA-IR was positively related to triglyceride, total cholesterol, LDL, total HDL and IDL concentrations in both DS and controls (all  $P<0.001$ ). In regression models, for a given HOMA-IR, youth with DS had higher triglycerides (Adj  $R^2=0.18$ ,  $P<0.001$ ), large VLDL (Adj  $R^2=0.14$ ,  $P<0.001$ ), and small LDL (Adj  $R^2=0.09$ ,  $P=0.01$ ) compared to controls. The relationship between HOMA-IR and lipid/ lipoprotein panel were the same in youth with and without DS. In summary, compared to controls of the same age, BMI and insulin resistant score, youth with DS had a higher cardiometabolic lipid and lipoprotein risk profile.

**Methods:** N/A

**Results:** N/A

**Conclusions:** N/A

P1-1113

#### EARLY CHILDHOOD BMI DEVELOPMENT IN MONOGENIC OBESITY DUE TO LEPTIN – OR LEPTIN RECEPTOR DEFICIENCY

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**Objectives:** To evaluate whether early childhood body mass index (BMI) and BMI standard deviation score (BMI-SDS) are appropriate indicators for monogenic obesity.

**Methods:** BMI, BMI-SDS and BMI courses in early childhood (0-5 years) were analyzed in a cohort of  $n=21$  children living in Germany or Austria with monogenic obesity due to leptin deficiency (group A,  $n=6$ ), leptin receptor deficiency (group B,  $n=6$ ) and MC4 receptor deficiency (group C,  $n=9$ ). BMI and BMI-SDS values at birth (T0), at 2 years (T1) and at 5 years of age (T2) were compared to severely obese controls ( $n=19$ ) sampled from a large representative pediatric cohort.

**Results:** Group A and B showed a tremendous increase of BMI during the first 2 years of life with all patients displaying a BMI  $>25.0$  kg/m<sup>2</sup> [27.2-38.4 kg/m<sup>2</sup>] at the age of 2 years and a BMI  $>30.0$  kg/m<sup>2</sup> [33.3-45.9 kg/m<sup>2</sup>] at the age of 5 years. BMI-SDS was  $>4.0$  at both time points. Group C and severely

obese controls had a later onset of obesity with significant lower BMI and BMI-SDS at both time points.

**Conclusions:** As result of the investigation of early childhood BMI courses in this large pediatric cohort with monogenic obesity we suggest that BMI  $>25.0$  kg/m<sup>2</sup> (or BMI-SDS  $>4.0$ ) at the age of 2 years and BMI  $>30.0$  kg/m<sup>2</sup> at the age of 5 years are indicators for monogenic obesity due to functional relevant mutations in the leptin gene or leptin receptor gene.

P1-1114

#### INSULIN RESISTANCE BETTER PREDICTS INCREASED ARTERIAL STIFFNESS IN OBESE CHILDREN THAN DYSLIPIDEMIA OR THE DEGREE OF OBESITY

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**Objectives:** Due to high prevalence of obesity in children and its grave health consequences, it is an imperative to screen early for those at an increased risk of cardiovascular complications. Determination of arterial stiffness by pulse wave velocity (PWV) measurement is a valid measure of cardiovascular risk in children. We aimed to assess which biochemical and clinical parameters most accurately predict increased arterial stiffness in obese children and adolescents.

**Methods:** PWV measurement using Arteriograph (TensioMed Ltd.) was performed in 29 consecutive obese children and adolescents (14 females, age (mean $\pm$ SD) 14.4 $\pm$ 3.5 years, BMI-SDS 2.7 $\pm$ 1.7), after obtaining informed consent/parental authorization. Besides clinical examination, an extensive biochemical evaluation was performed including the level of insulin resistance (HOMA-IR), dyslipidemia status (total cholesterol, LDL-C, HDL-C, triglycerides, APOA1, APOB, Lp(a)) and liver enzymes (AST, ALT). Collected data were analysed for outliers using ROUT method, followed by the Spearman's rank correlation analysis. All statistical calculations were made by GraphPad Prism 7.0 software.

**Results:** PWV was increased in the cohort, with significant deviation within the group (mean 2.03 SDS; range -1.12–8.99) and didn't correlate with BMI-SDS or waist circumference. PWV-SDS best correlated with HOMA-IR ( $r=0.49$ ,  $p=0.008$ ), however it didn't correlate with any of the other biochemical measures. On the other hand, HOMA-IR correlated well with the levels of TG ( $r=0.25$ ,  $p=0.03$ ), HDL ( $r=-0.33$ ,  $p=0.004$ ), apoB/apoA1 ( $r=.36$ ,  $p=0.002$ ), TG/HDL ( $r=0.3$ ,  $p=0.01$ ) and ALT ( $r=.28$ ,  $p=0.02$ ).

**Conclusions:** Insulin resistance (determined by HOMA-IR) was shown to be a superior predictor of increased arterial stiffness in obese children and adolescents, possibly better indicating their increased cardiovascular risk as compared to dyslipidemia or the degree of obesity.

# PEDIATRICIANS' PERCEPTION OF CHILDREN'S WEIGHT

Itay T Latzer, MD, Tel Aviv University, Tel Aviv, Israel; Orit Goz, MD, Jerusalem University, Jerusalem, Israel; Orit Pinhas-Hamiel, MD, Tel Aviv University, Tel Aviv, Israel

**Objectives:** Prevention of obesity demands early detection. Parents are known to underestimate their child's weight, but are more likely to show concern to the issue if it was brought to their attention by a pediatrician. In this work, we aimed to explore pediatricians' perception of child's degree of obesity in community centers and hospital clinics in Israel.

**Methods:** In a multicenter study, 42 pediatricians were surveyed by being asked to estimate children's weight, both by a verbal questionnaire and a sketch array divided and adjusted to the different age groups. The estimation was confronted by the real measurements of the patient. 250 children were included.

**Results:** The verbal calculated sensitivity for overweight and obese children was only 68% (CI 55-82%). Graphic sensitivity was the same: 68% (CI 54-82%). In younger children under 5 years old the sensitivity declined to 36% (CI 7.9-64%), whereas sensitivity increased in children older than 5 years, 79% (CI 65-93%). Verbal and graphic calculated sensitivity for obesity specifically was 35% (CI 14-55%). Most mistakes underestimated the child's weight. The physicians that participated in the study were 60% females, aged 33-56 years and had clinical experience of 2-33 years. Sensitivity was not influenced by years of practice, gender, subspecialty of the physicians and weight of the pediatricians. Children who were frequently observed due to a chronic illness were evaluated more accurately.

**Conclusions:** Pediatricians' verbal and graphic sensitivity for estimation of overweight and obese children is low, especially for those in the extreme weight category and under 5 years old.

P1-1116

# MEDICAL AND PSYCHOSOCIAL IMPLICATIONS OF ADOLESCENT EXTREME OBESITY – ACCEPTANCE AND EFFECTS OF STRUCTURED CARE PROGRAM – YES STUDY. A CONSORTIUM OF THE BMBF.

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Christine Teuner, PhD, Helmholtz Center, Munich, Germany; Susanna Wiegand, MD, Charité University medicine Berlin, Berlin, Germany; Barbara Wolters, MD, Vestische Kinderklinik, Datteln, Germany; Julia Von Schnurbein, MD, University Medical Center Ulm, Ulm, Germany; Johannes Hebebrand, MD, University Essen-Duisburg, Essen, Germany; Martin Wabitsch, Professor, University Medical Center Ulm, Ulm, Germany

**Objectives:** Adolescents with extreme obesity are at increased risk of early mortality, somatic and psychiatric comorbidity and social dysfunction. Nevertheless, only a small percentage seek medical care. Our goal was to characterize treatment seeking and non-treatment seeking adolescents with extreme obesity and to examine the acceptance and effects of a structured diagnostic program.

**Methods:** N=431 adolescents and young adults age 14 to 25 years, BMI  $\geq 30$  kg/m<sup>2</sup> were recruited from 4 medical centers and one job center in Germany. Participants were offered a comprehensive diagnostic program for somatic and psychiatric comorbidity. Participants were assigned to an obesity group (BMI 30-34.9 kg/m<sup>2</sup>, n=150), and 2 extreme obesity groups (BMI > 35-40 kg/m<sup>2</sup>, n=122; BMI >40 kg/m<sup>2</sup>, n=159). The groups were described and explored for differences applying a two-sided significance threshold of 0.01.

**Results:** 384 adolescents (91%) participated in the recommended diagnostic program. When comparing the groups with ascending BMI, we found decreasing acceptance of the diagnostic program (95% vs 89% vs 85%), whereas comorbidity rates increased: Hypertension (40% vs 55% vs 66%), dyslipidemia (36% vs 33 % vs 51%), dysglycemia (9% vs 19% vs 20%), transaminitis (15% vs 27% vs 32%), depression (BDI II) (46% vs 45% vs 55%). With increasing BMI, quality of life (DISABKIDS, EQ5D) decreased, and adolescents had higher rates of truancy / unemployment (24% vs 24% vs 46%), alcohol use (26% vs 32% vs 43%) and nicotine use (10% vs 21% vs 20%). Notably, when comparing treatment seeking vs non treatment seeking youth, somatic and psychiatric comorbidity did not differ between youth who were recruited through the job center vs medical centers or in youth who had or had not previously sought obesity treatment.

**Conclusions:** The rising morbidity, including in the non-treatment seeking youth, accompanied by a falling acceptance even of a mere diagnostic program, emphasizes the importance of accessible structured care to meet the needs of adolescents with extreme obesity. To implement and investigate such new care strategies is the goal of the ongoing YES study, which includes a longitudinal observation study, an interventional trial, an observational study of bariatric surgery, and an economic analysis of adolescent extreme obesity.

# METABOLIC AND EPIGENETIC ABNORMALITIES OF ADIPOSE TISSUE IN PIGLETS BORN TO SOWS OVERFED DURING GESTATION: PARTIAL NORMALIZATION BY POSTNATAL METFORMIN TREATMENT

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**Objectives:** Metabolic programming of the offspring following maternal overfeeding during gestation may be mediated by epigenetic changes in adipose tissue, the mechanisms of which remain to be elucidated. No studies have been reported on the pharmacological reversibility of such processes early in life. In this context, our aims were: (1) to study the effects of maternal overfeeding on the metabolic and epigenetic programming of adipose tissue; and (2) to test the potential of postnatal metformin treatment to reverse these changes.

**Methods:** We studied male and female piglets born to commercial production sows (*Sus scrofa domesticus*) who were fed during gestation with a standard diet (control feeding piglets: CF piglets; n=16), or a hypercaloric diet (piglets from overfed sows: OF piglets; n=16). Piglets received treatment with metformin or vehicle (1:1) during lactation, and were sacrificed at weaning (28 days). At sacrifice, weight was assessed and metabolic markers in serum were analyzed: glucose, insulin, fructosamine, C-reactive protein (CRP), lipids and adiponectin. Visceral adipose tissue hypertrophy (size of the adipocytes), inflammation (gene expression of *TNFA*, *IL6* and *CCL2*) and DNA methylation levels of adipogenesis genes (*NDN* and *DLK1*) were studied.

**Results:** OF piglets showed a worse metabolic profile (higher weight, increased levels of fructosamine and CRP, and lower HOMA- $\beta$  and adiponectin) together with an inflammatory phenotype in visceral adipose tissue (higher expression of *CCL2*) and adipocyte hypertrophy (increased area, perimeter and diameter), all  $p < 0.05$ . DNA methylation analysis of adipose tissue from OF piglets disclosed a decrease in the DNA methylation levels of the adipogenesis genes *DLK1* and *NDN* ( $p < 0.05$ ). Metformin treatment attenuated the metabolic alterations in adipose tissue from OF piglets, decreased hypertrophy of the adipose tissue (adipocyte area, perimeter and diameter) and increased *NDN* methylation levels (all  $p < 0.05$ ).

**Conclusions:** Maternal overfeeding during gestation induced metabolic and epigenetic abnormalities in the adipose tissue of the offspring, and postnatal metformin treatment was found to partially reverse these abnormalities.

P1-1118

# DEVELOPING PEDIATRIC REFERENCE VALUES FOR BODY COMPOSITION IN MEXICAN CHILDREN AND UNDERSTATING THEIR ROLE AS PREDICTORS OF METABOLIC DISORDERS.

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**Objectives:** Determine reference values of BC for Mexican children and establish their association with metabolic outcomes.

**Methods:** We carried a population based cross-sectional study in referred-as-healthy Mexican children aged 5-20 years. We carried clinical history & examination, anthropometric measurements, blood sampling for fasting serum glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, and triglycerides (TGL), and determined BC by dual-x-ray absorptiometry and multicomponent bioelectrical impedance analysis. We used descriptive statistics to report demographic and clinical data. We report BC by fat-mass (FM), lean-mass (LM), bone mineral content (BMC), fat-mass index (FMI), fat-free mass index. We developed age- and gender-specific smoothed percentile curves for LM, FM and BMC by means of lambda-mu-sigma (LMS) method. We assessed BC mean differences between groups according to metabolic outcomes and ran receiver operator curves (ROC) to assess classification potential of BC variables with metabolic outcomes.

**Results:** We have assessed 993 children and adolescents (515 males and 478 females). Nutritional status according to BMI classified 63% of subjects as normal weight, 15% overweight, 16% obese, and 6% underweight. Metabolic outcomes corresponded to 71% of subjects as healthy, 13% low HDL-C, 7% hyperTGL, 7% low HDL-C and hyperTGL, and 1% with blood pressure  $> 95^{\text{th}}$  percentile. Noteworthy 22% of subjects classified by BMI as normal weight had at least one metabolic disorder. Classifying subjects by gender and absence/presence of any metabolic disorder, showed significant mean FMI differences: females 6.64 (IC95% 6.34-6.9) vs 8.13 (IC95% 7.62-8.64), and males 5.31 (IC95% 5.05-5.56) vs 7.79 (IC95% 7.22-8.36);  $P < 0.05$ . ROC showed FMI cut-off values of 7 and 5.6 kg/m<sup>2</sup> for females and males respectively as best classifiers.

**Conclusions:** Ethnic-specific reference values and risk cut-off points must be generated to improve health-status



classification of children. We have developed such values for our population. We believe we have contributed to the improvement of nutrition and health status assessment. We present the smooth curves for total fat mass, lean mass and bone mine gender.

Figure 1. Fat mass in girls

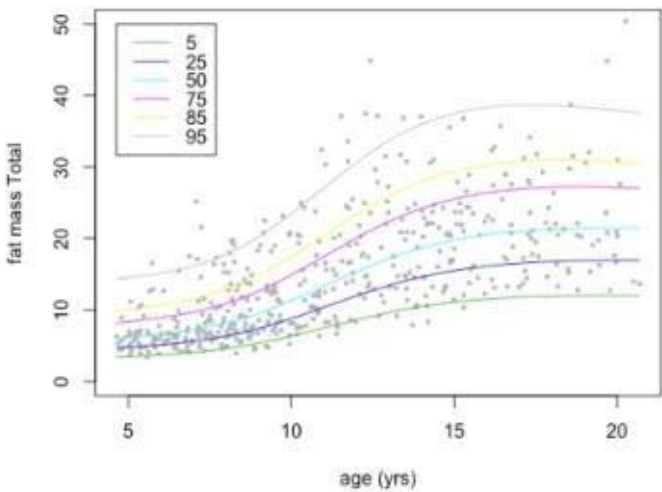
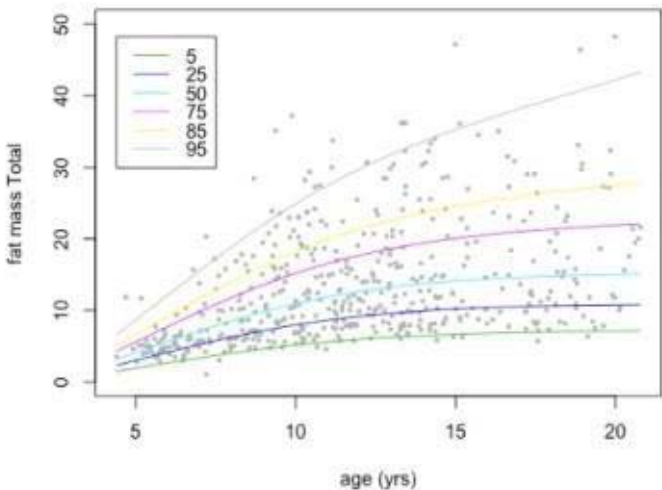


Figure 2. Fat mass in boys



P1-1119

LATE HYPERINSULINEMIC RESPONSE IN THE OGTT IS ASSOCIATED TO LOWER INSULIN SENSITIVITY AND A WORSE METABOLIC PROFILE IN OBESE CHIDREN

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**Objectives:** The insulin secretory pattern during the OGTT is associated to singularities in insulin sensitivity and predicts the development of T2DM in adults. Our aim was to study the insulin sensitivity indexes and metabolic profile in obese children according to their insulin pattern in the OGTT.

**Methods:** An OGTT for glucose and insulin (1.75g/kg, maximum 75g; fasting-30'-60'-120') was performed in 808 obese patients (373 females/435 males; age 10.97±2.94 years; BMI: +4.16±1.37 SDS; 71.8% Caucasians; 48.6% prepubertal) and the fasting lipid profile and uric acid levels determined. Patients were classified according to their peak insulin in the OGTT as **Early** (peak at 30'), **Middle** (60') or **Late** (120'). Groups were compared for BMI, uric acid, lipid profile, HOMA and WBISI, areas under the curve (AUC) for glucose (AUCg) and insulin (AUCi), and insulinogenic and oral disposition indexes (ODI) at 30 and 120 minutes. The influence of fasting hyperinsulinism (**FH**; > 15 mcU/ml; n=120 in prepubertal / n=230 in pubertal) on the studied parameters was also explored according to pubertal status (vs. patients without fasting or postprandial hyperinsulinism [n=191 in pre- / n= 126 in pubertal]).

**Results:** Patients with a **late peak** showed higher BMI-SDS, uric acid, triglyceride to HDL ratio and lower HDL than those with an earlier insulin peak (**TABLE**). They showed a higher AUCi and AUCi /AUCg ratio in the entire OGTT, as well as in the second hour of the test (all p<0.001). Despite their lower WBISI (p<0.001), the 120' ODI showed no difference between groups. The 30' insulinogenic index and ODI were higher and the AUCg lower in the **early peak** group (p<0.001; **TABLE**). In patients with a **late peak**, insulin sensitivity was lowest and metabolic profile worse when insulin secretion progressively increased throughout the entire test (30' < 60' < 120'). Patients with **FH** were more severely obese (p<0.01) and showed higher uric acid, triglycerides and lower HDL, fasting and post-ingestion insulin sensitivity index and ODI (all p<0.001) than those without **FH**, both in pre-pubertal and pubertal children.

**Conclusions:** **FH** and a **late insulin peak** in the OGTT are associated to lower insulin sensitivity and worse metabolic profile in obese children and adolescents.

	Early insulin peak (30')	Middle insulin peak (60')	Late insulin peak (120')	Inter-group comparison
BMI-SDS	4.08 ± 1.28	4.10 ± 1.43	4.43 ± 1.42	p < 0.01
Uric acid (mg/dl)	4.78 ± 1.07	5.01 ± 1.11	5.22 ± 1.19	p < 0.001
HDL (mg/dl)	46.15 ± 10.52	45.30 ± 10.28	43.53 ± 10.21	p < 0.01
Triglyceride/HDL ratio	1.95 ± 1.48	1.93 ± 1.34	2.32 ± 1.93	p < 0.05
HOMA	3.34 ± 1.84	3.57 ± 1.99	4.37 ± 3.78	p < 0.001
WBISI	3.82 ± 1.89	3.45 ± 1.91	3.10 ± 1.94	p < 0.001
AUC i (0-120')	165.9 ± 105.2	197.3 ± 127.5	220.3 ± 140.4	p < 0.001
AUC g (0-120')	235.2 ± 27.5	260.9 ± 33.7	260.5 ± 36.4	p < 0.001
AUC i / AUC g (0-120')	0.69 ± 0.40	0.74 ± 0.42	0.82 ± 0.48	p < 0.001
ODI 120'	9.54 ± 28.79	9.55 ± 19.01	9.46 ± 11.23	NS
Insulinogenic index (0-30')	2.70 ± 2.63	1.66 ± 1.49	1.94 ± 1.29	p < 0.001
ODI 30'	0.21 ± 0.17	0.11 ± 0.09	0.12 ± 0.72	p < 0.001
AUC i / AUC g (60'-120')	0.66 ± 0.42	0.86 ± 0.50	0.94 ± 0.55	p < 0.001

**TABLE:** Comparison between groups according to their insulin secretion pattern throughout the OGTT. **Abbreviations:** AUCi: Area under the curve for insulin; AUCg: Area under the curve for glucose; BMI: Body mass index; ODI: oral disposition index; WBISI: Whole body insulin sensitivity index.

P1-1120

BLACK HILLS PEDIATRIC OBESITY AND DIABETES PREVENTION PROGRAM

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**Objectives:** Childhood obesity has been a growing epidemic for decades with substantial health consequences including type II diabetes. In Rapid City, SD, the prevalence of obesity has grown from 11.6% in 2012 to 16.4% in 2015, and childhood type II diabetes has increased in parallel. Pediatric studies of type II diabetic patients show that over 1 year the beta cells of the pancreas decrease in function by 30% and the need for subcutaneous insulin in addition to oral therapy was 45%. Characteristics of children with type II diabetes in a clinical trial revealed: 26.3% with hypertension, 13% with microalbuminuria, 80% with high LDL cholesterol levels, and 10.2% with elevated triglycerides. These characteristics lead to early heart attacks, strokes, and kidney failure. In Rapid City, there are no organized obesity or diabetes prevention programs. CATCH (Coordinated Approach To Child Health) is an evidence-based program shown to reverse this trend of increasing obesity.

**Methods:** CATCH was first developed at the University of Texas and is now supported by 25 years and 120 academic papers that indicate an 11% decrease in obesity. CATCH incorporates physical activity, the lunchroom, the classroom, and the home to give adolescents a uniform message to help make healthy decisions. CATCH will first be integrated into pilot elementary and middle schools, and YMCA after school programs. Their success will be used to grow interest and support and proceed to involve all the schools in the district.

**Results:** Going forward, grant funding is being sought from pharmaceutical, health insurance, and local sources to pay for curriculum and training. The success of the CATCH program will be monitored by faculty researchers from Black Hills State University, and also based on student, parent, and faculty satisfaction.

**Conclusions:** A diverse team of highly qualified individuals is pursuing implementation of an evidence-based program, CATCH, in Rapid City. Moving forward, support of local school districts as well as identifying pilot schools to implement the program this upcoming school year will be essential. Looking ahead we hope to expand the number of schools using CATCH, and potentially establish a clinic-based treatment model for obesity and diabetes.

P1-1121

#### CENTRAL OBESITY IS ASSOCIATED WITH ALTERED CORTISOL METABOLISM IN GIRLS

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**Objectives:** Increased secretion of cortisol in adipose tissue has been implicated a mediator of central obesity in adult human and animal studies. However, evidence on altered cortisol metabolism in childhood obesity has been limited. We aimed to examine whether circulating cortisol metabolites and their ratios reflecting steroidogenic enzyme activities are associated with obesity in girls.

**Methods:** A total of 227 girls (131 control, 45 overweight, 51 obese; aged 7 to 13 yr) were enrolled. Serum cortisol metabolites and cortisone concentrations were analyzed by gas chromatography-mass spectrometry. Enzyme activities involving cortisol metabolism including 11 $\beta$ -hydroxylase, 11 $\beta$ -hydroxysteroid dehydrogenase (HSD) type 1, 3 $\alpha$ -HSD were assessed from the ratios of steroid metabolites.

**Results:** Allo-tetrahydrocortisol (allo-THF) levels were significantly higher in obese girls compared with overweight and control girls, but the concentrations of other cortisol metabolites were not significantly different by obesity status. Obese girls showed significantly increased activity of 3 $\alpha$ -HSD and marginally increased activity of 11 $\beta$ -HSD type 1, respectively, compared with overweight and control girls. Partial correlation analysis revealed positive associations of waist-to-height ratio and body fat percentage with allo-THF levels and activities of 3 $\alpha$ -HSD and 11 $\beta$ -HSD type 1. Girls with central obesity determined by waist-to-height ratio  $\geq 0.5$  had 1.3 times higher allo-THF levels (6.30ng/mL vs. 4.94 ng/mL). Also, activities of 3 $\alpha$ -HSD and 11 $\beta$ -HSD type 1 were significantly higher in girls with central obesity than controls.

**Conclusions:** Central adiposity in girls was associated with increased activation of 11 $\beta$ -HSD type 1, and increased metabolic clearance of cortisol by 3 $\alpha$ -HSD. Further studies are needed to reveal whether metabolic derangement of obesity are related with altered cortisol metabolism in adolescents.

P1-1122

#### REGIONAL BODY FAT AND METABOLIC COMPLICATIONS IN CHILDREN WITH FAMILIAL PARTIAL LIPODYSTROPHY, DUNNIGAN VARIETY (FPLD2)

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**Background:** FPLD2 is a rare autosomal dominant disorder due to heterozygous missense mutations in lamin A/C (LMNA) gene. Affected patients, particularly females, gradually lose subcutaneous (sc) fat from the extremities but gain fat in the face, neck and intra-abdominal region at the time of puberty; which results in insulin resistance and its complications such as dyslipidemia, diabetes, hepatic steatosis and premature atherosclerosis in adulthood. However, the precise onset of body fat changes and metabolic complications in children with FPLD2 remains unknown.

**Objective:** To compare metabolic parameters and regional fat in children with FPLD2 with the sex and age matched controls from the National Health and Nutrition Examination Survey (NHANES) 2005-2010.

**Methods:** We measured fasting triglycerides, glucose and various skinfold thicknesses; and determined regional body fat by dual energy X-ray absorptiometry (DEXA) in children ( $\leq 18$  years) with FPLD2 and compared the data to those from NHANES.

**Results:** A total of 48 children (34F, 14M) had FPLD2; 69% were Caucasians, 13% Asians, 10% native Americans, 2%

African American and 6% unknown. Patients had the following *LMNA* mutations: R482W (n=24); R482Q (n=10); R28W (n=3); R482L, R25L, R582S, and R582H (n=2 each), and G465D, K486N, and K515E (n=1 each). Females with FPLD2 did not develop metabolic complications or fat loss in early childhood (<12 y), but developed significant hypertriglyceridemia and loss of extremity fat from age 13-18 years; whereas FPLD2 males did not show significant changes till age 18 years (Table 1).

Table 1. Metabolic parameters and body composition in children with FPLD2 compared to NHANES controls.

**Conclusions:** Marked loss of extremity fat and hypertriglyceridemia occurs in late childhood in females with FPLD2 as compared to normal controls; whereas male children with FPLD2 do not show significant changes, possibly due to small sample size.

	Age group	FPLD2 Female			NHANES Female			p-value*	FPLD2 Male			NHANES Male			p-value*
		N	Median	Range	N	Median	FPLD2 vs NHANES median		N	Median	Range	N	Median	FPLD2 vs NHANES median	
Triglycerides (mg/dL)	0-6	2	140	76-204					2	83	74-92				
	7-12	7	123	47-198	117	68	0.047		4	84.5	55-147	121	68	0.38	
	13-18	17	292	84-1670	656	71	<.0001		6	105.5	41-223	722	71	0.25	
Fasting Glucose (mg/dL)	0-6	2	90	75-105					1	90	90-90				
	7-12	7	82	77-98	118	94	0.02		4	79.5	73-94	123	96	0.13	
	13-18	17	85	64-226	666	91	0.002		4	89.5	88-90	729	95	0.13	
Triceps skin fold (mm)	0-6	1	7.0	7-7	2514	9.8			1	5.5	5.5-5.5	2670	8.9		
	7-12	4	7.8	5.5-10.5	1702	13.6	0.13		3	8.0	4.5-13.5	1725	10.9	0.5	
	13-18	8	5.8	4.8-11	1601	17.8	0.008		4	5.4	4-10.5	1725	10.5	0.25	
Upper limb fat (%)	7-12	4	22.8	17.8-24.5	514	37.3	0.13		2	19.2	16.4-22	505	32.1	0.5	
	13-18	8	21.2	15-26.5	806	37.7	0.008		2	15.8	14.2-17.3	813	24.4	0.5	
Lower limb fat (%)	7-12	4	19.3	18.2-19.8	514	38.2	0.13		2	20.2	12.4-28.1	505	33.5	0.5	
	13-18	8	14.9	9.2-26.1	806	38.6	0.008		2	16.5	15.8-17.3	813	25.6	0.5	
	13-18	8	14.9	9.2-26.1	806	38.6	0.008		2	16.5	15.8-17.3	813	25.6	0.5	

\*P-value from Wilcoxon Signed-rank one-sample test. \* % fat by DEXA.

P1-1123

### A WEIGHTY ISSUE IN DOWN SYNDROME

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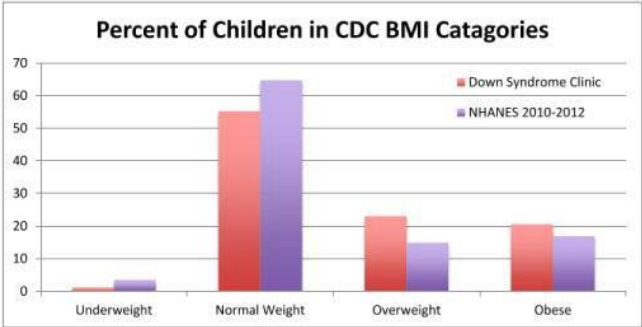
**Objectives:** Although obesity is a commonly discussed issue in the medical management of children with Down syndrome, there are no large studies published on its prevalence or associations with other common comorbidities in this population. This study seeks to calculate rates of overweight and obesity in a large cohort of children with Down syndrome.

**Methods:** Using a database of children from a single medical center specialty clinic, we calculated rates of overweight and obesity and examined possible associations with common comorbidities including cardiac disease, thyroid disease, sleep apnea, autism, and visual and hearing impairment. Overweight and obese were defined using the Center for Disease Control growth charts and BMI percentile cut-offs.

**Results:** 833 visits from 417 unique patients ranging in age from 2 years to 18 years of age. 1.2% were underweight, 55.2% were normal weight , 23% were overweight, and 20.6% were obese. BMI percentile increased with female gender, age, and height percentile for age. Sleep apnea was associated with higher BMI percentile, while autism was associated with lower BMI percentile.

**Conclusions:** Children with Down syndrome have higher rates of obesity that the general population, with especially high

risk for girls. Further research needs to be done to determine the age at which this increase starts to occur to target interventions for prevention, particularly in young girls.



P1-1124

### OMEGA 3 FATTY ACID SUPPLEMENTATION ATTENUATES ADIPOSE TISSUE INFLAMMASOME SIGNALING IN HEALTHY OBESE SUBJECTS

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**Objectives:** Adipose tissue inflammation is a crucial component of obesity-related metabolic dysfunction. The NLRP3 inflammasome, present in adipose tissue macrophages, is an integral sensor of diverse inflammatory stimuli. Activation of the inflammasome contributes to innate immunity; thus, inhibiting the inflammasome is a strategy for reducing obesity-related dysregulation. We aim to determine effects of the fish oil-derived long chain omega-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on adipose tissue inflammation and inflammasome gene expression in healthy obese subjects.

**Methods:** Healthy, non-diabetic obese subjects (BMI>30) aged 18-50 were recruited into the double-blind, placebo-controlled Fish Oils in Adipose Inflammation Reduction (FAIR) study. Subjects were randomized to receive Lovaza (1.86 mg EPA and 1.5 mg DHA) (n=15) 4 grams/day or placebo (n=14) for 8 weeks. Subcutaneous gluteal adipose tissue biopsy was performed on each subjects pre- and post-treatment. mRNA was isolated from adipose and reverse transcribed to cDNA for quantification of mRNA expression by qPCR and analyzed by the 2<sup>-delta delta CT</sup> method.

**Results:** After 8 weeks of treatment, subjects in the Lovaza group had a modest reduction in relative gene expression of the inflammatory markers IL6 (mean expression relative to baseline of 0.85, p=0.04), CCL2 (0.86, p=0.03), and CX3CL1 (0.96, p=0.06) as well as the inflammasome components IL1beta (0.81, p=0.03) IL18 (0.68, p=0.01), NLRP3 (0.91, p=0.05), and ILR7 (0.78, p=0.04) in subcutaneous adipose tissue. There was also downregulation of the M1-macrophage associated gene iNOS (0.75, p=0.03) with upregulation of the M2 macrophage gene MRC1 (1.2, p=0.04) in the Lovaza group.. By contrast, subjects in the placebo group had no

changes in gene expression of any of these markers (mean expression relative to baseline 0.98-1.1,  $p>0.05$  for all genes).

**Conclusions:** Omega 3 fatty acids reduce adipose inflammatory gene expression in human obesity, including those of the NLRP3 inflammasome. This dietary supplement represents a therapeutic option for preventing obesity-related inflammation and resultant metabolic disease.

P1-1125

#### VITAMIN D ANTAGONIZES EFFECTS OF HIGH-FAT DIET ON BRAIN TRANSCRIPTOME

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**Objectives:** Our lab has previously shown that vitamin D has actions in the hypothalamus of the brain to improve glucose tolerance and weight gain, but the known actions of vitamin D do not adequately explain how this may occur. Thus, we sought to analyze the transcriptomic effects of vitamin D in the hypothalamus in order to determine what pathways/genes vitamin D may regulate specific to the brain.

**Methods:** We treated both chow and high-fat fed male rats with either 1,25-dihydroxyvitamin D3 (1,25D3) or vehicle into the third-ventricle of the brain. We then used RNA from their hypothalami and the unbiased approach of RNA-seq through the Genomic and RNA Profiling Core to determine the transcriptomic effects of 1,25D3 in the hypothalamus.

**Results:** RNA-seq analysis revealed 98 genes differentially expressed ( $> 1.5$  fold) in the hypothalamus of high-fat diet fed male rats treated with 1,25D3. Through pathway analysis, we found that the most significantly affected processes were in nervous system development, transmission of nerve impulses, neurotransmitter release, and multiple ion channel pathways. Also of note, multiple inflammatory, glucose metabolism, and gluconeogenesis pathways were differentially expressed. We also performed RNA-seq on high-fat diet fed and chow-fed rats. Interestingly, vitamin D affected pathways differently in chow vs. high-fat diet fed animals, demonstrating that nutritional factors interact with vitamin D action through unknown mechanisms.

Additionally, in many cases, treatment with vitamin D caused regulation of genes in the opposite manner of the effects of the high-fat diet alone implying that 1,25D3 was returning the gene/pathway to a more "chow-fed-like" state. Of the top 50 differentially expressed genes by 1,25D3 treatment, the following genes were thought to be of particular importance to be suitable for further studies as potential targets of vitamin D in the brain: *ppara* (PPAR-alpha), *kcnh7* (potassium voltage-gated channel H), *adra1a* (alpha-1A adrenergic receptor), and *slc2a4* (GLUT4).

**Conclusions:** This data greatly expands the known role of vitamin D in the brain and provides insights into the mechanisms underlying vitamin D function in the brain which could lead to changes in health outcomes.

P1-1126

#### ASIAN OBESE CHILDREN ARE MORE METABOLICALLY UNHEALTHY COMPARED TO CAUCASIAN OBESE CHILDREN

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**Objectives:** To compare the metabolic parameters between Asian and Caucasian obese children.

**Methods:** 1) Children between age group 5-18 yrs with simple obesity (Defined as Body mass Index (BMI)  $>2$  SDS after excluding all secondary causes) who attended a tertiary referral hospital in Chennai, India were prospectively recruited over a period of 2 years (September 2014- August 2016).

2) All of them had their height, weight and blood pressure (BP) measured. Their fasting blood glucose, fasting insulin levels, alanine aminotransferase (ALT) and fasting lipid profile were checked.

3) Patients with BP  $>95$ th centile for their age and sex according to Fourth Report on High Blood Pressure were classified as hypertensive.

4) HOMA-IR was calculated and patients with HOMA-IR  $>2.5$  were classified as Insulin resistant.

5) These metabolic parameters were compared to an age matched cohort of Caucasian obese children recruited by the author in a previous study (unpublished) done during the period January 2006 till August 2007 in a tertiary referral hospital in Manchester, U.K.

**Results:** 1) 92 Indian obese children with a mean age 11.7 yrs (SDS 3.0) were compared with 56 Caucasian children with a mean age 12.2 yrs (SDS 3.4).

2) The mean birth weight of Indian children was significantly less compared to that of the Caucasian children (3.0 vs 3.36 kg).

3) 76.1% of Indian children had one or both parents obese compared to 50% of Caucasian children  $p=0.001$ .

4) Caucasian children had significantly higher BMI {BMI SDS 5.2(1.5)} compared to Indian children {BMI SDS 3.5(1.5)}  $p=0.000$ .

5) But significant percentage of Indian children (93.4%) were insulin resistant compared to Caucasians (82.1%)  $p=0.04$ .

6) Indian children also had high ALT compared to Caucasian children (mean=67.7 vs 46.7  $p=0.002$ ).

7) Hypertension and dyslipidemia were more common in Indian obese children compared to Caucasians but they were not statistically significant ( $p>0.05$ ).

**Conclusions:** Even at a lower BMI, Indian obese children become more metabolically unhealthy compared to Caucasian obese children. Hence it is justified to have a lower BMI cut-off for evaluation and treatment of metabolic problems in Indian obese children compared to western standards.

### MC4R VARIANTS ARE RELATED WITH SEVERE EARLY ONSET OBESITY AND EXTREME GROWTH IN CHILDREN YOUNGER THAN 3 YEARS OF AGE

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**Objectives:** The objective of this study is to verify the association of *Melanocortin-4-receptor (MC4R)* mutations with very early onset of severe obesity and particularly before the age of 3 years. Children carrying such mutations show an overgrowth phenotype with very early onset of hyperphagia, extreme obesity, and rapid height acceleration starting even in infancy. To verify the association of *MC4R* mutations with this particular phenotype, *MC4R* gene was screened in a group of severely obese children selected on the basis of their phenotype.

**Methods:** Patients (n=16) included in the study should meet the following criteria; 1) hyperphagia and obesity onset before the age of 3 years, 2) body mass index (BMI) z-score equal or more than +3SDS, 3) rapid growth acceleration with height z-score equal or more than +2SDS and 4) growth velocity (GV) z-score equal or more than +2SDS for age and gender. Direct sequencing of the *MC4R* gene was performed to all of the patients enrolled in the study.

**Results:** A novel heterozygous *MC4R* p.M215del (c.643\_645delATG) deletion was identified in two siblings. Another 2 unrelated patients were found heterozygotes for the *MC4R* p.Val103Ile polymorphism known to be associated with metabolic syndrome in adulthood. In the rest of the patients there were found no mutations.

**Conclusions:** These preliminary data identified a novel p.M215del deletion as a disease causing mutation and confirmed the association between *MC4R* variants and overgrowth phenotype even in heterozygous patients. Identifying these patients at a very young age is crucial for early intervention and management of obesity and its complications.

P1-1128

### THE IMPORTANCE OF CDC BMI GROWTH CHART USE INSTEAD OF NEW DS-SPECIFIC BMI CHART FOR CARDIOMETABOLIC SCREENING OF YOUTH WITH DOWN SYNDROME

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**Objectives:** Obesity is prevalent in Down syndrome (DS), but obesity implications for cardiometabolic risk (CMR), previously downplayed in DS, are unknown. Updated growth charts based upon a contemporary U.S. DS cohort recently became available, but the extent to which the DS-specific BMI 85%ile identifies increased CMR is unknown. We aimed to determine differences in prevalence of abnormal CMR factor levels in DS youth identified using the CDC BMI 85%ile vs DS-specific BMI 85%ile, and the extent to which glucose and lipid abnormalities would be missed using the DS-specific chart.

**Methods:** Youth with DS (10-20yrs) were enrolled at two children's hospitals. Age and sex-specific BMI z-scores were generated using both the 2000 CDC reference data (CDCz), and the DS-specific reference data (DSz). Fasting lipids and oral glucose tolerance tests (OGTT) were performed. Lipid abnormalities were defined using NHLBI guidelines. The prevalence of dyslipidemia and abnormal glucose tolerance (AGT) detected using screening of BMI  $\geq$  85%ile (z-score=1.04) on the CDC vs DS-specific BMI charts were compared using the PR-test. The proportion of children with abnormal CMR missed using DSz 85%ile instead of CDCz for screening is reported.

**Results:** 144 DS youth (mean age 14.6 $\pm$ 3.3y, 56.1% F, 19.6% African American, BMI 27.0 $\pm$ 7.9) were studied. Prevalence of abnormal lipids and glucose was significantly higher using the CDCz  $\geq$  1.04 as a screening cut-off, compared with the DSz  $\geq$  1.04, and many youth with abnormal CMR would be missed using the DSz: (listed as CDCz vs DSz, p-value, %missed using DSz): total cholesterol  $\geq$  170mg/dl- 38.2% vs 19.3%, p=0.0004, 18.9%; triglycerides (TG)  $\geq$  90 mg/dl- 36.8% vs 20.0%, p=0.002, 16.8%; TG  $\geq$  130 mg/dl- 22.9% vs 10.7%, p=0.006, 12.2%; LDL-C  $\geq$  110 mg/dl- 34.3% vs 17.5%, p=0.001, 16.8%; non-HDL-C  $\geq$  120 mg/dl- 43.8% vs 25.0%, p=0.0009, 18.8%; HDL-C  $\leq$  40 mg/dl- 31.9% vs 18.6%, p=0.01, 13.3%; AGT (includes impaired fasting glucose and/or impaired glucose tolerance by OGTT)- 26.4% vs 11.4%, p= 0.02, 15.0%.

**Conclusions:** For CMR screening in youth with DS, providers should use the 2000 CDC BMI  $\geq$ 85%ile as opposed to the DS-specific BMI  $\geq$ 85%ile, to avoid missing a significant proportion of DS youth with glucose and lipid abnormalities.

P1-1129

### PARENTAL OBESITY INFLUENCES THE EARLY ONSET OF OBESITY AND THE OVERWEIGHT DEGREE IN CHILDREN.

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**Objectives:** Childhood obesity is known to be associated with an increased risk of cardiovascular and metabolic complications in adulthood.



In this cross-sectional, observational study authors investigated which variables may influence precocious onset and severity of overweight and which laboratory alterations were already proven at the first assessment in a population of overweight and obese children.

**Methods:** We recruited 260 boys and girls (from 2 to 18 years), with simple overweight/obesity. Each patient underwent anamnestic evaluation, physical examination and fasting blood sampling for glucose, insulin and lipid profile. HOMA-IR, triglyceride-to-HDL-cholesterol ratio and atherogenic index of plasma were evaluated.

**Results:** Family history for obesity and/or arterial hypertension and/or diabetes was related to a more severe degree of overweight among children ( $p=0.002$ ). A more severe obesity was demonstrated in younger children ( $p<0.0005$ ). HOMA-IR resulted higher among children with the most severe obesity ( $p=0.04$ ), who were younger. BMI SD was a significant predictor of HOMA-IR  $>2.5$  (OR 2.39; 95% CI 1.15 to 4.97;  $p=0.01$ ).

**Conclusions:** Family history of obesity and cardiometabolic disease must be considered a risk factor for precocious obesity onset in children. Insulin resistance is demonstrated even among the youngest. BMI SD is useful to stratify the severity of obesity in order to estimate the cardiometabolic risk of each patient.

P1-1130

#### TREATMENT OF HYPOTHALAMIC OBESITY WITH DEXAMPHETAMINE – A CASE SERIES

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**Objectives:** Published case reports and anecdotal experience suggest a positive effect of Dexamphetamine, a central nervous system stimulant on impetus and weight in patients with hypothalamic obesity. Based on these observations, patients presenting to our obesity clinic with hypothalamic obesity are offered off-label treatment with dexamphetamine.

**Methods:** Between 2010 and 2013, patients starting dexamphetamine treatment were enrolled in a prospective observation study. BMI z-score was determined and impetus was rated at baseline and every three months. A retrospective chart review was conducted to establish BMI z-score development prior to treatment initiation. Dexamphetamine administration was initiated at a single dose of 5 mg per day, and titrated to effect up to a dose of 20 mg/day in 2-3 single doses. Side effects were recorded in a standardized fashion. BMI z-score velocity was calculated as change in BMI z-score over standardized intervals of 12 months.

**Results:** 9 Patients (3 males) mean age 17.2 years (range: 13.0-23.8) were included in the study. The primary diagnoses were craniopharyngeoma (n=6 patients), ganglioglioma WHO

I (n=1), astrocytoma (n=1), and neonatal meningitis (n=1). Time from initial CNS insult to initiation of dexamphetamine treatment was 5.7 years on average (range 4 mo-17.4 yrs). All patients demonstrated a steady increase in BMI z-score from the time of initial diagnosis until initiation of treatment. Of the nine Patients, two were excluded from the evaluation because of proven non-compliance. Mean baseline BMI z-score of the remaining 7 patients was  $3.17 \pm 0.93$  (1.9-4.4). Mean BMI z-score velocity decelerated to  $-0.18 \pm 0.12$  during the first year of treatment, and stabilized at  $0.05 \pm 0.32$  during the second year of treatment. Over the two-year treatment period, mean score for impetus improved from 1.3 to 2.8. No significant side effects were reported.

**Conclusions:** Dexamphetamine treatment led to improved impetus and stabilization or reduction of BMI-SDS in a cohort of 7 patients with hypothalamic obesity. Considering the projected increase in BMI z-score according the natural course of the disease, these findings are promising and warrant further study.

P1-1133

#### ELUCIDATING THE MOLECULAR MECHANISMS OF METABOLIC IMPROVEMENT FOLLOWING BARIATRIC SURGERY IN OBESE ADOLESCENTS

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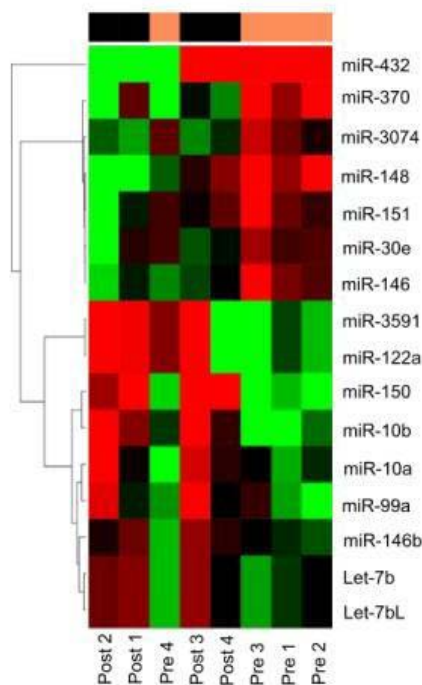
**Objectives:** Bariatric surgery is increasing in popularity among pediatric patients with severe obesity due to its profound benefits including weight reduction and metabolic health outcomes, such as diabetes. The objective for our study is to perform comprehensive analyses focusing on circulating factors to elucidate the molecular mechanisms of the metabolic improvement following bariatric surgery.

**Methods:** We recruited patients (n=20; age range 12-19 years) undergoing elective abdominal surgical procedures, including bariatric surgery. Data collected included blood samples for molecular analyses, such as circulating RNA sequencing, at baseline and 1,3,6, and 12 months after surgery. Adolescents undergoing bariatric surgery were compared to lean and obese controls undergoing non-weight loss abdominal procedures.

**Results:** We observed a significant shift of circulating RNA expression pattern in obese adolescents before and 1 month after bariatric surgery, despite patients remaining quite obese (Figure 1). For example, miRNA-122a, a known hepatocyte associated microRNA showed increased expression pattern after surgery, whereas, miRNA-146, a known inflammation associated microRNA showed lower expression level following the surgery.

**Conclusions:** We observed drastic molecular changes in the circulating RNA expression pattern 1 month after bariatric surgery in obese adolescents. These effects seem to be independent of weight reduction. Whether these changes are

associated with the profound metabolic improvement following bariatric surgery remains to be elucidated.



**Figure 1.** MicroRNA analysis demonstrates a drastic shift of expression pattern 1 month after surgery. (Pre 1-4: pre-surgery, Post 1-4: post-surgery)

P1-1134

**PREVALENCE OF FOOD ADDICTION IN CHILDREN WITH OVERWEIGHT AND OBESITY**

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**Objectives:** Obesity is a worldwide public health problem that has reached alarming numbers affecting adults, teenagers and children.

One way of facing this health problem is by placing it under a similar perspective used with problems of addiction where the individual becomes physically and psychologically dependent to food rich in sugars and fats.

The main objective was to determine the prevalence of food addiction in children that suffer of overweight and obesity problems with the YFAS-C. (Yale Food Addiction Scale in Children).

**Methods:** A prospective, descriptive and a prevalence study was realized, where a survey of addiction to food in children (YFAS-C) was applied to 285 children from April 2016 to April 2017, in the pediatrics area of a tertiary hospital at Monterrey Nuevo Leon, México.

The following data was obtained: gender, age, weight, height, BMI (Body Mass Index) and with these the percentile of each patient was obtained and according to the graphics of BMI of the CDC (Centers for Disease Control and Prevention) each patient was classified as overweight or obese. This survey was applied to 285 patients classified with overweight or obesity.

The average of age was of 13.2 years old (range 8-17 years old) 56% male and 43.9% female.

**Results:** Survey results showed that 13.7 % of the children turned out with food addiction.

There is a higher prevalence in women and teenagers, plus, it was found that there is more relation of food addiction in children with obesity versus children that are overweight.

**Conclusions:** This is the very first study realized in a Hispanic population with the Yale scale for children, proving that food addiction in children has a prevalence of 13.7%.

**Table 1**

**Prevalence of food addiction in children.**

Meets criteria?	Cases (N=285)	Percent
No	246	86.3 %
Yes	39	13.7 %
Total	285	100 %

P1-1135

**ASSESSMENT AND TRACKING OF GROWTH IN SEVERELY OBESE OR UNDERWEIGHT CHILDREN USING Z-SCORES AND PERCENTILE METHODS**

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**Objectives:** To illustrate the difficulties in optimal growth monitoring of children with severe obesity or underweight using the Centers for Disease Control and Prevention (CDC) 2000 age-sex-specific body mass index (BMI) percentile growth charts. To examine the utility of a new modified CDC BMI z-score chart to monitor growth in children with normal and extreme BMI percentiles using real-life clinical scenarios.

**Methods:** Modified BMI z-score charts were created using the 2000 CDC algorithm. Three cases of children with extreme BMI values and abnormal growth patterns were plotted using the standard CDC 2000 clinical growth chart, the modified BMI z-score chart, and the CDC BMI percentile chart with additional percentage of the 95<sup>th</sup> percentile curves (%BMI<sub>p95</sub>). Figures show two cases of obesity and one case of underweight, each plotted on the three different growth charts for comparison.

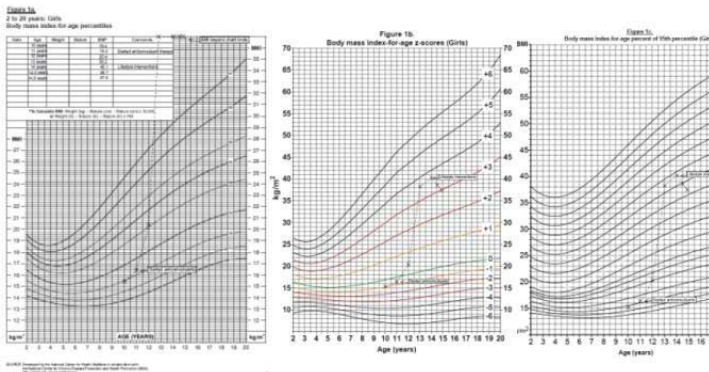
**Results:** Children with severe obesity could not be plotted on the standard CDC BMI percentile chart, as their BMI points lay above the chart cutoff. Children with low BMI (<3%) were also difficult to track on the standard BMI percentile chart. The addition of the %BMI<sub>p95</sub> scale to the standard BMI% chart allowed tracking of severely obese children; however, it did not address severely underweight children and required a change of units within the chart when transitioning from



normal to obese BMIs. The modified BMI z-score chart allowed uniform tracking in all categories.

**Conclusions:** The modified CDC z-score chart is suitable for growth tracking of children with normal and extreme growth patterns without changes in units or limits at either extreme. The measures correlate well with the %BMI<sub>p95</sub>, and the chart can be incorporated easily into existing electronic health record systems for clinical use.

Case 1: 13yo female referred for excessive weight gain. Figure 1a plots her BMI using the 2000 CDC BMI-for-age chart. One challenge of using the 2000 CDC BMI chart is that the maximum BMI that can be plotted is 35 kg/m<sup>2</sup>, and even a BMI of 35 kg/m<sup>2</sup>, the data box covers much of the upper BMI area (Figure 1a). Figures 1b and 1c illustrate the plot using modified BMI-for-age z-score chart and a modified 2000 CDC percentile chart with %BMI<sub>p95</sub>. With either of these charts, more extreme BMIs can be tracked, although the modified z-score chart uses a uniform unit of measurement and provides more continuous tracking. Cases 2 and 3 show examples of other extreme BMI plots in similar format (both obese and underweight).



P1-1136

## NOVEL MUTATION IN LEPR GENE CAUSING MONOGENIC OBESITY IN A CHILD

Maria Jose Ramirez, *Pediatr Endocrinol, Centro Hospitalario Pereira Rossell, Montevideo, Uruguay*; Victor Raggio, *Geneticist*; Alejandra Tapie, *Geneticist*; Rosario Guecaimburu, *Geneticist*; Ana Batalla, *Geneticist*; Laura Garcia, MD, PhD., *Universidad de la Republica, Montevideo, Uruguay*; Gabriela Canela, *Pediatrician*; Eliana Perez, MD; Martin Vazquez, *Pediatrician*; Catalina Pinchak, *Pediatr Neumologist*; Isabel Moreira, *Pediatr Neumologist, Centro Hospitalario Pereira Rossell, Montevideo, Uruguay*

**Objectives:** The objective is to present a novel mutation in LEPR gene.

A 16-months-old boy, born at term and with no complications, from consanguineous parents is brought due to severe obesity despite nutritional treatment since he was 1 year-old. There are no obesity cases in the family. Body weight increased from 50<sup>th</sup> percentile to 97<sup>th</sup> percentile from birth to 2 month and has increased since then. Length was 50<sup>th</sup> percentile at birth and crossed 97<sup>th</sup> percentile at 10 month of age, also increasing until now. Weight/length index has increased since birth and was always above 97<sup>th</sup> percentile. On physical exam, the child was tetchy, weight 35 Kg (Z-score of +11), height 88 cm (Z-score of +2.89), head circumference with Z-score of +6, and BMI 45 Z-score of +10, abdominal perimeter 90cm, micropenis, normal testes, no dysmorphic signs. Vital signs were: BP 110/65, HR 110, and RR 48, and his temperature was 36°C. The child is able to stand up with help but is not able to walk. Complementary studies confirmed dyslipidemia with hepatic steatosis.

**Methods:** Monogenic obesity was the presumptive diagnosis. Genes of the leptin/melanocortin pathway: MC4R, LEP, LEPR, PC1, PCSK1, SIM1, NTRK2 and POMC, and other 30 obesity-related genes were analyzed.

Next Generation Sequencing was performed using Sure Select Target Enrichment Kit (Agilent) for libraries generation and enrichment, and Illumina HiSeq 2000/2500 equipment. Raw data was aligned against the reference genome (UCSC hg19) using the BWA and the variants were determined with the GATK pipeline.

**Results:** A variant, not previously described, was found in homozygosity in the LEPR (leptin receptor) gene: NM\_001003679.3:exon10:c.1305\_1306del:p.S435fs. This mutation causes a change in the open reading frame and a stop in the following codon (the gene is 1165 aminoacids long and the variant is in S435) probably leading to severe leptin receptor deficiency. Since it is a variant that is expected to cause a loss of function of the gene product, in homozygosity for a recessive phenotype and compatible with the clinical presentation in the patient, it should be considered as a probably pathogenic variant which explains the phenotype of the patient.

**Conclusions:** This finding confirms, in practice, the diagnosis of monogenic obesity due to leptin receptor deficiency.

## POSTER SESSION 1

Thursday, September 14, 2017, 5:45-6:45pm

P1 - Other

P1-1200 – P1-1216

P1-1200

## THE RELATIONSHIP OF OBESITY AND INSULIN RESISTANCE WITH HYPERANDROGENEMIA, ANTI-MÜLLERIAN HORMONE, INHIBIN A, INHIBIN B AND INSULIN-LIKE PEPTIDE-3 LEVELS IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME

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**Objectives:** To investigate the relationship of obesity and insulin resistance (IR) with hyperandrogenemia, AMH, INH-A, INH-B and INSL3 levels, the factors which had an impact on IR and which contribute to the emergence of the disease in adolescent girls.

**Methods:** 52 adolescent girls diagnosed with PCOS [subgroups: non-obese (NO), n=23; obese (O), n=29] and 26 girls without PCOS [NO, n=14; O, n=12] were included. Blood samples were obtained to measure leptin, AMH, INH-B, INH-A and INSL3 levels, together with hormonal and biochemical assessments. OGTT was performed in girls with PCOS and the Matsuda index (ISI<sub>comp</sub>) was calculated.

**Results:** The frequency of IR obtained by HOMA-IR (30.4%) was markedly lower than that by OGTT (56.5%) in the PCOS-NO, but no difference was in the PCOS-O group (72.4% and 79.3%, respectively). The androstenedione (D4-A) and leptin levels were higher in the PCOS-O than in the PCOS-NO ( $p=0.004$  and  $p<0.001$ , respectively). While there was no difference between the PCOS subgroups in terms of AMH and INH-A levels, INH-B and INSL3 levels were lower in the PCOS-O than in the PCOS-NO ( $p=0.014$  and  $p=0.028$ , respectively). AMH level was markedly increased in the PCOS-O without IR. While INH-B was correlated with both HOMA-IR and  $ISI_{comp}$ . In linear regression analysis, INH-B ( $p=0.02$ ) and FAI ( $p<0.001$ ) were found to have an effect on HOMA-IR ( $R^2=0.602$ ) and similarly INH-B ( $p=0.002$ ) and FAI ( $p<0.001$ ) were found to have an effect on BMI SDS ( $R^2=0.654$ ). HOMA-IR ( $p=0.002$ ) and AMH level ( $p=0.028$ ) were found to have an effect on D4-A level ( $R^2=0.261$ ). In the logistic regression analysis, FAI ( $p=0.042$ ) and AMH ( $p=0.024$ ) were found to be associated with presence of IR in the adolescent girls with PCOS.

**Conclusions:** HOMA-IR is an insufficient criterion in specifying IR, especially in non-obese girls with PCOS in whom OGTT measurements were found more reliable. IR per se may contribute to the disease unrelated to obesity. Hyperandrogenemia was associated with IR and obesity parameters. AMH levels seem to be more valuable in terms of diagnosis, especially in obese girls without IR. INH-B levels are closely related to both obesity and IR parameters, so it can be used as IR indicator.

P1-1201

**MODY IN UKRAINE: GENES, CLINICAL PHENOTYPES AND TREATMENT**

Eugenia Globa, PhD, Ukrainian Center of Endocrine Surgery, Kyiv, Ukraine; Nataliya Zelinska, Professor; Iryna Shevchenko, PhD, Ukrainian Scientific Center of Endocrine Surgery, Kyiv, Ukraine; Lenka Elblova, PhD, Second Faculty of Medicine/Charles University in Prague/University Hospital Motol, Prague, Czech Republic; Petra Dusatkova, PhD; Ondrej Cinek, Prof., Charles University and University Hospital Motol, Prague, Czech Republic; Jan Lebl, MD, Motol University Hospital in Prague, Prague, Czech Republic; Kevin Colclough, PhD; Sian Ellard, Prof., University of Exeter Medical School, Exeter, United Kingdom; Stepanka Pruhova, PhD, Second Faculty of Medicine/Charles University in Prague/University Hospital Motol, Prague, Czech Republic

**Objectives:** Maturity-Onset Diabetes of the Young (MODY) has not previously been studied in the Ukraine. We investigated the genetic etiology in a selected cohort of patients with onset of diabetes aged more than 9 months and less than 25 years at the time of diagnosis.

**Methods:** Genetic testing was undertaken for 41 families (44 affected individuals) with a clinical suspicion of MODY. We identified mutations by Sanger sequencing or targeted next generation sequencing. All probands met the current diagnostic criteria for MODY with the exception of positive family history of hyperglycemia or diabetes inherited in an

autosomal dominant pattern. The parents of probands, who have not been diagnosed with diabetes, underwent a random blood glucose measurement followed by a standard oral glucose tolerance test (OGTT) or a mixed meal tolerance test (MMTT).

**Results:** We made a genetic diagnosis of MODY in 20/44 affected individuals from 17/41 families (41.5%). *HNF1A/HNF4A* mutations were most common, accounting for 9/20 cases with a genetic diagnosis (table 1). In patients with confirmed MODY 40% of probands did not report first-degree family history of diabetes, among them in two families “without diabetes” (11.8%) OGTT/MMTT identified IGT and diabetes in parents. In the other three families (17.6%) without history of diabetes OGTT/MMTT did not reveal diabetic changes in parents and other family member. Among 9 investigated families (parents and siblings of probands) in 2 families (22%) with *HNF4A* and *HNF1B* the mutation had arisen *de novo*. Nine patients with *HNF1A/HNF4A* and *ABCC8* mutation with inadequate glycemic control were able to stop insulin injections and to transfer to sulfonylureas. Median HbA1c decreased from 67.2 (58-69) to 46.9 (43-50) mmol/mol; 8.3% (7.5-8.5) to 6.4% (6.1-6.7), respectively 3 months after transfer ( $p=0.006$ ).

**Conclusions:** Genetic testing for patients identified *HNF1A/HNF4A* mutations as the most common cause of MODY in Ukraine. We can assume that the incidence of MODY might be higher than reported since in most studies the selection was limited by absolute cut-offs MODY criteria and using of Sanger sequencing.

Table 1. Genetic causes of MODY.

Genes	<i>HNF1A</i>	<i>HNF4A</i>	<i>GCK</i>	<i>HNF1B</i>	<i>ABCC8</i>	<i>INS</i>	<i>WFS1</i>
Number of patients (n=20)	7 (35%)	2 (10%)	5 (25%)	2 (10%)	2 (10%)	1 (5%)	1 (5%)

P1-1202

**LOCAL TOLERABILITY AND SAFETY PROFILE OF SOMATROPIN (RECOMBINANT HUMAN GROWTH HORMONE) IN PEDIATRIC PATIENTS WITH GROWTH HORMONE DEFICIENCY OR TURNER SYNDROME**

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**Objectives:** Somatropin is indicated for treatment of pediatric growth hormone deficiency (GHD) in the United States and for treatment of pediatric GHD and Turner syndrome (TS) in the European Union. This study assessed the local tolerability and safety profile of somatropin administered using the ZomaJet™ needle-free transjector.

**Methods:** This prospective, open-label, multicenter study enrolled children (aged 3–17 years) with GHD or TS receiving recombinant human growth hormone for ≥6 months. Patients received 12 weeks of individualized doses of somatropin 10 mg administered with the ZomaJet. The primary endpoint

was proportion of patients discontinuing treatment due to unacceptable transjection-related local tolerability reactions. Secondary endpoints included cumulative assessment of local tolerability reactions at initiation and weeks 2, 6, and 12 by the local investigator, followed by evaluation of transjection area photographs by a central dermatologist. Immediate local tolerability reactions and adverse events (AEs) were also assessed. Patients at 1 site were then enrolled in a 24-week extension study.

**Results:** Patients (N=27) with a mean (SD) age of 10.3 (3.8) years received a mean (SD) number of 78.6 (14.6) transjections. One patient (3.7%; 95% confidence interval: 0.1%, 19.0%) withdrew because of an unacceptable transjection-related local tolerability reaction. The majority of reactions (74%–98%) were classified as mild in severity. Bruising and punctual hemorrhage were the most frequently reported reactions by week 12 per both local (58%–62%) and central (50%–58%) assessments. One reaction (bruising) was classified as severe by the local investigator but moderate by the central assessor. Most immediate local tolerability reactions decreased in incidence starting 15 minutes after transjection. Three AEs were reported: influenza (n=2) and application site pain (n=1; patient withdrew). No AEs or unexpected reactions occurred in the 24-week extension (n=6).

**Conclusions:** Incidence of local tolerability reactions with somatropin 10 mg administered via the ZomaJet needle-free transjector was low; more data are needed to precisely determine the incidence of unacceptable reactions.

P1-1203

## TWO NOVEL CASES OF PERMANENT NEONATAL DIABETES MELLITUS CAUSED BY HOMOZYGOUS MUTATIONS IN THE GLUCOKINASE GENE

*Nancy S Elbarbary, MD; Mona A Salem, MD, Ain Shams University, Cairo, Egypt; Elisa De Franco, PhD; Sian Ellard, Prof., University of Exeter Medical School, Exeter, United Kingdom*

**Objectives:** Permanent neonatal diabetes (PND) caused by homozygous mutations in the glucokinase gene (*GCK*) is rare and only few cases have been reported so far. Heterozygous *GCK* mutations cause maturity-onset diabetes of the young (MODY2).

**Methods:** We report two girls, first cousins, 1<sup>st</sup> in order of birth, born to consanguineous parents. Both were born full-term with intra-uterine growth-retardation after an uneventful pregnancy. Both patients presented with persistent hyperglycaemia and glycosuria within the first two days of life and were treated with insulin. They both tested negative for anti-insulin and islet cell antibodies at the age of 4 months. Excluding diabetes, both are otherwise healthy children with no diabetes-related chronic complications and good glycemic control. Both fathers have non progressive, impaired fasting glucose and slightly elevated HbA1c values. The mothers were found to be mildly hyperglycaemic and

both had gestational diabetes during their subsequent pregnancy.

**Results:** Genetic analysis using PCR and direct sequencing found a novel homozygous missense mutation, p.H50D, in exon 2 of the *GCK* gene in both patients. This C>G mutation at nucleotide 148 (c.148C>G) results in the substitution of the amino acid aspartic acid (acidic charged polar) for histidine (basic charged polar) at codon 50 (p.His50Leu). Current evidence suggests this mutation is likely to be pathogenic. The parents were heterozygous for the mutation.

**Conclusions:** We report two PND cases caused by a novel homozygous missense mutation in the *GCK* gene in two families with MODY2. Coexistence of PND, parental consanguinity and a family history of mild hyperglycaemia should always prompt testing of the *GCK* gene since heterozygous carriers have a mild phenotype (MODY2) and homozygotes present with PND. As MODY2 is usually a silent disorder, fasting blood glucose testing in the parents of every infant with PND should be a must, even if there is no family history of diabetes.

P1-1204

## NON-INSULINOMA HYPERINSULINEMIC HYPOGLYCEMIA IN ADOLESCENT

*Ana G Garibay-Aldana, MD; Jeorgina Borda-Riveros, MD; Alexandra Vimos-Tixi, MD; Nicole M Monteverde, MD; Arturo Del Monte-Moran, MD; Elisa M Vazquez-Rochin, MD; Ana Paola De Cossio, MD; Ana Paola Lopez-Lopez, MD; Iñaki Gonzalez-Baque, MD; Viviana Gonzalez-Muñoz, MD; Leticia Ramos-Avellaneda, MD; Netzi Sanchez-Cruz, MD, Instituto Nacional de Pediatría, Mexico DF, Mexico*

**Objectives:** Hyperinsulinemic hypoglycemia (HH) presents as hypoglycemia during fasting, exercise or the postprandial period. These symptoms are either adrenergic (sweating, tremor, palpitations, tachycardia, agitation or hunger) or neuroglycopenic (impaired consciousness, speech, memory or blurred vision, ataxia, seizures or loss of consciousness). In adults the Whipples triad is seen more frequent.

**Methods:** We present a 17 year old female patient, who visited to neurologist for intermittent episodes of altered mental status including auditory, visual hallucinations, and seizures. Because of her Neurological symptomatology she was hospitalized and treated with antipsychotics and benzodiazepines. They documented hypoglycemia in several times, and was referred to our Hospital for the investigation of this recurrent severe hypoglycemia episodes. No family history events compatible with hypoglycemia. She presented predominantly postprandial hypoglycemia.

**Results:** Documenting plasma glucose 30mg/dl, normal state acid-base balance, b-hydroxybutyrate 0.1mmol/L, insulin 28.3U/ml, C-peptide 6.6ng/mL, cortisol 14.3ug/dL, ACTH 50.3pg/mL. Hyperinsulinemic hypoglycemia was diagnosed. Molecular study was requested. Imagine studies, Ga-68-DOTA-TOC, showed increased and diffuse uptake throughout the pancreas. We started treatment with low carbohydrate

meals and diazoxide, allowing reduction of intravenous glucose supply.

**Conclusions:** In children congenital Hyperinsulinism is the most common cause for HH and it typical presents in early infancy. Beyond infancy HH may also be due to another diagnosis than insulinoma, that are considered to be rare and some patients (4% in adults) with fasting endogenous hyperinsulinemic hypoglycemia, having islet hypertrophy, hyperplasia, enlarged and hyperchromatic beta cell nuclei. The first-line is medical therapy, if there is no response, surgical management (partial pancreatectomy) is recommended.

P1-1205

**THE EFFECTIVENESS IF SIROLIMUS TREATMENT IN TWO RARE DISORDERS WITH NONKETOTIC HYPOINSULINEMIC HYPOGLYCEMIA**

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**Objectives:** “Nonketotik-hypoinsulinemic hypoglycemia (NkHH)” is a very rare problem of increasing glucose consumption without hyperinsulinism. This disorders was first reported in cases with AKT2 mutation that functions at the insulin signalling pathway. Rarely, a similar type of hypoglycemia can be developed with the mutation of a tumor suppressor gene called PTEN. In those cases, no effective therapy was implemented in addition to frequent feeding to counter hypoglycemia.

mTOR inhibitor Sirolimus was being used in hyperinsulinemic hypoglycemia that was unresponsive to other medical treatment. In insulin signaling pathway, both AKT2 and PTEN play a role before mTOR. However, the role of sirolimus on hypoglycemia in AKT2 and PTEN mutations is not known.

**Methods:** In this paper, the effect of sirolimus in two cases with NkHH is presented.

**Results:** Case 1: Six monts old female patient was admitted to the clinic with proptosis, achantosis nigricans and NkHH. Genetic analysis revealed the AKT2 mutation (c.49G>A (p.E17K). Frequent feeding was unsucesful for treating the hypoglycemia, and proptosis was getting worse. Sirolimus was started at 3 years of age. Blood glucose (BG) levels were increased to normal levels (mean BG before treatment: 48-52 mg/dl/day, after treatment 77-108 mg/dl/day) .

Case 2: A male case with epidermal nevi, lypomatosis, mental retardation, gastrointestinal poliposis, cronic renal insufficiency was diagnosed with tumor hamartomatous syndrome, and genetic analysis revealed a PTEN mutation (p.G132V (c.395G>T). NkHH was appeared at 16 years of age (fasting BG: 27 mg/dl, fasting insulin1.5 mmol/L, while ketone negative). Hypoglycemia was persistent, even though there was no known causes of hypoglycemia, including congenital metabolic disorders were not detected. Sirolimus was started, and hypoglycemia was succesfully controlled (mean

BG before treatment: 46-64 mg/dl/day, after treatment 86-92 mg/dl/day).

**Conclusions:** NkHH is a very rare and important disorder, which carried some difficulties in both diagnosis and treatment. AKT2 and also PTEN mutations could lead to NkHH. Sirolimus treatment, as making mTOR inhibition, seems to be effectively controlling the peristent hypoglycemia, and could be a lifesaving tool for those kind of disorders.

P1-1206

**CONTINUOUS GLUCOSE MONITORING SYSTEM AND CYSTIC FIBROSIS**

*Mariana Zorron Mei Hsia Pu, MD; Aline C Gonçalves, Dentist; André Moreno Morcillo, PhD; Walter J Minicucci, MD; José D Ribeiro, PhD; Antonio F Ribeiro, PhD, University of Campinas, Campinas, Brazil*

**Objectives:** To determine the glycemic profile of patients with cystic fibrosis using a continuous glucose monitoring system (CGMS).

**Methods:** Observational study that evaluated CGMS data from 39 patients with cystic fibrosis who were treated at a referral center. The patients were 10–19.9 years old, and were categorized according to whether they had normal results (27 patients) or glucose intolerance (12 patients) during the OGTT.

**Results:** The maximum interstitial glucose level among individuals with normal OGTT results was 174.9 ± 65.1 mg/dL, compared to 170.4 ± 40.9 mg/dL among individuals with glucose intolerance (p = 0.773). The CGMS revealed that 18 of the 27 patients with normal OGTT results had peak interstitial glucose levels of >140 mg/dL, and that 12 of these individuals had peak levels of >200 mg/dL.

**Conclusions:** The present study revealed that CGMS could detect hyperglycemia among patients with cystic fibrosis and "normal" OGTT results.

Table 1. Interstitial glucose values and lengths of CGMS according to OGTT results.								
		n	Média	DP	Min.	Mediana	Máx.	p
Mínimo do Sensor (mg/dL)	NGT	27	60,8	12,7	40	63	80	0,360
	IGT	12	56,7	10,3	40	58,5	73	
Média do Sensor (mg/dL)	NGT	27	97	10	78	100	116	0,419
	IGT	12	95,3	7,2	79	96,5	103	
Máximo do Sensor (mg/dL)	NGT	27	174,9	65,1	98	164	400	0,773
	IGT	12	170,4	40,9	119	158	267	
Tempo Total (min.)	NGT	27	4193,5	496	2475,0	4255,0	5800,0	0,573
	IGT	12	4151,3	315,1	3520,0	4282,5	4475,0	

OGTT: oral glucose tolerance test; SD: standard deviation; Min: minimum; Max: maximum; NGT: normal glucose tolerance; IGT: impaired glucose tolerance.  
P-values were calculated using the Mann-Whitney test.

# CONTINUOUS INTRAGASTRIC DEXTROSE AS AN ADJUNCTIVE THERAPY FOR REFRACTORY HYPOGLYCEMIA IN CONGENITAL HYPERINSULINISM

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**Objectives:** Patients with congenital hyperinsulinism (HI), the most common cause of persistent hypoglycemia in infants and children, may benefit from dextrose given continuously via gastrostomy or nasogastric tube if medication or pancreatectomy do not result in euglycemia. Little is known about the long-term effects of this therapy. We sought to describe growth, feeding patterns, and adverse events in infants with HI exposed to continuous intragastric dextrose (IGD).

**Methods:** Retrospective cohort study of infants with HI treated with continuous IGD at our institution from 2009 - 2015. Data are from caregiver interviews and medical record review. Primary outcomes were proportion of subjects overweight at 0, 6, and 12 (+/- 2) months after initiation and changes in weight-for-length (WFL) Z-scores. Secondary outcomes included proportion receiving enteral nutrition (EN) and adverse events while managed with IGD.

**Results:** Of 27 subjects, 20 (14 M) had complete data for analysis. *ABCC8* mutation was the most common cause of HI (15/20), and diffuse disease was predominant (17/20). All subjects were placed on continuous IGD due to failure to maintain adequate fasting euglycemia despite medical management or pancreatectomy ( $\geq 90\%$  removal in 12/14). Median age at IGD initiation was 73 days (range 17-316). At 6 and 12 months after initiation, WFL Z-scores were unchanged from baseline (median Z-scores at 0, 6, 12 months: 0.97, 1.38, 1.12;  $p > 0.05$  for all, Wilcoxon signed-rank test), and percentage obese (WHO WFL  $> 97.7^{\text{th}}$  percentile for age/sex) was unchanged (26%, 35%, 30%,  $p > 0.05$  for all, McNemar's test). At 12 months, supplemental EN use was significantly lower than baseline (38% vs 71%,  $p = 0.02$ , McNemar's test).

Hyperglycemia was noted in 4/23 subjects, and hypoglycemia in 6/23 while managed with IGD. Emesis (4/23), diarrhea (1/23), and edema (0) while receiving IGD were infrequent, while tube/pump malfunction was common (18/23).

**Conclusions:** Over a median follow-up of 1 year, IGD was well-tolerated, with no increased risk of becoming obese or experiencing significant adverse events. Further studies are needed to determine whether IGD, by maintaining euglycemia while allowing on-demand oral feeding, may facilitate transition from EN to oral feeds.

# SERUM LEPTIN LEVELS IN ACUTE MALNOURISHED CHILDREN : ROLE IN METABOLIC ADAPTATION.

Sangita Yadav, MD; Priyanka Meena, MBBS; Prof T K Mishra, MD; Prof A P Dubey, MD, Maulana Azad Medical College, University of Delhi, New Delhi, India

**Objectives:** Background: Malnourished children have decreased subcutaneous fat leading to low serum leptin levels, stimulating hypothalamic-pituitary –adrenal(HPA) axis and hypothalamic – pituitary-growth hormone (HPG) axis to maintain high cortisol and growth hormone levels for effective lipolysis to ensure energy supply to brain and peripheral tissues during nutritional deprivation. Limited studies suggested role of serum leptin in metabolic adaptation to prolonged nutritional deprivation.

**Objective:** Evaluation of serum leptin in children with acute malnutrition and its role in metabolic adaptation.

**Methods:** Thirty 6-36 months malnourished children (weight for length/height 0 to +2 SD) after approval of institutional ethical committee and parental consent, growth parameters evaluated and fasting venous sample collected for estimation of serum leptin using enzyme linked immunoassay (ELISA) test, serum insulin by electrochemiluminescence and blood sugar by glucose oxidase method. Insulin resistance measured by Homeostasis Model Assessment index (HOMA-IR), value of  $^32$  taken as indicator of insulin resistance. Statistical analysis done using software version SPSS 23.0.

**Results:** Mean age, weight, height, BMI in cases and controls were  $16.6 \pm 9.07$  and  $16.3 \pm 0.89$  months,  $6.4 \pm 1.53$  and  $10.1 \pm 1.96$  kgs,  $70.8 \pm 8.48$  and  $77.0 \pm 8.96$  cms and  $12.7 \pm 1.09$  and  $16.9 \pm 0.93$  kg/ respectively ( $p = 0.00$ ). Serum leptin in cases  $0.9 \pm 0.28$  ng/ml and in controls  $3.96 \pm 1.09$  ng/ml,  $p = 0.00$  and it had positive correlation with BMI in both groups ( $r = 0.94$ ,  $r = 0.86$ ,  $p = 0.00$ ). Mean HOMA in cases  $0.5 \pm 0.21$  and in controls  $1.43 \pm 0.62$ ,  $p = 0.00$  which did not correlate with BMI. Controls had positive correlation between HOMA and leptin ( $r = 0.75$ ,  $p = 0.00$ ) though it was not significant in malnourished ( $r = 0.01$ ,  $p > 0.05$ ). Receiver operator characteristic (ROC) analysis of serum leptin to predict malnutrition was 1.16 ng/ml, with a sensitivity 88% and specificity 80%.

**Conclusions:** Serum leptin is lower in malnourished children and had positive correlation with BMI, making it a sensitive indicator of nutritional status. Lower HOMA in malnourished children indicated no insulin resistance. However, absence of correlation of HOMA with leptin in malnourished but correlation among controls shows metabolic adaptation to nutritional deprivation.

THE USE OF CASE-BASED VIDEO LECTURES TO IMPROVE RESIDENTS' KNOWLEDGE AND CONFIDENCE IN PEDIATRIC SUBSPECIALTY ROTATIONS

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**Objectives:** To determine the effectiveness of case-based video lectures on residents' knowledge and confidence in pediatric sub-specialty rotations.

**Methods:** 1) Kern's 6 step process to medical education curriculum development was followed.

2) Three pediatric sub-specialty rotations are participating in the study in order to improve power and generalizability. (inpatient pediatric ID, inpatient pediatric neurology, and outpatient pediatric endocrinology)

3) In order to determine effectiveness of case-based video lectures, a pre-test and post-test has been developed to determine baseline knowledge and confidence prior to the rotation, as well as after the rotation has been completed.

4) The tests are being reviewed by other fellows and faculty for fairness and relevance. Test/re-test reliability is being assessed.

5) The first 6 months of the study will be collection of historical control data used to assess the current curriculum in place.

6) Brief and easily implementable video lectures are being created to cover cases residents will most likely encounter while on the respective rotation. This should improve ease and uniformity of teachings.

7) The new curricula will be implemented. Residents will have protected time on the first day of the rotation to complete the 5-7 short video lectures. Pre-test/post-test data will be collected for 6 months. This will occur immediately after the initial 6 months of the historical control data collection. This is to maintain ethical standards of an educational study

8) Faculty/fellows involved with creation of curriculum will be assessed on ease of implementation of curriculum

9) Data will be analyzed. We expect at least 18 residents to be in historical control group as well as intervention groups

**Results:** In progress

**Conclusions:** Not available

METABOLOMICS OF PRADER WILLI SYNDROME: MACRONUTRIENT REGULATION OF INCRETIN SECRETION AND LIPID METABOLISM

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**Objectives:** Striking increases in body fat and reductions in lean body mass in Prader Willi syndrome predispose to glucose intolerance and sleep apnea. Attempts to control

weight and prevent metabolic decompensation in PWS through dietary interventions have had variable and limited success, in part because the pathogenesis of hyperphagia and weight gain and roles of macronutrients in weight control have not been elucidated. We compared fasting and postprandial levels of hormones and metabolites in 8 PWS children fed, sequentially, *low carb*(15%carb; 65%fat; 20% protein) and *low fat* diets (65%carb; 15%fat; 20% protein) diets matched for calories and protein content.

**Methods:** Blood was obtained prior to and during controlled administration of diets for 72 hours.

**Results:** Relative to the low fat (LF) diet, the low carbohydrate (LC) diet increased fasting and post-prandial GLP-1 levels; reduced post-prandial insulin and the ratio of ghrelin/GLP-1; increased FFA and fatty acid oxidation (FAO), as assessed by even-chain acylcarnitines; and reduced fasting TG and the TG/HDL ratio despite increases in branch chain amino acids (BCAA). There were no changes in glucose, GIP, PYY, or adiponectin; CRP (10.9 vs 4.2 ug/ml, p<0.01), AST (25.9 vs 17.8 U/L, p<0.001), and ALT (18.3 vs 9.9 U/L, p<0.01) were higher with LC feeding. (See Table 1)

**Conclusions:** Potential benefits of carbohydrate restriction in PWS may include fat mobilization and oxidation; reductions in the TG/HDL ratio, a marker of insulin resistance; and a decrease in the ratio of fasting ghrelin to GLP-1, which might limit food intake. However increases in CRP, AST, and ALT warrant concern.

	LC fasting	LF fasting	LC post-prand	LF post-prand
GLP-1, pg/ml	20.0±3.6*	12.3±2.9	34.2±5.0*	22.4±5.1
Insulin, pg/ml	595.8±195.4*	564.9±111.2	833.5±239.6*	2663.0±1015.0
Ghrelin/GLP-1	50.6±17.1*	103.4±28.6	24.9±3.6	47.4±12.2
FFA, mmol	1.14±0.17*	0.62±0.06	0.65±0.09**	0.16±0.03
FAO (even-chain acylcarnitines)	Increased***		Increased***	
TG, mg/dl	71.3±6.9*	120.1±26.0	83.6±15.2	118.6±33.9
HDL, mg/dl	55.3±4.7*	48.5±3.8	54.7±5.3	50.8±3.3
TG/HDL	1.40±0.21*	2.75±0.73	1.63±0.28	2.64±0.93
BCAA (sum uM)	639.1±40.2**	438.4±24.2	762.0±38.6	639.1±40.2

Values are mean±SE. \*p<0.05, \*\*p<0.01, \*\*\*p<0.001, LC vs LF

STEROID INDUCED CUSHING SYNDROME: THE CLINICAL APPLICATION OF SERIAL PLASMA SYNTHETIC GLUCOCORTICOID MEASUREMENTS VIA LIQUID CHROMATOGRAPHY-TANDEM MASS SPECTROMETRY

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**Objectives:** Cases of pediatric iatrogenic Cushing syndrome due to intraarticular or intradermal administration of triamcinolone acetonide have been reported. Some affected individuals also develop adrenal insufficiency requiring supplemental steroid (i.e. hydrocortisone). There have been no reports regarding the utility of plasma synthetic glucocorticoid measurements in addition to routine clinical evaluation to guide hydrocortisone treatment. We now



present a case series of patients diagnosed with iatrogenic Cushing syndrome secondary to triamcinolone, a potent hydrocortisone analog, and discuss the value of serial plasma synthetic glucocorticoid measurements via liquid chromatography-tandem mass spectrometry (LC-MS/MS) as a guide for clinical management.

**Methods:** We describe the clinical and laboratory findings of two patients referred to the pediatric endocrinology clinic for cushingoid features after receiving intradermal injections of Kenalog-40 (triamcinolone acetonide 40 mg/ml). Sequential laboratory testing was done to monitor patient progress. The laboratory tests included LC-MS/MS measurements of plasma synthetic glucocorticoid levels, morning serum cortisol, and ACTH.

**Results:** Patient 1 was a 15-year-old who developed cushingoid symptoms after receiving a total of 1840 mg of intradermal Kenalog-40 over 2 months for right-sided macrodactyly. This patient presented to the pediatric endocrinology clinic 3 months after the last injection. Patient 2 was a 17-year-old who developed cushingoid symptoms after receiving a total of 2800 mg intradermal Kenalog-40 over 2 months for kerosene burns. This patient presented to the clinic 2 months after the last injection. Both patients were confirmed to have elevated levels of triamcinolone. They were also diagnosed with iatrogenic adrenal insufficiency based on laboratory testing. Serial plasma synthetic glucocorticoid measurements were utilized to provide appropriate counseling and guide subsequent weaning of hydrocortisone.

**Conclusions:** Synthetic steroid levels as assessed by LC-MS/MS should be incorporated to provide objective criteria for hydrocortisone wean and to provide reassurance to the patient and their families.

Tables:

Patient 1			
Approximate duration since the last triamcinolone acetonide injection	3 months	5 months	8 months
Time when the sample was drawn	9:12 AM	9:36 AM	9:20 AM
Triamcinolone acetonide level (mcg/dL)	0.59	0.42	0.22
Reference range: Less than or equal to 0.10 mcg/dL			
Cortisol level (ug/dl)	<0.5	17.1 <sup>A</sup>	<0.1 <sup>B</sup>
Reference range: Morning cortisol: 7-22 ug/dl			
ACTH level (pg/ml)	<5	---	<5
Reference range: 5-52 pg/ml			
<sup>A</sup> Receiving Hydrocortisone 5 mg twice per day (~7.1 mg/m2/day)			
<sup>B</sup> Receiving Hydrocortisone 5 mg once per day (~3.6 mg/m2/day)			

Patient 2							
Approximate duration since the last triamcinolone acetonide injection	2 months	3 months	4 months	6 months	8 months	13 months	18 months
Time when the sample was drawn	8:48 AM	10:21 AM	12:17 PM	12:17 PM	16:13 PM	13:43 PM	7:42 AM
Triamcinolone acetonide level (mcg/dL)	0.47	0.22	0.15	0.23	Negative	Negative	---
Reference range: Less than or equal to 0.10 mcg/dL							
Cortisol level (ug/dl)	<0.5	---	---	---	---	---	11.0 <sup>A</sup>
Reference range: Morning cortisol: 7-22 ug/dl							
ACTH level (pg/ml)	<5	---	---	---	---	---	---
Reference range: 5-52 pg/ml							
<sup>A</sup> Receiving Hydrocortisone 5 mg every other day (~1.1 mg/m2/day) - sample drawn 24-28 hours after dose of hydrocortisone.							

P1-1216

**TODDLER WITH MATURITY ONSET DIABETES OF THE YOUNG (MODY) TYPE 4**

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Trainee & Intern , Rainbow Children's Hospital , Bangalore, India; Anshuman Senapati, Trainee & Intern, Rainbow Children's Hospital, Bangalore, India

**Objectives:** To screen for monogenic diabetes in a toddler with autoantibodies negative diabetes mellitus and preserved pancreatic beta-cell function

**Methods:** We present a 2 year 10 month old girl with episodic polyuria, polydipsia and hyperglycemia with absence of ketoacidosis and elevated HbA1C of 9% at diagnosis. Autoantibodies titres (Islet Cell Antibody, Insulin Antibody and Glutamic Acid Decarboxylase [GAD 65] Antibody) were negative, she had detectable C-peptide level of 1.6 ng/ml and elevated random insulin level of 23.6 mcU/ml at a plasma glucose level of 209 mg/dl before starting treatment. Strand Clinical Exome Test was performed on the patient's DNA. Nextera technology was utilized in the enrichment of target sequences. The generated library was subjected to next-generation sequencing (NGS) on the Illumina NGS platforms (MiSeq and NextSeq). Variations were identified using the STRAND-NGS software and interpreted using the StrandOmics platform.

**Results:** It was found that the individual harbored one copy (heterozygous) of a missense variant in exon 1 of Pancreatic Duodenal Homeobox protein 1 (PDX1) gene.

**Conclusions:** Homozygous PDX1 mutations are a rare but important cause of isolated autosomal recessive permanent neonatal diabetes mellitus. Heterozygous mutations of the PDX1 gene cause a rare subtype of autosomal dominant MODY type 4, hitherto reported only in a few adults from few families. Our case report represents not only the youngest patient with MODY type 4 reported so far but also a unique PDX1 mutation.

All toddlers with diabetes mellitus and negative autoantibodies need to be screened for monogenic causes.

**POSTER SESSION 1**  
**Thursday, September 14, 2017, 5:45-6:45pm**  
**P1 - Puberty**  
**P1-1300 – P1-1321**

P1-1300

**MEASUREMENT OF ESTRADIOL IN SERUM BY GAS CHROMATOGRAPHY-TANDEM MASS SPECTROMETRY; COMPARISON WITH A SENSITIVE EXTRACTION-RIA FOR APPLICATION IN PEDIATRICS**

Carina Ankarberg-Lindgren, PhD; Jovanna Dahlgren, Professor, Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden; Mats X Andersson, PhD, University of Gothenburg, Göteborg, Sweden

**Objectives:** Serum estradiol (E2) serves as an important diagnostic marker in a variety of clinical conditions. At present, rapid high-performance automated immunoassay instruments are most commonly used. However, these assays



commonly overestimate the low concentrations found in children. The use of specific and sensitive mass spectrometry methods is growing rapidly. Nevertheless, a challenge is still to enhance assay sensitivity for determination of E2 in the lowest range such as in prepubertal children.

The objective was to validate a recently developed gas chromatography-tandem mass spectrometry (GC-MS/MS) method for determination of E2 in children and compare with ultra-sensitive extraction-RIA (lower limit of detection (LoD) 4 pmol/L).

**Methods:** E2 (200µl sample) was extracted in hexane:ethyl acetate solution from serum spiked with isotopically labelled internal standard and derivatized sequentially with pentafluorobenzyl bromide (PFB-Br) and pentafluoropropionic acid anhydride. Pure reference compounds (17β-E2, Cerilant<sup>tm</sup>, Sigma-Aldrich) were used to optimize chromatography and mass transitions for multiple reaction monitoring. GC-MS/MS was carried out on an Agilent (Montréal, Canada) GC 7890B coupled to an Agilent 7000 triple quadrupole mass spectrometer. The detector was operated in negative mode using methane as reagent gas. To evaluate the concordance between GC-MS/MS and extraction E2 RIA and validity of GC-MS/MS for pediatrics, left-over routine samples were used.

**Results:** LoD for the GC-MS/MS method was assessed to 2 pmol/L (0.5 pg/mL). Total imprecision was 20% for 9 pmol/L (2.5 pg/mL), 6% for 36 pmol/L and 5% for 270 pmol/L. The correlation coefficient was r=0.97, p<0.001, n=184 between extraction-RIA and GC-MS/MS. Prepubertal girls had significantly lower E2 concentrations (median <2; range <2-12 pmol/L, n=11, p<0.001) compared to girls at Tanner breast stage 2 (B2) (22; <2-89 pmol/L, n=15, p<0.001). Girls with B2 had lower E2 than girls at Tanner breast stage 3-5 (130; 37-1160 pmol/L, n=14, p<0.001).

**Conclusions:** We report development of a GC-MS/MS method sensitive enough to accurately determine serum levels of estradiol in children.

P1-1301

**CLINICAL AND ULTRASOUND REPRODUCTION PARAMETERS IN A COHORT OF 317 HEALTHY TEENAGE GIRLS**

*Maria Assens, MD; Liv Dyre, BS/BA; Anette T Pedersen, Associate Professor; Karin Sundberg, MD; Lisa N Jensen, MD; Katharina M Main, MD, PhD, Professor, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark*

**Objectives:** The objective of this cross sectional study is to ascertain reproductive function in a cohort of 317 healthy teenage girls examined 2015-2016.

**Methods:** 317 girls with a median age of 16 years had a clinical examination including transabdominal ultrasound of the internal genitalia, serum sample and a questionnaire on menarche and menstrual bleedings. 2D and 3D ultrasound scans aimed for cycle day 2-5 included number of follicles 2-5mm, 5-8mm, >8mm and volume measurements of ovaries and uterus. Ovaries with cysts were excluded prior to statistical analyses.

All ultrasound scans were conducted with Voluson E8 Ultrasound System (GE Healthcare Medical Systems, Zipf, Austria) with a multifrequency transabdominal probe (RM6C, 3– 8 MHz) and analyzed with 4D View software (GE Medical System, v 9.1). Anti-Müllerian hormone (AMH) was analyzed with immunoassay and DHEAS with LC-MS/MS. Statistical significance was tested with Pearson correlation analyses.

**Results:** Table 1 shows characteristics of the girls and ultrasound scans. Three of four girls with an ovary volume above 20 cm<sup>3</sup>, had a dominant follicle over 15 mm. 18 girls (6.1%) had more than 25 2-8mm follicles and 112 girls more than 20. Uterine volume was significantly correlated to years since menarche (p<0.001, r=0.29) and to age at examination (p<0.001, r=0.20).

14 girls were examined further due to incidental findings: 10 ovarian cysts (one dermoid cyst was surgically removed, one hemorrhagic cyst), 3 for evaluation of growth and 1 was known with Turner syndrome.

296 out of 305 (97%) had experienced menarche. 200 girls (68.5%) reported regular menstruation, 67 girls (23%) irregular and 25 girls (8.5%) did not know. 161 girls (67.1%) out of 240 girls who were not on oral contraceptives reported cycle length of 21-35 days, 17 (7%) reported cycle length >35 days and 5 girls (2.1%) reported cycle length <21 days. 62 girls (20.7%) were on hormonal contraceptives. 199 (66.3%) answered no to any current use of contraceptives including condoms.

**Conclusions:** Two third of healthy girls age 16 years reported regular menstrual patterns 3 years after menarche and no use of contraceptives. The number of small follicles was higher than in adult women, which most likely reflects their younger age.

Table 1 – Age at time of examination and menarche and time since menarche. Ultrasound volume measurements and sum of follicles for both ovaries.

	n	10p	Median	90p
Age of girls at time of examination, years	317	14.9	16.1	17.2
Age of girls at time of menarche, years	284	11.6	13.3	14.6
Years since menarche	284	1.1	2.9	5.0
Uterus volume, cm <sup>3</sup>	293	31.8	46.8	63.1
Right ovarian volume, cm <sup>3</sup>	292	4.1	7.0	11.5
Left ovarian volume, cm <sup>3</sup>	289	3.4	6.2	10.4
Number of follicles 2-4.9 mm	293	9	13	18
Number of follicles 5-7.9 mm	270	2	5	9
Number of follicles > 8 mm	145	1	1	3
AMH	285	11.6	24.6	50.0
DHEAS	282	2030.7	4279.8	7542.7

P1-1302

**FASTING INSULIN PREDICTS ELEVATED FREE TESTOSTERONE LEVELS AFTER RECOMBINANT HUMAN CHORIONIC GONADOTROPIN IN OVERWEIGHT GIRLS**

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San Diego, La Jolla, CA, United States; John C. Marshall, MD; Christopher R. McCartney, MD, University of Virginia, Charlottesville, VA, United States

**Objectives:** In our studies, 60% of obese pubertal girls have androgen excess (a precursor to polycystic ovary syndrome), but sources remain unclear. We examined ovarian androgens in overweight (OW) girls using adrenal suppression and ovarian stimulation tests.

**Methods:** We studied girls, Tanner stages 3-5, who were normal weight ([NW] BMI%-for-age<85; n=11; age 14.0±2.8 [mean±SD]) or OW (BMI%-for-age ≥85; n=12; age 13.9±2.6). In the mid-follicular phase, we measured LH q10min from 7pm–7am, and gave dexamethasone 1mg po at 10pm. At 7am, testosterone (T) was drawn and recombinant hCG given (r-hCG; 25 mcg IV). T and hCG were measured 24h later. Group data were compared using t-tests. Determinants of free T were analyzed via multiple linear regression.

**Results:** Fasting insulin was 3.3-fold higher (NW 6.7±1.5 [mean±SEM]; OW 22.1±4.6 uU/mL; p=0.008) and SHBG 51% lower (NW 45.6±5.7; OW 23.2±4.4 nmol/L; p=0.006) in OW girls. Mean LH (NW 4.5±0.6; OW 4.7±0.7 mIU/mL; p=0.8) and post-treatment hCG (NW 28.7±1.6; OW 28.6±6.6 mIU/mL; p=1.0) were not different.

Mean post-dexamethasone free T was 2.4-fold higher in OW girls, but was not significant (NW 7.4±1.3; OW 17.5±4.8 pmol/L, p=0.07). Post-r-hCG free T was 2.4-fold higher in OW girls (NW 10.4±1.6; OW 24.5±5.6 pmol/L; p=0.03). Absolute (NW 3.0±1.0; OW 7.0±7.1 pmol/L; p=0.1) and percent (NW 60±26; OW 77±24%; p=0.6) free T changes with r-hCG were not significantly different.

The regression model mean LH+insulin\*+BMI SD best predicted post-dexamethasone free T ( $R^2=0.67$ ,  $p<0.0001$ ; \*independent predictor [ $p<0.05$ ]). The model mean LH+insulin\*+BMI SD+hCG best predicted free T 24-h after r-hCG ( $R^2=0.69$ ,  $p<0.0001$ ). Insulin alone gave similar  $R^2$  values ( $p<0.0001$ ) for both models. Absolute free T change was best predicted by insulin\*+hCG ( $R^2=0.20$ ,  $p=0.04$ ).

**Conclusions:** Our data imply higher ambient non-adrenal (i.e., non-ACTH-dependent) free T levels in OW girls. Significantly higher free T post-r-hCG suggests increased capacity for ovarian androgen production in OW girls. Fasting insulin was the strongest predictor of both post-dexamethasone and post-hCG free T. Taken together, these data suggest a central role of insulin-augmented ovarian androgen excess in OW late pubertal girls.

P1-1303

#### LONGITUDINAL DESCRIPTION OF GONADAL FUNCTION IN SICKLE CELL PATIENTS TREATED WITH BONE MARROW TRANSPLANT USING ALKYLATOR BASED CONDITIONING REGIMENS

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**Objectives:** Alkylator based conditioning regimens for bone marrow transplant (BMT) place patients at high risk for gonadal dysfunction. Reduced intensity of the alkylators cyclophosphamide(CY) and busulfan(BU) for BMT conditioning have been used in sickle cell anemia (SCA) in hopes of reducing gonadal late effects. The purpose of this study is to describe the longitudinal effect of different conditioning regimens on gonadal function after alkylator based BMT for SCA.

**Methods:** A retrospective chart review was done to abstract gonadal outcomes and BMT treatment data on sixty subjects (31 females, 29 males) with SCA (HgbSS, HgbSC) who received a matched-sibling BMT. Mean age at time of BMT was 8.9 years (range 1.8-19.9 years) and mean time from BMT was 8.5 years (range 0.75-23 years). Twenty-eight subjects received cumulative doses of CY 200mg/kg, BU 14mg/kg and anti-thymocyte globulin (ATG), 27 subjects CY 180mg/kg, BU 12.8mg/kg, ATG and fludarabine (FLU), with 4 receiving a similar regimen with the CY dose decreased to 120mg/kg. One subject received a cumulative BU dose 12.8mg/kg, rabbit ATG and FLU. Charts were reviewed for serial measurements of gonadotropins, testosterone in males and serum anti-mullerian hormone (AMH), a marker of ovarian reserve, in females.

**Results:** Sixty-two percent (13/21) of pubertal aged females had gonadal failure (Follicle-Stimulating Hormone(FSH) >40mIU/L x2). AMH levels were obtained in 4 females prior to BMT with all normal for age and assay. Post-BMT all AMH levels were undetectable for 7 years after transplant. Three females had a small increase in AMH in years 8,9 and 12 but levels were still below the normal range for age and assay. One subject treated with CY 200mg/kg, BU 14mg/kg and ATG had a spontaneous pregnancy at age 18 with prior menopausal FSH and undetectable AMH. Serum testosterone in males remained at age-appropriate levels despite time from BMT and conditioning regimen; FSH was normal in 78% (14/18) and mildly elevated in 4 (max 14 IU/L).

**Conclusions:** Conditioning regimens for BMT in SCA, despite decreasing doses of CY and BU, result in most females having gonadal failure and all females having low AMH levels while males have normal testicular hormonal function.

P1-1304

#### DIURNAL VARIATION OF GONADOTROPIN LEVELS IN GIRLS WITH EARLY STAGES OF PUBERTY

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**Objectives:** Pubertal gonadotropin secretion shows circadian pattern and the luteinizing hormone (LH) levels tend to rise in later stages of puberty in girls. We studied the usefulness of basal LH in the evaluation of central precocious puberty with emphasis on the influence of sampling time.

**Methods:** Medical records of 334 girls that underwent gonadotropin-releasing hormone stimulation test (GnRHST)

were reviewed. Auxological and laboratory data were compared between those with early morning (EM, before 10AM) and late morning/afternoon (LM/A, after 10AM) basal samples. To compare the EM and LM/A data in the same patient, subgroup analysis was performed in 16 girls (all of whom were in SMR 2) who underwent GnRHST on different time range. To determine the optimal cutoff of basal LH levels for predicting the positive result, the receiver operating characteristic (ROC) curves were analyzed.

**Results:** Among subjects in sexual maturity rating (SMR) 2, EM samples showed higher basal LH compare to LM/A samples ( $0.32 \pm 0.56$  vs.  $0.15 \pm 0.27$ ,  $P=0.004$ ), whereas those in SMR 3 showed no difference in LH levels between EM and LM/A samples ( $0.42 \pm 0.65$  vs.  $0.41 \pm 0.66$ ,  $P=0.986$ ). Among girls with pubertal response, EM group showed higher basal LH and follicular stimulation hormone (FSH) than LM/A group ( $0.49 \pm 0.67$  vs.  $0.31 \pm 0.50$ ,  $P=0.031$  and  $3.9 \pm 1.9$  vs.  $3.2 \pm 1.5$ ,  $P=0.008$  for LH and FSH, respectively). The EM basal LH was more closely related with the peak stimulated LH than the LM/A basal LH did ( $r_s=0.871$  vs.  $r_s=0.524$ ) in subgroup analysis. In ROC curve analysis, the area under the curve (AUC) of basal LH in EM group was 0.773 (95% confidence interval [CI], 0.704 to 0.841,  $P<0.001$ ) and that in LM/A group was 0.732 (95% CI, 0.641 to 0.823,  $P<0.001$ ). The optimal basal LH cutoffs to predict a pubertal response to GnRHST were 0.11 IU/L with a sensitivity of 66.7% and a specificity of 78.7% in EM group, and 0.07 IU/L with a sensitivity of 60.0% and a specificity of 78.9% in LM/A group, respectively.

**Conclusions:** In girls with early stages of puberty, the early morning basal LH level is a more sensitive screening tool than the late morning or afternoon basal LH. Diurnal variation should be considered in evaluating girls with precocious puberty, especially in those with early stages of puberty.

P1-1305

#### THE IMPACT OF OVERWEIGHT AND OBESITY ON LUTEINIZING HORMONE SECRETION IN GONADOTROPIN-RELEASING HORMONE STIMULATION TESTS IN KOREAN GIRLS WITH CENTRAL PRECOCIOUS PUBERTY

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**Objectives:** Excess adiposity may influence various aspects of pubertal development, including the timing of pubertal initiation and hormonal parameters during puberty. Recent studies have showed that obesity and overweight appears to influence gonadotropin secretion. The aim of this study is to evaluate the impact of obesity and overweight on luteinizing hormone (LH) secretion in response to gonadotropin-releasing hormone (GnRH) stimulation testing in Korea girls with central precocious puberty (CPP).

**Methods:** Retrospective cohort study was carried out in all girls who were diagnosed with CPP and underwent GnRH stimulation tests at three tertiary centers in Korea. Subjects were classified as normal weight (BMI  $\geq 5$ th percentile and BMI  $\geq 85$ th percentile), overweight (BMI  $\geq 85$ th percentile and BMI  $< 95$ th percentile), and obese (BMI  $\geq 95$ th percentile).

**Results:** A total 233 girls with CPP was identified and included in final analysis. Mean age at diagnosis was  $7.5 \pm 0.8$  years. Of the 233 girls, 172 (73.8%) girls were normal weight, 40 (17.2%) were overweight, and 21 (9.0%) were obese. Median peak LH levels after GnRH stimulation were 12.0 (interquartile range [IQR], 6.1–17.1), 9.9 (IQR, 6.7–13.2), and 6.0 mIU/ml (IQR, 5.5–11.1) among normal weight, overweight, and obese subjects, respectively ( $P = 0.03$  for all comparisons). Peak LH/FSH ratio was not different in three groups (median 0.68, 0.61, and 0.70;  $P = 0.93$  for all comparisons). BMI standard deviation score was significantly and negatively associated with peak LH ( $\beta = -1.105$ ,  $P = 0.03$ ). Multivariate linear regression analysis indicated that Tanner stage ( $\beta = 4.573$ ,  $P = 0.009$ ) and difference between bone age and chronological age ( $\beta = 4.489$ ,  $P < 0.001$ ) were independently associated with peak LH after GnRH stimulation.

**Conclusions:** Our results suggest that overweight and obesity may influence the LH response to GnRH-stimulation testing in girls with CPP.

P1-1306

#### THE INFLUENCE OF GONADOTROPIN-RELEASING HORMONE AGONISTS ON BODY MASS INDEX IN GIRLS WITH CENTRAL PRECOCIOUS PUBERTY

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**Objectives:** Gonadotropin-releasing hormone agonist (GnRHa) is widely used for the treatment of central precocious puberty (CPP). However, there has been a concern about obesity after GnRHa administration. This study aimed to investigate the change in body mass index (BMI) in the course of and after GnRHa treatment among girls with CPP.

**Methods:** A total of 127 girls with CPP were included who were treated with GnRHa for  $\geq 2$  years. BMI standard deviation score (zBMI) for chronological age (CA) and bone age (BA) at start of GnRHa treatment (Visit 1) was compared to BMI at 1 year after GnRHa treatment (Visit 2), at the end of GnRHa treatment (Visit 3) and at 6-12 months follow up after GnRHa discontinuation (visit 4) according to BMI status at Visit 1.

**Results:** At the Visit 1, normal weight group was 97 (76.4%) and overweight and obese group was 30 (23.6%). CA and BA at Visit 1 were  $8.5 \pm 0.5$  and  $10.1 \pm 0.7$  years, respectively. Total duration of GnRHa treatment and follow-up after discontinuation were  $2.8 \pm 0.5$  and  $0.73 \pm 0.27$  years, respectively. No statistical difference in zBMI for CA was detected in both groups between Visit 1 and Visit 4 ( $-0.06 \pm 0.61$  vs.  $0.00 \pm 0.76$  for normal weight group,  $P = 0.357$ ;  $1.54 \pm$

0.36 vs.  $1.50 \pm 0.54$  for overweight and obese group,  $P = 0.591$ ). However, zBMI for BA in both groups showed an increasing tendency between Visit 1 and Visit 4 ( $-0.47 \pm 0.61$  vs.  $-0.10 \pm 0.67$  for normal weight group,  $P < 0.001$ ;  $1.10 \pm 0.43$  vs.  $1.36 \pm 0.54$  for overweight and obese group,  $P = 0.002$ ). The number of study participants with normal weight, overweight and obesity was 97, 22 and 8 at Visit 1 and 100, 16 and 11 at Visit 4, which showed no significant difference ( $P = 0.480$ ).

**Conclusions:** Overall, zBMI for CA in girls with CPP showed no significant increase after discontinuation of GnRHa treatment, regardless of BMI status at Visit 1. However, zBMI for BA increased after follow up period. Long-term follow-up among girls with CPP is required to monitor BMI changes till they attain adult height.

P1-1307

# OVARIAN FUNCTION IN YOUNG ADOLESCENTS CONCEIVED AFTER ASSISTED REPRODUCTIVE TECHNIQUES

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**Objectives:** The aim of the study was to evaluate ovarian function, including menstrual cycle patterns, ovulation and granulosa cell function in adolescents conceived after assisted reproductive techniques (AcART), compared with adolescents that were spontaneously conceived (AcSP). **Methods:** We evaluated AcART ( $n=12$ ) and AcSP ( $n=49$ ) during 2 years following menarche. Clinical evaluation and hormonal profiles were performed during follicular phase. Ovulation was determined by salivary progesterone measured on days 13,18,23,28 of the menstrual cycle in two consecutive cycles. A cut-off level  $>0.06$  ng/ml was used to diagnose ovulation (Sensitivity 90% and specificity 100%). Granulosa cell function was evaluated by the measurement of Anti-Müllerian Hormone (AMH) and Inhibin-B (INHB). Menstrual disorders were not an exclusion criteria for control adolescents. Oligomenorrhea was defined by persistent cycles  $>45$  days. Non parametric statistics were used. All parents and patients gave their informed consent and assent, respectively.

**Results:** AcART were born at a similar gestational age, but had lower birth weight compared with AcSP ( $3314 \pm 608$  and  $3467 \pm 484$ g,  $p=0.031$ , respectively). Both groups were evaluated at similar age, and had similar pubertal development and age of menarche ( $12.3 \pm 1.1$  and  $11.9 \pm 1.0$  years in AcART and AcSP,  $p=0.96$ , respectively). Oligomenorrhea was more prevalent in AcART than in AcSP (27% vs 6.5%,  $p=0.044$ , X<sup>2</sup>-Pearson), despite similar cycle length (AcART:  $36.0 \pm 13.7$  and AcSP:  $33.2 \pm 7.8$  days,  $p=0.92$ ). The adolescents in both groups showed no differences in

anthropometric variables, and similar prevalence of acne and hirsutism.

AcART showed similar ovulation frequency compared to AcSP (50% vs. 47.4%,  $p=0.6$ , respectively). However, AcART had lower AMH ( $3.1 \pm 1.6$  vs.  $6.0 \pm 3.7$  ng/ml,  $p=0.024$ ), and higher serum INHB ( $67.8 \pm 30.7$  vs.  $43.7 \pm 27.4$  pg/ml,  $p=0.049$ ) than AcSP. Both groups showed similar gonadotrophins, estradiol and testosterone levels (Table).

**Conclusions:** Despite an increased prevalence of oligomenorrhea, ovulatory function is preserved in AcART. The finding of lower serum AMH and higher serum INHB levels suggest impaired granulosa cell function. Future studies should investigate whether these preliminary results are indicative of a risk of ovarian dysfunction later in life in AcART (Fondecyt11130240).

	AcSP (n=49)	AcART (n=12)
Age at evaluation (years)	$13.9 \pm 1.4$	$13.9 \pm 1.2$
AMH (ng/ml)	$6.0 \pm 3.7$	$3.1 \pm 1.6^*$
Inhibin B (pg/ml)	$43.7 \pm 27.4$	$67.8 \pm 30.7$
FSH (mIU/ml)	$5.7 \pm 1.6$	$6.7 \pm 1.2$
LH (mIU/ml)	$2.9 \pm 1.4$	$3.4 \pm 1.6$
Estradiol (pg/ml)	$43.5 \pm 15.0$	$41.7 \pm 16.3$
Testosterone (ng/dl)	$40 \pm 18$	$38 \pm 18$

\* $p<0.05$ , \*\* $p<0.005$

P1-1308

# EARLY/PRECOPIOUS PUBERTY IN CHILDREN WITH PRE/PERINATAL HYDROCEPHALUS

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**Background.** It has been reported previously that children with hydrocephalus (HC) run increased risk of developing early or precocious puberty (E/PP). This has been shown in children in which HC was combined with myelomeningocele (MMC) (1, 2) and in children with HC operated with shunt (3). **Aim.** To study incidence of E/PP in patients afflicted by HC and to identify risk factors for development of early or precocious puberty.

**Methods:** All patients with pre/perinatal HC, born 1980-2002, treated with shunt, living in the counties of Uppsala, Västmanland and Örebro ( $n=117$ ) were included. Data was obtained from hospital records. One hundred and one patients (48 girls) had sufficient data for evaluation of puberty. Twenty-seven of the 48 girls (56%) and 18 of the 53 boys (33%) had MMC. Early puberty was defined as pubertal signs before 9 years and 2 months of age for girls and 10 years and 2 months for boys. Precocious puberty was defined as pubertal signs before 8 years in girls and 9 years in boys. **Results:** Early or precocious puberty occurred in 48/30 girls (63%) and 12/53 boys (23%). Median ages for start of puberty were 8.5 and 9.3 years for girls with and without MMC, respectively. Corresponding figures for boys were 11.0 years and 11.6 years. Twenty-one of the 27 girls with MMC (78%) had E/PP. Eight of these were precocious. Nine of the 21 girls without MMC (43%) had E/PP and four of these were precocious. Three of the 18 boys with MMC (17 %) had E/PP. None of these was precocious. Nine of the 35 boys without

MMC (26%) had E/PP and one of these was precocious. Girls with MMC and E/PP had higher head circumference at birth compared with girls with MMC without E/PP ( $p < 0.001$ ).

**Conclusions:** HC is a strong risk factor for E/PP in both genders. However, girls with HC particularly those with MMC, have a higher risk to develop E/PP than boys. Increased head circumference already at birth further increases the risk to develop E/PP.

References:

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P1-1309

#### **PREMATURE PUBARCHÉ CAN BE CAUSED BY EXOGENOUS TESTOSTERONE GEL OR DIAPER RASH PREVENTION CREAM**

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**Objectives:** To describe the clinical features of 15 children who were referred to endocrine evaluation due to premature pubarche. All of them were exposed to exogenous androgenic or non-hormonal products.

**Methods:** We studied fifteen children (10 girls and 5 boys, aged from 0.3 to 6.8 years) with premature pubarche and/or virilization. Six of them were unintentionally exposed to testosterone gel (parental use). Nine cases were exposed to chronic and frequent use of diaper rash prevention creams.

**Results:** Moderate to severe virilization was detected in the 6 patients (two siblings) who were exposed to testosterone gel. These patients had pubic hair development (Tanner stage II and III) associated penile enlargement (2/2) or clitoromegaly (3/4), acne (2/6) and accelerated growth, but no bone age advance. All patients were tested for serum testosterone levels, but elevated testosterone levels were detected in only 4 patients, whose parents were still on testosterone gel usage (median: 90.5 ng/dL, range 44 - 685 ng/dL) associated with prepubertal gonadotropin levels and normal adrenal androgen precursors. Regarding of the 9 children, who were exposed to frequent diaper rash prevention creams, they had mild pubarche or pseudo pubarche (intermediate hair) without any other clinical manifestation of precocious pubertal development. Three of these patients exhibited a reduction of the pubic hair stage with cream discontinuation and 6 kept usage less without progression. Potential hair follicle growth stimulators (zinc oxide) present in the diaper rash prevention can be involved in the occurrence of intermediate hair in pubic region. Ten of 15 patients from both groups underwent unnecessary hormonal and imaging workup.

**Conclusions:** Unintentionally exposure of children to androgen products has been associated with virilization in both sexes. A intermediate pubic hair development could be secondary to chronic and intense use of diaper rash prevention cream. Physicians evaluating children with precocious pubarche and/or virilization signs must inquire during medical history about the use of androgen by the parents or the extreme use of diaper rash prevention cream to avoid misdiagnosis and further and expendable investigation.

P1-1310

#### **THE CHANGING PROFILES OF HORMONES IN PROGRESSING PUBERTAL BOYS —BASED ON THE PROSPECTIVE TREATMENT RESEARCH OF IDIOPATHIC HYPOGONADOTROPIC HYPOGONADISM (IHH)**

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**Objectives:** To investigate the changing hormone profiles of progressing pubertal boys and get the cutoffs of hormones starting point of puberty in boys.

**Methods:** Perspective design lasting 12 weeks observation, a total of 22 male 13-16 years old. IHH patients from October 2015 to November 2016 were recruited. These patients were treated with the same regime of GnRH pump. The testicular volume and gonadotropin, testosterone, AMH, INHB levels were measured at week 0, the end of the first week, the 4<sup>th</sup> week and the 12<sup>th</sup> week with the LHRH stimulation test. We observed the changes of testes volume and hormones during treatment. We developed the picture of the hormones profiles. At last we used the ROC to get the cutoffs value of different hormones.

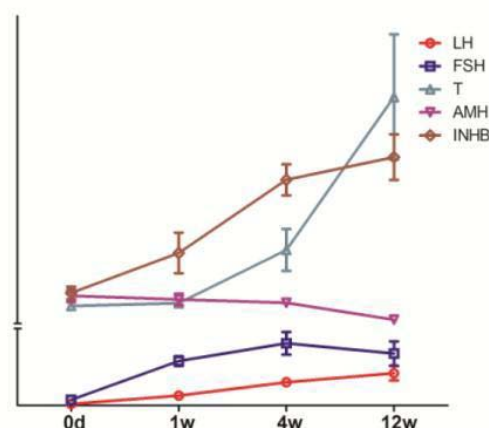
**Results:** The basal FSH at the end of first week after treatment was significantly higher than that pretreatment. Then it did not climb up obviously at week 4 and 12. The basal LH was dramatic increase. And it was still significantly increased at week 4 and showed no differences from then on to week 12. While, the basal T was undetectable until week 4 it was rise in 45% subjects. Stimulated LH began increase at the end of week 4. Stimulated T increased gradually and 50% patients have begun to rise until week 4. Meanwhile, 100% patients of stimulated T already elevated until week 12. Anti-Müllerian hormone (AMH) was persistent at a high level until 12<sup>th</sup> week began to fall down followed by increasing of Inhibin B (INHB) starting from week 1 gradually to week 4 and 12. Moreover, INHB were significant difference in week 1, 4 and 12 (Figure1). Our data showed that INHB increased from 52.70±19.44 pg/ml to 80.10±24.88 pg/ml during the first week and 4<sup>th</sup> week. Furthermore, there is a positive correlation between LH and T from week 4 to 12 and a negative correlation between FSH and INHB from week 4 to 12 (Figure2). Based on week 4 hormones rising, the receiver operating characteristic (ROC) curve analysis was introduced to obtain the cutoff of LH it means puberty initiating when LH  $\geq 5.96$  mIU/ml (Area= 0.804,  $p < 0.05$ ). Sensitive was 100% and specific was 64.3%. Testis volumes were increased in all

patients after 12 weeks therapy. Testis volumes increased significantly than penis, and earlier than penis. Extended follow up, the patients began to appear beards or pubic hair. And 3 patients appear spermatorrhea after 6 months.

**Conclusions:** Hormones profiles of progressing puberty boys presented increasing sequence are INHB and FSH in week 1. Subsequently, LH and T began to increase in 4<sup>th</sup> week. Then AMH was fell at week 12. We demonstrated that puberty was initiated when the range of INHB is 50-80 pg/ml. AMH is not sensitive to the onset of puberty. The changes of related characteristics were fall behind the changes of hormones.

The changing profiles of hormones in progressing pubertal boys

Figure 1



P1-1311

## WHEN DO CAMEROONIANS REACHED THEIR PUBERTAL STAGES?

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**Objectives:** We aimed to determine the timing of onset of sexual maturity indicators among Cameroonian children and factors that influence the onset of this maturation.

**Methods:** We did a cross-sectional study including 1382 children of both sex aged 8-15 years and living in urban areas. For each participant, we collected sociodemographic data, nutritional status and anthropometrics parameters. Secondary sexual characteristics were recorded according to Tanner staging.

**Results:** In girls, the median ages (95% CI) of stage 2 pubic hair growth (P2) and stage 2 breast development (B2) were 8.73 (8.31-9.04) years and 8.89 (8.53-9.17) years, respectively. The median age of menarche was 13.03 (12.47-13.83) years. In boys, the median ages (95% CI) of stage 2 testicular development (G2) and stage 2 pubic hair growth (P2) were 9.63 (9.32-9.89) years and 10.05 (9.73-10.09) years respectively.

**Conclusions:** Cameroonian boys and girls, living in urban areas reach their puberty precociously as the African American children.

P1-1312

## CHANGES IN HORMONE LEVELS AND UTERINE SIZE IN KOREAN GIRLS ACCORDING TO THEIR BREAST TANNER STAGES

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**Objectives:** The purpose of this study was to measure changes in the mean levels of major hormones that can affect pubertal development, breast tanner stage, and uterine size in Korean girls according to their pubertal development stages, thereby evaluating their sexual maturity.

**Methods:** The participants of this study were the patients who visited Cheju Halla General Hospital with suspected precocious puberty between January 2015 and January 2017. The participants were divided into 4 groups according to their Tanner stages I,II,III and IV using a breast sonogram. For each stage, their E2 (estradiol), LH, FSH, DHEA, IGF-1, and IGFBP3 levels that could affect their pubertal development were measured. During the same period, their uterine sizes were measured using a pelvic sonogram.

**Results:** The total sample of 269 subjects consisted of 42 girls at stage 1, 119 girls at stage 2, 71 girls at stage 3, and 37 girls at stage 4. The mean E2 levels(pg/mL) were  $3.07 \pm 6.59$  at stage 1,  $9.35 \pm 13.30$  at stage 2,  $11.18 \pm 14.85$  at stage 3, and  $26.20 \pm 14.52$  at stage 4 ( $p=0.000$ ). The mean Basal LH levels(IU/L) were  $0.37 \pm 0.50$  at stage 1,  $0.62 \pm 0.85$  at stage 2,  $1.42 \pm 2.20$  at stage 3, and  $3.89 \pm 2.99$  at stage 4 ( $p=0.000$ ). The mean DHEA levels(ug/dl) were  $49.79 \pm 30.70$  at stage 1,  $67.73 \pm 43.13$  at stage 2,  $73.92 \pm 60.91$  at stage 3, and  $89.71 \pm 40.55$  at stage 4 ( $p=0.002$ ). The mean IGF-1 levels(ng/ml) were  $316.73 \pm 701.09$  at stage 1,  $258.00 \pm 63.54$  at stage 2,  $359.82 \pm 495.97$  at stage 3, and  $428.49 \pm 103.56$  at stage 4 ( $p=0.085$ ). The mean IGFBP-3 levels(ng/ml) were  $4205.72 \pm 1001.29$  at stage 1,  $4582.77 \pm 643.67$  at stage 2,  $4796.15 \pm 937.37$  at stage 3, and  $5219.19 \pm 762.64$  at stage 4 ( $p=0.000$ ). A GnRH stimulation test showed that the mean LH peak levels(IU/L) were  $2.69 \pm 1.32$  at stage 1,  $9.45 \pm 9.58$  at stage 2,  $17.43 \pm 15.84$  at stage 3, and  $31.39 \pm 19.07$  at stage 4 ( $p=0.000$ ). The mean uterine lengths(cm)were  $1.93 \pm 0.40$  at stage 1,  $2.49 \pm 0.60$  at stage 2,  $2.94 \pm 0.67$  at stage 3, and  $4.12 \pm 0.71$  at stage 4 ( $p=0.000$ ).

**Conclusions:** The study showed statistically significant increases in hormone levels and uterine size in the subjects according to their pubertal development stages. Therefore, using these variables may have diagnostic values in evaluating sexual maturity.

PLEASE SEE TABLE ON FOLLOWING PAGE

**Table 1.** Demographic characteristics of the patients in each breast tanner stage.

	STAGE I	STAGE II	STAGE III	STAGE IV	P
N	42	119	71	37	
CA	8.10±1.43	8.70±0.85	8.92±0.88	9.62±1.03	0.000
BA	9.09±1.06	10.09±0.87	10.51±0.90	11.55±0.91	0.000
BA-CA	0.92±0.96	1.4±0.82	1.59±0.87	1.93±1.03	0.000
Ht	127.38±7.78	131.47±6.30	134.2±6.16	141.96±8.02	0.000
Ht-SDS	0.27±1.04	0.42±0.94	0.65±1.07	1.14±1.18	0.002
Wt	32.17±6.19	31.19±6.88	33.82±7.32	38.29±8.18	0.000
Wt-SDS	1.03±1.07	0.47±0.95	0.72±1.03	0.9±0.89	0.001
BMI	19.76±2.84	17.89±2.67	18.62±2.79	18.82±2.38	0.000
BMI-SDS	1.22±1.07	0.39±1.02	0.61±1.02	0.56±0.75	0.000

Data expressed as mean±standard deviation. P values were among the groups. N, numbers; CA, chronological age; BA, bone age; BA-CA, difference between bone age and chronological age; Ht, height(cm); Ht-SDS, height standard deviation score; Wt, weight(kg); Wt-SDS, weight standard deviation score; BMI, body mass index; P, percentile.

**Table 2.** Hormonal characteristics of the patients in each breast tanner stage.

	STAGE I	STAGE II	STAGE III	STAGE IV	P
N	42	119	71	37	
E2	3.07±6.59	9.35±13.30	11.18±14.85	26.20±14.52	0.000
LH	0.37±0.50	0.62±0.85	1.42±2.20	3.89±2.99	0.000
FSH	2.14±1.99	2.87±1.62	3.89±4.79	5.04±1.79	0.000
DHEA	49.79±30.70	67.73±43.13	73.92±60.91	89.71±40.55	0.002
IGF-1	316.73±701.09	258.00±63.54	359.82±495.97	428.49±103.56	0.085
IGFBP3	4205.72±1001.29	4582.77±643.67	4796.15±937.37	5219.19±762.64	0.000
GnRH test N	16	78	52	24	
GnRHtest%	38.09	65.55	73.24	64.86	
GnRHtest: LH peak	2.69±1.32	9.45±9.58	17.43±15.84	31.39±19.07	0.000

Data expressed as mean±standard deviation. P values were among the groups. N, numbers; E2, estradiol(pg/mL); LH, luteinizing hormone(IU/L); FSH, follicle stimulating hormone(IU/L); DHEA, dehydroepiandrosterone(ug/dl); IGF-1, insulin-like growth factor 1(mg/mL); IGFBP3, insulin-like growth factor binding protein(ng/mL); GnRH, gonadotropin-releasing hormone; P, percentile.

**Table 3.** Uterine size in each breast tanner stage.

	STAGE I	STAGE II	STAGE III	STAGE IV	P
Uterine length(cm)	1.93±0.40	2.49±0.60	2.94±0.67	4.12±0.71	0.000
Uterine transverse diameter(cm)	1.2±0.41	1.5±0.36	1.67±0.33	2.29±0.66	0.000

Data expressed as mean±standard deviation. P values were among the groups.

and sex matched controls who were seen at the general pediatrics clinic from 2010 to 2011. The primary outcome investigated was change in BMI Z score from baseline to two time points. Statistical analysis was completed using two-sample Wilcoxon rank-sum tests.

**Results:** Children with ICPP had a higher baseline BMI Z score when compared to normal children (0.985 vs 0.45, p=0.002). This difference persisted throughout treatment. At time of cessation of treatment, however, there was no statistically significant difference in BMI change from initial BMI between treatment and control groups (0.135 vs -0.01, p=0.284).

**Conclusions:** For children with ICPP treated with leuprolide compared to controls, BMI Z scores were significantly higher prior to and after completion of therapy. However, there was no significant difference in BMI Z score change from start to completion of treatment. Therefore, the absolute difference in BMI at the end of treatment may be attributable to differences in baseline BMI. Thus, our data support that leuprolide does not cause a significant increase in BMI in children with ICPP. In fact, suppression of puberty may help to reduce the rate of BMI increase seen in ICPP. Our study was limited by small sample size and subjects lost to follow up. Additional studies with larger sample sizes are needed to further investigate the relationship between ICPP, leuprolide, and BMI.

**Table 1:** Differences in change in median BMI Z scores between patients treated with leuprolide and control group

	Change in Median BMI z-score Treatment Group	Change in Median BMI z-score Control Group	P value
Time 1	0.985 (n=66)	0.45 (n=198)	0.002
Time 2	0.165 (n=66)	-0.02 (n=189)	0.002
Time 3	0.135 (n=26)	-0.01 (n=184)	0.284

**Table Key:**

Time 1 = BMI at Initial visit

Time 2 = Change in BMI at 1 year into treatment vs control BMI at 1 year +/- 6 months

Time 3 = Change in BMI at cessation of treatment vs control BMI at 25 months +/- 6 months

**Table 2:** Descriptive Statistics of treatment group

	Median	Q1	Q3	IQR
Age start	8.8	7.92	9.75	1.83
Treatment duration	2.5	1.42	3.36	1.94
Tanner stage at start	3	2	3	1
Bone Age at start	11	10	11.75	1.75
<b>BMI z scores</b>				
Pre treatment	0.985	0.27	1.5	1.23
1 yr into treatment	1.1	0.25	1.54	1.29
0-6 mo post treatment	1.31	0.46	1.79	1.33

P1-1313

## THE EFFECT OF LEUPROLIDE ON BMI IN TREATMENT OF IDIOPATHIC CENTRAL PRECOCIOUS PUBERTY : A RETROSPECTIVE COHORT STUDY

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**Objectives:** Gonadotropin releasing hormone analogs (GnRHa) are an accepted treatment for idiopathic central precocious puberty (ICPP). However, there have been conflicting reports of the effect of treatment with GnRHa on future obesity. In the current literature, little research specifically studies leuprolide, and available research primarily follows longitudinal changes in an individual's BMI during treatment. This retrospective cohort study investigates the impact of treatment of ICPP with leuprolide on BMI by comparing BMI Z score change during and after treatment with BMI change in controls.

**Methods:** We identified 66 cases of ICPP treated with leuprolide for at least one year between January 2000 and November 2015 at A.I. DuPont Hospital for Children. These patients were compared to a 3:1 randomized selection of age



### THE PHYSIOLOGICAL INCREASE OF GH SECRETION IN PUBERTY REDUCES INSULIN SENSITIVITY - A RANDOMIZED CLINICAL CLAMP TRIAL

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**Objectives:** Puberty is defined by the development of secondary sex characteristics and accelerated linear growth velocity. Although overt type 2 diabetes is uncommon in adolescents, reduced insulin sensitivity of up to 50% is recorded in puberty. Excessive growth hormone (GH) secretion causes type 2 diabetes e.g. in acromegaly, but it is uncertain whether the physiological increase of GH secretion during puberty directly reduces insulin sensitivity. This study was designed to investigate the role of GH in reduced insulin sensitivity during puberty.

**Methods:** GH deficient (GHD) subjects without other hormonal deficiencies in puberty constitute a clinical model to study the physiological effect of GH on insulin sensitivity. Six boys with GHD in Tanner stage II to IV (daily GH dose  $1.4 \pm 0.2$  mg, age  $13.2 \pm 0.5$  years, height  $154 \pm 2$  cm, BMI  $19.5 \pm 1.0$  kg/m<sup>2</sup>, HbA1c  $36.2 \pm 1.6$  mmol/mol) were included. GHD was diagnosed according to international guidelines. Each subject was investigated in the basal postabsorptive fasting state for 2.5 hours followed by a hyperinsulinemic euglycemic clamp (insulin i.v.  $40$  mU/m<sup>2</sup>/min) for 2.5 hours three times in a randomized trial: With 1) regular GH substitution dose (GH), 2) an extra GH bolus of 50% of usual GH dose (GH+), and 3) no GH substitution for 6 days (control). Plasma glucose was clamped at  $5.0$  mmol/l and insulin sensitivity was estimated by glucose infusion rates (GIR) during the last 30 minutes of the clamp.

**Results:** Baseline plasma glucose was not affected by GH treatment (mmol/l):  $5.3 \pm 0.3$  (GH) vs.  $5.0 \pm 0.1$  (GH+) vs.  $4.8 \pm 0.1$  (control),  $P = 0.18$ . Insulin sensitivity was reduced by GH treatment (mg glucose/kg/min):  $5.5 \pm 0.6$  (GH) vs.  $5.8 \pm 0.8$  (GH+) vs.  $7.9 \pm 0.8$  (control),  $P = 0.015$ .

**Conclusions:** GH treatment did not impact on fasting basal plasma glucose concentrations, but induced insulin resistance as measured by the hyperinsulinemic euglycemic clamp. We propose that the physiological increase of GH secretion during puberty directly reduces insulin sensitivity.

P1-1315

### RANDOM SERUM LH LEVEL AND PELVIC SONOGRAPHIC FINDINGS IN SCREENING FEMALE CENTRAL PRECOCIOUS PUBERTY

*Seung Heo, MD, Dankook University Hospital, Cheonan, Korea, Republic Of; Jeeseuk Yu, MD, Dankook University College of Medicine, Cheonan, Korea, Republic Of*

**Objectives:** GnRH stimulation test (GnRHST) is considered as the gold standard in diagnosing central precocious puberty (CPP). The authors conducted a study to find a cutoff value of random LH level and pelvic sonographic findings as the screening method of female CPP.

**Methods:** Study subjects were divided into 4 groups according to the chronological ages and the results of GnRHST. Retrospective review and statistical analysis of medical records were done including clinical characteristics, blood test, bone age, and pelvic sonographic findings.

**Results:** Among 126 girls, 25 belonged to CPP group (age <8 and peak LH  $\geq 5$  IU/L), 19 into non-CPP group (age <8 and peak LH <5 IU/L), 61 into EP group ( $8 < \text{age} < 9$ , and peak LH  $\geq 5$  IU/L), and 21 into non-EP group ( $8 < \text{age} < 9$ , and peak LH <5 IU/L). Random LH and FSH levels as well as dominant ovary volume were significantly different in CPP compared to non-CPP by univariate and stepwise multivariate logistic regression analysis. The study showed that LH level of  $0.245$  IU/L and ovary volume of  $1.67$  mL could be used as cutoff values in screening CPP.

**Conclusions:** The serum LH level and ovary volume measurement were found to be useful for the screening test of CPP. The best cut-off values were  $0.245$  IU/L and  $1.67$  mL, respectively.

P1-1316

### PRIMARY OVARIAN FAILURE AND POLYCYSTIC OVARIAN SYNDROME – PART OF A SPECTRUM?

*Laila Al-Hashmi, MD, Central Manchester University Hospitals NHS foundation Trust, Manchester, United Kingdom; Maria Estabanez, MD, Central Manchester University Hospital NHS Foundation Trust, Manchester, United Kingdom; David Ray, Professor; Kay Metcalfe, MD; Jill Urquhart, PhD; Newman William, Professor; Leena Patel, Professor, Central Manchester University Hospital NHS Foundation Trust, Manchester, United Kingdom; Peter Clayton, Professor, University of Manchester, Manchester, United Kingdom*

**Objectives:** Ovarian dysfunction (OD) in adolescence has many causes, which include the development of the polycystic ovarian syndrome (PCOS), characterised by irregular periods or amenorrhoea, abnormal gonadotrophin secretion and hyperandrogenism. A rare cause of OD is primary ovarian failure (POF), characterised by oligo or amenorrhoea and raised gonadotrophins, due to a single gene mutation (including STAG3, SYCE1, MCM8, MCM9 and HFM1).

**Methods:** We describe three sisters from consanguineous parents, exhibiting features of both PCOS and POF. One sister has recently been identified to carry a homozygous mutation in MCM9 c.244C.T; p. (Gln82Ter). The other two are being asked if they wish to be tested for this mutation.

**Results:** All three 46XX sisters presented in mid to late adolescence with hirsutism, obesity, and raised LH and/or FSH (Table 1). Two have never menstruated; including the one with the MCM9 mutation, and the third had a normally-timed menarche but now has irregular periods. Two have acanthosis nigricans, including the one with the MCM9

mutation. The sister with the MCM9 mutation has learning difficulties. Mother also has hirsutism.

**Conclusions:** Homozygous mutations in MCM9 are associated with POF and short stature (Am J Hum Gent 2014). These sisters have a mixed picture of POF and PCOS, in particular the index case (II). If cases I and III are shown to carry the MCM9 mutation, this will extend the phenotype of this condition.

Cases	Age (yrs)	Age of presentation (yrs)	Height At presentation (SDS)	Spontaneous puberty – breast stage	Menarche (yrs)	FSH (lu/L)	LH (lu/L)	Oestradiol (pmol/L)	Testosterone / SHBG (nmol/L)	Other features	Treatment	MCM9 gene mutation
I	22	20	-	5	13	8.8	52	909	2.1 / 40	Hirsutism Obesity	-	Consent sought
II	20	13	-1.1	4	Not achieved	43	19	65	0.9/ 25	Hirsutism obesity AN Learning difficulty	Ethinyl estradiol	Positive
III	18	15	1.2	3	Not achieved	5.8	13	114	4.4/15	Hirsutism Obesity AN	-	Consent sought

**Table (1):** Clinical and biochemical data on the three siblings, FSH: Follicle Stimulating Hormone, LH: Luteinising Hormone, SHBG: Sex Hormone Binding Globulin, AN: acanthosis nigricans, MCM9: Minichromosome Maintenance Protein 9.

P1-1317

**PSEUDOPUBERTY IN A 7 YEAR OLD BOY SUFFERING FROM CONGENITAL EXTRAHEPATIC BILIARY ATRESIA: IMPACT OF LIVER FAILURE AND PORTOCAVAL SHUNT ON STEROID METABOLISM.**

*Stefanie Graf, MD; Marie-Anne Burckhardt, MD, Department of Pediatrics (Division of Pediatric Endocrinology and Diabetology), Inselspital Bern, Bern University Hospital, University of Bern, Switzerland, Bern, Switzerland; Valérie Schwitzgebel, Professor, Children's University Hospital, Geneva, Switzerland; Susanne Schibli, MD, Department of Pediatrics (Division of Pediatric Gastroenterology, Hepatology and Nutrition), Inselspital Bern, Bern University Hospital, University of Bern, Switzerland, Bern, Switzerland; Christa E Flück, Professor, Department of Pediatrics (Division of Pediatric Endocrinology and Diabetology), Inselspital Bern, Bern University Hospital, University of Bern, Switzerland, Bern, Switzerland*

**Objectives:** Precocious puberty is defined as sexual development before the age of 8 years in girls and 9 years in boys. Central precocious puberty is caused by early maturation of the hypothalamic-pituitary-gonadal axis and is clinically apparent as breast development in girls and testicular enlargement in boys. By contrast, precocious pseudopuberty is gondadotropin independent and caused by either sex hormone production from gonads and adrenals, or from an hCG or sex hormone secreting tumor directly. Alternatively, exogenous hormone exposure may also cause pseudopuberty.

We report on an actually 11 year old boy with congenital extrahepatic biliary atresia, who had a Kasai procedure after birth and developed signs of precocious pseudopuberty some months after installation of a mesocaval shunt for portal hypertension at age 7.5 years. After surgery the patient showed penis enlargement without testicular growth and advanced bone age. Biochemically no signs of central precocious puberty, but elevated serum androgens

(androstendione, testosterone (T)) were found. The urinary steroid profile revealed excess excretion of T and DHT for age. Therefore, we hypothesized that the observed androgen excess (AE) was due to liver failure and mesocaval shunt causing decreased hepatic metabolism of steroids.

**Methods:** To prove our hypothesis, we performed imaging studies to rule out an androgen producing tumor. Furthermore, serum and urinary steroid profiling was performed basal and after dexamethasone inhibition.

**Results:** Ultrasound and CT scan revealed no tumor. Dexamethasone suppressed overall androgens in serum and in the 24h urine suggesting that steroids produced in the adrenals may not be metabolized once secreted in the blood stream. In addition, after the patient received a liver transplant, androgen levels normalized and pseudopuberty came to a halt.

**Conclusions:** Steroids are metabolized in the liver and thus hepatic cirrhosis and mesocaval shunt may cause androgen excess and pseudopuberty through lack of steroid inactivation. In the literature, we found 5 girls reported with androgen excess syndromes owing to liver failure and/or portocaval shunts. Our case seems to be the first description in a boy.

P1-1318

**TESTOTOXICOSIS WITH AN EPISODIC COURSE: AN UNUSUAL CASE WITHIN A SERIES**

*Zeina M Nabhan, MD, Indiana Univeristy School of Medicine, Indianapolis, IN, United States; Erica A. Eugster, MD, Indiana University School of Medicine and Riley Hospital for Children, Indianapolis, IN, United States*

**Objectives:** Familial male limited precocious puberty (FMPP) is caused by an activating mutation of the LH receptor. Affected males usually present at 2-6 years of age with precocious puberty (PP).Objective: To describe an unusual case of FMPP characterized by periodic remission compared to a series of boys with typical testotoxycosis.

**Methods:** Medical records of boys with FMPP followed at our institution from 2001-2016 were reviewed. Variables analyzed included age, family history, physical exam, hormone levels, bone age and treatment.

**Results:** A 2 10/12<sup>th</sup> year old boy with no family history of FMPP presented with PP, growth acceleration, and masturbatory behaviors. On exam he had 6 ml testes, an enlarged phallus (10.5 x 2.5 cm), and Tanner 2 pubic hair. Bone age (BA) was 5 6/12<sup>th</sup> years (BA/CA 1.97). Gonadotropins were undetectable, testosterone was 242 ng/dl (nl ≤ 30 ng/dl), 17-hydroxyprogesterone and βhCG were normal. Genetic testing revealed an Asp578Gly LH receptor mutation. Anastrozole 1 mg and bicalutamide 50 mg daily were started. During 7 1/2 years of follow-up, two periods of spontaneous remission occurred lasting > 3 years and 10 months, respectively. Both were characterized by prepubertal testosterone levels (10-28 ng/dl) a decrease in growth velocity to 4 cm/year and arrested pubertal development despite discontinuation of therapy. Relapses were marked by

elevated testosterone, growth acceleration up to 11 cm/year, pubertal progression and bone age advancement. At 9 4/12<sup>th</sup> years, central puberty was noted. Ten additional boys aged  $3.46 \pm 0.72$  years with FMPP were identified, one of whom also had an Asp578Gly mutation. Average testosterone at presentation was  $335 \pm 193$  ng/dl (range 146-778) and average BA/CA was  $2.02 \pm 0.47$ . All were treated with bicalutamide in combination with anastrozole in 9 and letrozole in 1. Eight patients developed secondary central PP.

**Conclusions:** We report a case of intermittent FMPP in contrast to a series of boys with a characteristic clinical course. To our knowledge a similar case has not previously been reported. This suggests modifying factors that can significantly ameliorate PP in testotoxicosis. Our case expands the clinical spectrum of this rare condition.

P1-1319

### OPTIMIZATION OF GROWTH IN PRECOCIOUS PUBERTY WITH GNRH ANALOGUES

Garima Chawla, MD, Sir Ganga Ram Hospital, New Delhi, India; Archana Arya, DO, Sir Ganga Ram Hospital, New Delhi, New Delhi, India

**Objectives:** To analyse the improvement in final/ predicted adult height (PAH) with early intervention in precocious puberty.

**Methods:** 102 patients with CPP had presented to our hospital from year June 2004 to June 2015 and were treated with the Triptorelin depot 3.75mg subcutaneous every 28 days.

Patients who were affected by other associated conditions like CAH and hypothyroidism, girls postmenarche and patients who received Growth hormone therapy in addition to GnRH analogs were excluded from the study. Radiographs of hand and wrist were evaluated according to Greulich and Pyle method. Adult height prediction both at the onset (PAH1) and at the end of the treatment (PAH 2) were performed by the Bayley Pinnaeu method. The patients were evaluated every three months.

Treatment was discontinued at a comparable bone age (BA) in relation to chronological age or when height velocity had decreased to <2cm/year.

Final height was defined as a growth rate of <0.5cm/year during preceding year with a bone age of >15 year.

Long term height gain was assessed by evaluating the difference between final height and PAH at the onset of therapy.

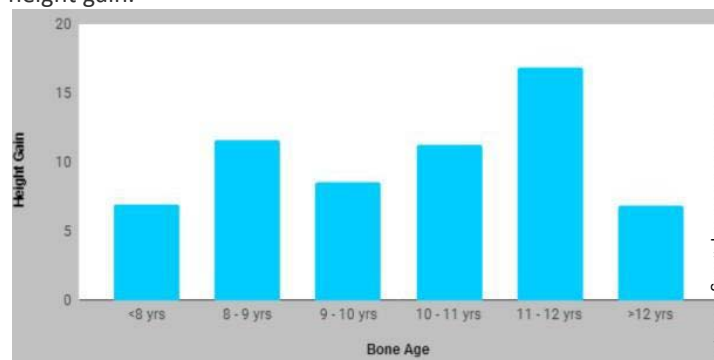
**Results:** Total 81 patients with CPP were included in the study which showed a female preponderance with 73 girls and 9 boys. Pituitary abnormality was detected in MRI brain of 6 patients, CPP being idiopathic in the rest of 76 cases. Delta (BA-CA) showed a significant decline post treatment. Mean difference of  $0.867 \pm 1.46$  was seen in Delta (BA-CA) pre and post GnRHa therapy which was highly significant with a value of <0.001.

Final height data of 24 patients was available and long term height gain was assessed which was found to be highly significant with a p value of 0.005.

Height gain showed a negative correlation with pre treatment BA with a p value of 0f <0.001 thereby proving a better outcome if treatment is started at an earlier BA. Initiating GnRHa after the BA of 12 compromised the height gain. However, no significant difference in height gain was seen in different age groups.

**Conclusions:** GnRha is an effective means to halt the advancing BA and reclaim the height potential in patients with a compromised PAH.

Initiating therapy at a lesser BA proves beneficial in terms of height gain.



P1-1320

### HORMONAL PARAMETERS IN PUBERTAL GYNecomastia

Zerrin Orbak, MD, Ataturk University, Erzurum, Turkey

**Objectives:** Gynecomastia is a benign proliferation of the mammary gland in males which might be unilateral or bilateral. It has been thought that the development of gynecomastia is due to the imbalance of between estrogens and androgens. The aim of this study was to define the auxologic features of children with pubertal gynecomastia and to investigate possible hormonal factors that may lead to development of gynecomastia.

**Methods:** This study is performed on 45 boys with gynecomastia and 45 control boys who are between 9-17 years old.

**Results:** Mean age of the study group was  $13.2 \pm 1.8$  years. Body mass index was found to be significantly higher in the study group ( $p < 0.01$ ). In cases with gynecomastia, total testosterone, estradiol, estradiol/testosterone rates, and FAI levels were higher ( $p < 0.001$ ). DHEA-S levels were higher but not statistically significant ( $p > 0.05$ ). Sex hormone binding globulin levels were similar ( $p > 0.05$ ). DHEA-S/testosterone ratio and DHEA-S/estradiol ratio were decreased in group with gynecomastia ( $p < 0.001$ ).

**Conclusions:** Our study showed that the imbalance between DHEA-S and testosterone levels, and also DHEA-S and estradiol levels as well as testosterone and estradiol levels may have a role in the development of pubertal gynecomastia.

# A NOVEL MKRN3 MUTATION IN SPORADIC CENTRAL PRECOCIOUS PUBERTY: A FIRST JAPANESE CASE

Miyuki Kitamura, MD, Kurume University School of Medicine, Fukuoka, Japan; Hirohito Shima, MD; Maki Fukami, PhD, National Research Institute for Child Health and Development, Tokyo, Japan; Junko Nishioka, MD; Shuichi Yatsuga, MD; Takako Matsumoto, MD, Kurume University School of Medicine, Fukuoka, Japan; Kikumi Ushijima, MD, National Research Institute for Child Health and Development, Tokyo, Japan; Yasutoshi Koga, Professor, Kurume University School of Medicine, Fukuoka, Japan

## Objectives: Background

Timing of puberty is defined by the complex interactions, such as environmental, nutritional, racial and genetic factors. Brain tumor, brain trauma, and gene mutations, including *KISS1R* mutation, are known to cause central precocious puberty (CPP). However, in a large number of cases, the main causes of CPP remain uncertain. To date, some articles have reported *MKRN3* mutations is a cause of CPP and its mutations is the most common genetic factor of familial CPP. Here we report the first case of CPP caused by *MKRN3* mutation in Japan.

## Methods: Case report

An 8-year-old Japanese girl was referred to our hospital by premature menarche. Her thelarche started at the age of 5 years. Her pubertal stage was Tanner 3 for breast and Tanner 2 for pubic hair. She showed growth acceleration with advanced bone age. Gonadotropin releasing hormone (GnRH) stimulating test showed pubertal stage. She was treated with appropriate GnRH analog immediately after diagnosing CPP, and is now well controlled. Genetic analysis was performed, and we found a novel frame shift mutation (p.Glu229Argfs\*3) in the *MKRN3* gene. Familial segregation analysis demonstrated that her father was an unaffected carrier of the same mutation.

## Results: Discussion

*MKRN3* encodes makorin RING-Finger 3 protein, an intronless gene located on chromosome 15q11.2, in the Prader-Willi syndrome critical region, suppress up-stream for hypothalamic-pituitary-gonadal axis. *MKRN3* mutations was reported to be the main genetic cause of familial CPP. Since this gene is maternally imprinted, and only the paternal allele is expressed, *MKRN3* mutations in maternally inheritance shows carrier state and have no CPP phenotype. To date, although we have investigated 25 Japanese patients with apparently sporadic CPP, we have found a *MKRN3* mutation only in this case. Since our patients were sporadic CPP cases, we cannot compare the prevalence of this mutation among familial CPP between previous reports and our study. However, we speculate that the prevalence of *MKRN3* mutations in the familial CPP is not common in the Japanese population.

## Conclusions: Conclusion

We show a novel *MKRN3* mutation in a Japanese CPP patient. The prevalence of CPP with *MKRN3* mutations may be rare in Japanese population.

# POSTER SESSION 1

Thursday, September 14, 2017, 5:45-6:45pm

## P1 - Quality improvement

### P1-1400 – P1-1413

P1-1400

## IMPLEMENTATION OF TRANSITION READINESS ASSESSMENT QUESTIONNAIRE (TRAQ) FOR ADOLESCENTS WITH TYPE 1 DIABETES: A QUALITY IMPROVEMENT PROJECT

Jacqueline T. Chan, MD; Claudia Boucher-Berry, MD; Karen Bernstein, MD, University of Illinois at Chicago, Chicago, IL, United States

**Objectives:** A growing body of literature addresses the need for transition programs for adolescents and young adults with chronic conditions, including T1DM. TRAQ is non-disease-specific self-report measures that assess self-management and advocacy skills of youth with special health care needs and is designed to measure skills needed to successfully transition from pediatric to adult healthcare. Implementing this tool as a first step for having a transition program in an institution will facilitate in the evaluation and process of transitioning adolescents with T1DM to an adult care provider

Objective is to assess readiness to transition of 80% of adolescents with type 1 diabetes ages 14 years old and older within 6 months using TRAQ tool

**Methods:** The intervention involved using TRAQ tool to assess readiness to transition. Physician staff and trainees were given instruction regarding the need for implementing a tool to assess readiness to transition of adolescents with T1DM. At the end of each phase, which lasted two months, medical records of adolescents with T1DM were reviewed. Using the Plan-Do-Study-Act (PDSA) cycle, interventions were added or adjusted at the start of subsequent phase in order to implement the tool better.

**Results:** At baseline, there were 0% of adolescents assessed. Seventy-six adolescents aged 14 years old to 20 years old were assessed for transition readiness from July 2016 to January 2017. Result show that the TRAQ tool can be successfully implemented in a routine office visit achieving response rate of > 80%. Phase 1 resulted in a 88% assessed patients. Phase 2 resulted in a 89% assessed patient. Finally, phase 3 resulted in a 100% assessed patients

**Conclusions:** TRAQ tool may be helpful for evaluating readiness to transition of adolescents with type 1 diabetes to an adult care provider. Interventions put in place between phases 1 and 3 resulted better percentages of assessed patients. With this initial assessment, scores of adolescents will be reviewed especially those who are 18 years and older. Interpreting the scores and evaluating who requires further education prior to transition is yet to be explored

IDENTIFYING FACTORS ASSOCIATED WITH SUCCESS FOR PEDIATRIC ENDOCRINOLOGIST PHYSICIAN-SCIENTISTS

Cecilia Gállego Suárez, MD; Julie Sturza, M.P.H.; Brigid Gregg, MD; Kanakadurga Singer, MD, University of Michigan, Ann Arbor, MI, United States

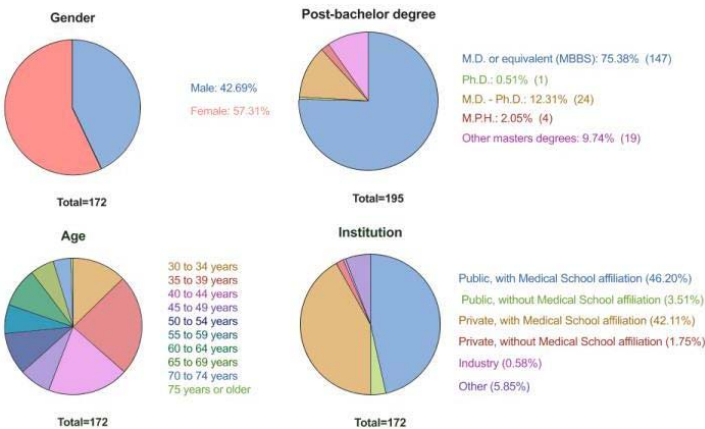
**Objectives:** With funding for research becoming increasingly difficult to obtain, research careers for physician-scientists are in jeopardy. Previous reports have pointed out a leak in the pipeline for academic physicians entering research careers. With these forecasts in mind, we designed a survey to elucidate factors associated with failure to advance in a career as a physician-scientist. This Qualtrics survey was distributed to Pediatric Physician Scientists across multiple disciplines in the U.S. Here we analyze the data from the Pediatric Endocrinology respondents.

**Methods:** Qualtrics survey distributed through the Pediatric Endocrinology Society email list. These were voluntarily answered with no compensation given. All responses were anonymous. Univariate analysis was used to describe sample characteristics and chi-square testing was used to look for associations between position characteristics and success or burnout in one’s current position.

**Results:** There were 172 respondents to the PES survey with completed surveys. Gender, age, post-bachelor degrees and Institution affiliation are shown in figure 1. The majority of respondents were 35-44 years old (43.03%) and a majority were female (57.31%). 22.1% had K level funding and 27.3% had R01 level funding. There were no responses that were significantly associated with promotion, burnout or leaving the tenure track. When we analyzed for predictors, 76% of those who had received funding for their research responded that their percent of protected research effort assigned was possible compared to the 48% of those who had not received funding for their research (p= 0.007)\*. Also associated with success in funding was an offer letter, which included receiving lab space, protected research time and start-up funds.

**Conclusions:** When we surveyed Pediatric Endocrinologist Physician Scientists, we found several factors involved in the initial offer package that were associated with being successful in obtaining research funding. This work needs to be examined across other pediatric subspecialties to identify key barriers and motivations, in order to improve the pediatric academic research pipeline.

PLEASE SEE TABLE IN NEXT COLUMN



P1-1402

IMPROVEMENT IN CHILDREN’S EMOTIONAL QOL AND IN PARENTAL PERCEPTION OF THEIR CHILDREN’S HEIGHT-SPECIFIC QUALITY OF LIFE AFTER ONE YEAR OF GH TREATMENT - OUR EXPERIENCE WITH THE QOLISSY QUESTIONNAIRE.

Laura G. González Briceño, MD; Magali Viaud, BS/BA; Isabelle Flechtner, MD; Yamina Dassa, MD, Hôpital Necker-Enfants Malades. Université Paris Descartes, Paris, France; Dinane Samara-Boustani, MD, University of Paris, Necker-Enfants Malades Hospital, Paris, France; Caroline Thalassinou, MD; Christian Pauwels, MD, Hôpital Necker-Enfants Malades. Université Paris Descartes, Paris, France; Jacques Beltrand, MD, Faculte de médecine Paris Descartes, Hôpital Universitaire Necker Enfants Malades, Paris, France; Kanetee Busiah, MD, PhD, Hôpital Armand Trousseau and Hôpital Necker Enfants Malades, Assistance Publique Hopitaux de Paris, Paris, France; Graziella Pinto, MD, Hopital Necker - Enfants Malades. Université Paris Descartes, Paris, France; Michel Polak, Professor, INSERM U1016, Cochin Institute and INSERM U1163, Imagine Institute, Paris Descartes University, Sorbonne Paris Cité, Necker Children's University Hospital, Paris, France

**Objectives:** Short stature may be a source of social and affective stress in children and their parents, and thus impact negatively on their quality of life (QoL). Treatment by growth hormone (GH) may improve QoL through normalisation of height.

Our objective was to evaluate general and height-specific QoL in short stature children after 1 year of GH treatment.

**Methods:** Prospective study. Inclusion criteria were: having started GH treatment at Hôpital Necker-Enfants Malades between April 2012 and September 2015, age ≥ 4 years and short stature (≤-2 SDS). Exclusion criteria were presence of a serious chronic disease (e.g. brain tumour), syndromic cause (e.g. Turner syndrome), or developmental delay. Two questionnaires (general PedsQoL 4.0 and height-specific QoLISSY) were completed on the day of first GH injection (T0) and one year later (T12), both by parents and children. The QoLISSY questionnaire (Quality of Life in Short Stature Youth) was developed by an international European group of QoL



researchers (Bullinger et al, 2013), with the aim of evaluating height-specific QoL. Paired t-test was used to evaluate changes in QoL, Pearson correlation coefficient was used to compare parents and children's scores and correlation between height gain and improvement in QoL.

**Results:** Of 80 patients initially included, 73 completed the T12 evaluation, 32 girls and 41 boys. Mean age: 10.1±3 years (4.1-16.6). In general PedsQoL questionnaires, children reported a statistically significant improvement of their emotional QoL ( $p=0.043$ , initial score: 72.21±19.46, final score: 77.62±18.18). In QoLISSY scores, a statistically significant improvement was noted in parental perception of their child's emotional ( $p=0.001$ , gain: +0.30 SD), social ( $p=0.005$ , gain: +0.26 SD) and total ( $p=0.002$ , gain: +0.25 SD) QoL, which were not apparent in children's questionnaires. There was a moderate positive correlation between height gain in SDS and improvement in QoL ( $R=0.5204$ ,  $p<0.001$ ).

**Conclusions:** We conclude that after one year of GH treatment, children's general emotional QoL is significantly improved, and according to parental perception so are height-specific emotional and social QoL. Supported in part by Pfizer.

P1-1403

#### IMPROVED FREQUENCY OF WAIST CIRCUMFERENCE MEASUREMENT AND UTILIZATION OF WAIST-TO-HEIGHT RATIO IN CARDIOMETABOLIC RISK COUNSELLING AMONG CHILDREN: A QUALITY IMPROVEMENT INITIATIVE

Nidhi Gupta, MD; Aida Lteif, Associate Professor; Ana Creo, MD; Anoop M Iqbal, MD; W. Frederick Schwenk, MD; Siobhan Pittock, MD; Peter J Tebben, MD; Janet Hansen, RN; Mary Heyrman, RN; Rebecca Spee, RN; Lori Scanlan-Hanson, RN, Mayo Clinic College of Medicine, Rochester, MN, United States; Seema Kumar, Associate Professor, Mayo Clinic, Rochester, MN, Rochester, MN, United States

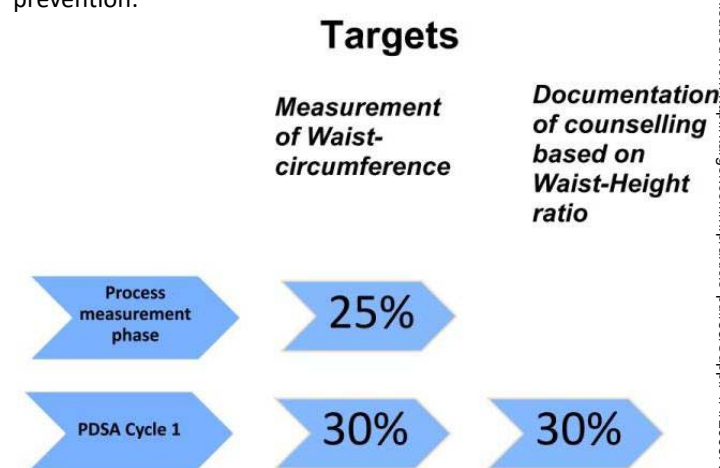
**Objectives:** Central adiposity predicts cardiometabolic risk. Waist-circumference (WC) and waist-to-height ratio (WHtR) are superior surrogate markers of central adiposity than body mass index (BMI). Waist circumference is not measured routinely in pediatric clinics. The aim of this quality improvement (QI) initiative was to implement and increase WC measurement rates to a target goal of  $\geq 30\%$  over 8 months. Additional aim was to utilize WHtR in cardiometabolic risk counselling in  $\geq 30\%$  of children with central obesity (defined as WHtR  $\geq 0.5$ ).

**Methods:** This study is a single-center QI project including children aged 2-20 years, evaluated in the pediatric endocrinology clinic at a tertiary medical center. The Plan-Do-Study-Act (PDSA) methodology was employed. Interventions focused on effective training, key stakeholder buy-in, real-time process improvement and continuous outcome measurement.

**Results:** During the 3 month planning period, WC was not measured in any of the patients ( $n=619$ ). Soon after introduction, the rate of WC measurement increased to 33% ( $n=132/401$ ) over 2 months. After implementing the change

on a wider scale, the rate of WC measurement was 37% ( $n=215/584$ ) and rate of counselling based on WHtR was 66% ( $n=69/104$ ) in the three months before end of study period. Majority of patients with normal BMI ( $< 85^{\text{th}}$  percentile) had normal WHtR, however 14% patients in this BMI category ( $n=15$  out of 107 for whom WC was measured) had elevated WHtR. About 40% patients categorized as overweight (BMI  $\geq 85^{\text{th}}$  to  $< 95^{\text{th}}$  percentile) had a WHtR  $< 0.5$ .

**Conclusions:** Application of an evidence-based PDSA cycle led to a significant change in practice over an 8-month period. Meticulous planning and execution, frequent reinforcement and integrating feedback from the involved multi-disciplinary team were important factors in sustaining a successful QI project. In addition, the project provided insight that children with normal BMI ( $< 85^{\text{th}}$  percentile) can potentially be misclassified as healthy despite presence of central obesity, and not be screened or counselled for cardiometabolic risk prevention.



P1-1404

#### TARGETING IA-2 AND GAD 65 AS A COST-SAVING APPROACH FOR ANTIBODY TESTING IN CHILDREN WITH NEW-ONSET DIABETES

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**Objectives:** The American Diabetes Association (ADA) requires demonstration of one or more autoantibodies for the diagnosis of type 1 diabetes (T1DM). Current practice in our institution is to test for GAD65, Zinc Transporter 8, IA-2 and Islet Cell Antibodies (ICA). This study assesses diagnostic accuracy and costs of selective antibody testing for the diagnosis of T1DM.

**Methods:** Retrospective chart review of a series of 91 consecutive patients who underwent antibody testing for suspected new onset diabetes at UW American Family Children's Hospital-Madison. Frequency of positive antibody tests was assessed. Cost of individual lab tests was based on charges from ARUP laboratories (IA-2 and Zinc Transporter 8) and Mayo Medical System Laboratories (GAD65 and ICA). Results were stratified based on age to analyze differences in positivity in each age group.

## PARENT EDUCATIONAL INTERVENTION IMPROVES MEDICAL ALERT ID UTILIZATION IN YOUTH WITH ADRENAL INSUFFICIENCY

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**Objectives:** Adrenal insufficiency (AI) is a potentially life-threatening condition that can affect children from birth, and adrenal crisis is a major cause of morbidity and mortality in these high-risk youth. Patient/parent education on treatment of adrenal crisis with emergency glucocorticoids, along with medical alert identification (ID) to explain the need for treatment to health personnel, could prevent complications with a more timely intervention. Although low awareness levels have been identified in adults with primary AI, and in health professionals, little is known about parent awareness levels in pediatric AI. Our objective was to evaluate awareness, ownership and usage of medical alert IDs in parents of AI youth, and to determine the effect of an in-clinic educational intervention on ID utilization.

**Methods:** A quality improvement (QI) framework using plan-do-study-act (PDSA) process improvement cycles was utilized to study 50 parents of children with AI due to congenital adrenal hyperplasia ( $11.4 \pm 4.9$  years old) at a large tertiary referral center. This prospective cohort study involved: (1) a baseline survey of parents at a clinic visit to evaluate outcome measures of awareness, ownership, and usage (> 3 times/week was deemed frequent) of medical alert IDs for AI, (2) an in-clinic educational intervention (brochure on IDs given to surveyed parents), and (3) a follow-up phone call 1 month post-intervention.

**Results:** At baseline, 19/50 (38%) owned a medical alert ID, 8/50 (16%) reported frequent usage, and 24/50 (48%) were aware of ID options. One month post-intervention, ownership increased to 33/50 (66%;  $p < 0.05$ ), frequent usage increased to 23/50 (46%;  $p < 0.05$ ), and awareness increased to 39/50 (78%;  $p < 0.05$ ). Six Spanish-speaking families were aware of, but did not own an ID pre- or post-intervention, due to the inability to access electronic payment methods for purchase of IDs online.

**Conclusions:** Only a small percentage of children with primary AI wear a medical alert ID, but an educational brochure given to parents improves awareness, ownership and ID usage. Patient education is greatly needed in AI, and further study is merited to assess reduction of morbidity and mortality of adrenal crisis with increased medical alert ID utilization.

**Results:** Among 91 patients, 18 (19.8%) were age 6 or younger. Seventy six (83.5%) had more than one positive antibody. In 15 (16.5%) subjects with a single positive result, positivity was equally distributed among IA-2, GAD65, or zinc transporter 8 antibody (Table 1). For those < 6 years of age, only IA-2 and GAD 65 were ever a single positive result. Six patients (6.6%) were negative for all 4 antibodies, of which 4 (4.4%) were later diagnosed with Type 2 Diabetes. Eighty (88%) patients with suspected diabetes had either one or both the IA-2 or GAD65 tests positive. The cost for four antibody tests was \$1,189 per patient, of which the Zinc was the most expensive and the ICA least expensive.

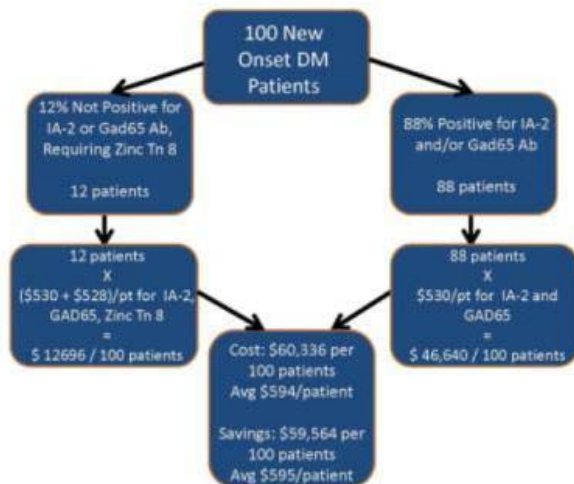
**Conclusions:** In children presenting with signs/symptoms of diabetes mellitus in our region, 88% had either a positive IA-2 or GAD65 antibody. None had only a positive ICA antibody. Zinc transporter antibody added to the diagnosis in only 5/91 (6%) of patients, and never in those less than age 6 years. From this analysis, it appears cost effective to screen for T1DM with the IA-2 and GAD65 tests (\$530 per patient), followed by the zinc transporter Ab if these are negative, and with elimination of ICA (Figure 1).

This research is supported by a T32 grant DK077586.

Table 1. Results and Cost of Individual Antibody Lab Tests.

	Positive Tests (N=91)(%)	Only Positive Antibody (%)	Positive Antibody Below Age 6 (N=18) (%)	Only Positive Antibody Below Age 6 (%)	Cost of Tests
IA-2	71 (78%)	5 (5.5%)	15 (83.3%)	2 (2.2%)	\$356
GAD65	51 (56%)	5 (5.5%)	11 (61.1%)	1 (1.1%)	\$174
Zinc Transporter 8	69 (75.8%)	5 (5.5%)	13 (72.2%)	0 (0%)	\$528
Islet Cell	50 (54.9%)	0 (0%)	12 (66.7%)	0 (0%)	\$131

Figure 1. Cost savings estimate would be over 49% per patient with a change in antibody ordering protocol. This would save the healthcare system over \$59,000 per 100 patients within our institution.





### DIABETES CAMP AS AN OPPORTUNITY TO DEVELOP HEALTH PROMOTER COMPETENCIES IN PEDIATRICS AND ADULT ENDOCRINOLOGIST FELLOWS.

Carola Goecke, MD; Javiera Hansen, MD; Monica Arancibia, MD; Cristian Seiltgens, MD; Alejandro Martinez-Aguayo, MD, Pontificia Universidad Catolica de Chile, Santiago de Chile, Chile

**Objectives:** Health promotion practice involves the process of enabling people to increase control over, and to improve, their health. It moves beyond a focus on individual behavior towards a wide range of social and environmental interventions and is an important competency to develop by our fellows. To evaluate if the Diabetes Camp is an opportunity to perform a health promotion activity with the aim to respond to an individual patient's health needs.

**Methods:** **Design:** Descriptive study. **Subjects:** pediatric endocrinologist or adult diabetologist fellows whom were attending to diabetes camp between 2000 to 2017 (N=26). **Methods:** Setting: Diabetes Camp. Risk factor: unhealthy habits and /or poor metabolic auto-control Approaches: education, skills buildings and environment support, 4) Audiences: Children and adolescents with diabetes type 1 (8 to 14 years old). An electronic survey, oriented to clarify if this activity allows the fellows to develop health promoter competencies, was performed. We grouped answers in 4 statements. *Statement 1:* Work with patients to identify determinants of health that affect them and their access to needed health services or resources (2 questions), *Statement 2:* Work with patients to increase opportunities to adopt healthy behaviors (education) (3 questions), *Statement 3:* Evaluate if the attendees incorporate health promotion during the diabetes camp (2 questions), *Statement 4:* Identify directs benefits for the fellow who attend to diabetes camp (4 questions). The answer could be: no, partial or successfully accomplished. **Results:** The survey were returned by 26 medical doctors. Successfully accomplished were observed in *Statement 1* (Q1 66.7%; Q2 60.9%), *Statement 2* (Q3 62.5%; Q4 50%; Q5 50%), *Statement 3* (Q6 83.3%; Q7 91.7%) and *Statement 4* (Q8 70.8%; Q9 79.2%; Q10 45.8%; Q11 79.2%). **Conclusions:** Diabetes Camp is a good opportunity to perform health promotion for the individual patient's health needs; and a professional experience with personal benefits to develop health promoter competencies for pediatrics and adults fellows. We identify some weakness in the development of this activity. We suggest to use the "Health Promotion Cube" model to improve it.

### TEACHING STRATEGIES APPLIED BY PEDIATRIC ENDOCRINOLOGIST FELLOWS TO UNDERGRADUATE STUDENTS

Javiera Hansen, MD; Carola Goecke, MD; Monica Arancibia, MD; Cristian Seiltgens, MD; Alejandro Martinez-Aguayo, MD, Pontificia Universidad Catolica de Chile, Santiago de Chile, Chile

**Objectives:** Introducing teaching skills in residents curriculum is important as they could have teaching roles as future faculty members.

**Purposes:** 1) To prepare our residents in medical education for their future roles as teachers (according to the CanMEDS' scholar competency), and 2) to determine the most effective teaching strategy applied by pediatric endocrinologist fellows to undergraduate students.

**Methods:** We created a pilot teaching program between July 2016 to February 2017 entitled 'medPed-ENDO': 1) We introduce some teaching skills during the pediatric endocrinology training, 2) we design the course for undergraduate student using three different teaching/learning processes (on-line video, auto-learning guidelines or face-to-face seminars) in the following topics: Short Stature, Thyroid Diseases and Pubertal Disorders, and 3) we apply a formative mini-test (multiple choice tests) to evaluate the acquired knowledge after the teaching/learning processes.

**Results:** A total of 172 formative mini-test were analyzed, the scores were between 1 to 7. The score (mean  $\pm$  standard deviation) was different between groups (ANOVA;  $p < 0.001$ ); the auto-learning guidelines ( $n = 57$ ;  $5.06 \pm 1.11$ ) had the lower score compared with on-line video ( $n = 52$ ;  $5.96 \pm 0.91$ ; Bonferroni;  $p < 0.001$ ) and face-to-face seminars ( $n = 66$ ;  $5.58 \pm 0.96$ ; Bonferroni;  $p = 0.015$ ). No statistical differences was observed between on-line video and face-to-face seminars ( $p > 0.05$ ).

**Conclusions:** The lower mean score and the higher standard deviation observed in auto-learning guidelines could be explained by differences in the study skills of the students. On-line video emerges as a good learning method. Innovative teaching tools by endocrinologist fellows could have a double impact: to improve the education skills of the residents with patients, students and colleagues; and to reach our learning objectives for our undergraduate students.

### CRETINISM DESPITE NEWBORN SCREENING DUE TO LOSS TO FOLLOW-UP: DEVELOPING PREVENTATIVE MEASURES THROUGH QUALITY IMPROVEMENT

Kristal A Matlock, MD; Christopher Alexander, MSQSM; Michelle Biery, CPN; Sarah Boyd, LISW; Sarah Corathers, MD; Samantha Ellsworth, MPH; Sherry Elmore, MBA; Ann Planicka, CPN; Madeline Campbell, MSN; Nana-Hawa Yayah Jones, MD, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States

**Objectives:** A case of cretinism in a child with congenital hypothyroidism (CH) uncovered healthcare system failures; subsequently, the study objective was to prevent loss to follow-up by decreasing the percentage of patients with CH from ages 0-3 years without an Endocrinology visit within the past 180 days from 25% to <5%.

**Methods:** Quality Improvement (QI) methodology informed the design and iterative testing of interventions and tracking of results over time. Key drivers addressed consistent application of clinical practice guidelines, standardization of scheduling, effective coordination of care between patients and providers, as well as reporting system for high-risk patients.

**Results:** Over 12 months, 306 patients with CH were identified and 96 were  $\leq 3$  years of age. Interventions included: review of practice guidelines with providers and families, arranging follow-up during clinic visits, establishing communication between providers and care team, and implementing a scheduling and reporting algorithm for high-risk patients.

Initially, only 23% of patients had a follow-up visit frequency that adhered to the standard of care. Though patient cohort varied and etiology of improvement was multi-factorial, 53% of patients saw their provider at a frequency within practice guidelines after intervention. The percentage of patients who scheduled a future appointment prior to leaving their clinic visit increased from 40% to 100%. Twelve patients (12.5%) were identified as lost to follow-up, defined as >180 days since their last visit, and all were seen by providers at study completion. Variation from baseline data in our aim is due to systematic elimination of patients who were discharged or transferred care. Currently, <5% of patients are considered lost to follow up after numerous attempts at contact by providers, nursing, social work, and Child Protective Services.

**Conclusions:** A sentinel case of cretinism prompted a systematic intervention to prevent loss to follow-up for children with CH. QI initiatives successfully resulted in a proactive, population approach to ensure timely future visits as well as a reliable, responsive mechanism to identify children with lapses in care. Consequences of untreated CH are preventable with reliable health system interventions.

P1-1409

#### THE CORE OUTCOME MEASURES IN PEDIATRIC ENDOCRINOLOGY (COMPARE) INITIATIVE

*Richard G McGee, PhD, The Children's Hospital at Westmead, Sydney, NSW, Australia; Geoffrey Ambler, Professor, The Children's Hospital at Westmead, The University of Sydney, Sydney, NSW, Australia; Shubha Srinivasan, PhD, The Children's Hospital at Westmead, Sydney, NSW, Australia*

**Objectives:** Currently, outcomes measured in research trials are varied, often lack meaning for patients and are hard to compare. The Core Outcome Measures in Pediatric Endocrinology (COMPARE) Initiative aims to develop core outcome sets in pediatric endocrinology. The outcomes will be based on the shared priorities of patients, caregivers,

clinicians, researchers and other relevant groups in a global collaborative effort. The COMPARE Initiative is currently developing core outcomes for trials of pediatric onset diabetes (COMPARE-Diabetes).

**Methods:** The first step being conducted is a systematic of what outcomes have been reported in trials of pediatric onset diabetes to date. The review will be followed by an international Delphi survey and consensus workshop leading to the creation of a core outcome set. A protocol for the COMPARE-Diabetes project is being prepared for publication.

**Results:** Type 1 diabetes mellitus is one of the most common chronic diseases in childhood, with an increasing incidence worldwide. Despite this, to date no research has focused on core outcomes in pediatric endocrinology, in particular within the field of diabetes. This systematic review will assess which outcomes have been measured in clinical trials of treatments for children with diabetes mellitus between 1988 and 2017, in order to determine whether all relevant domains were represented, and whether there was consistent selection of outcomes within these domains. Secondary objectives were to determine whether the selection of outcome domains has changed between 1988 and 2017, whether domains measured in RCTs exclusively involving children differ from those in studies involving both children and adults, and whether domains measured in publically funded trials differed from those in trials funded by the pharmaceutical industry.

**Conclusions:** Through the creation of collaborative core outcome sets, the COMPARE Initiative aims to improve the applicability and quality of research across the spectrum of pediatric endocrinology. Further information will be available from the COMPARE Initiative website: [www.compare.org.au](http://www.compare.org.au).

P1-1410

#### PRACTICE VARIANCE REDUCTION IN DIAGNOSIS AND MANAGEMENT OF INFANTS WITH PRIMARY CONGENITAL HYPOTHYROIDISM

*Bhavana Narala, MD; David Wyatt, MD, Medical College of Wisconsin, Milwaukee, WI, United States; Peter Wolfram, MD, Medical College of Wisconsin, Milwaukee, WI, United States*

**Objectives: Background:** Congenital hypothyroidism (CH) screening can allow for timely identification and prompt treatment. However, practice variance may persist without clear and uniformly accepted management guidelines

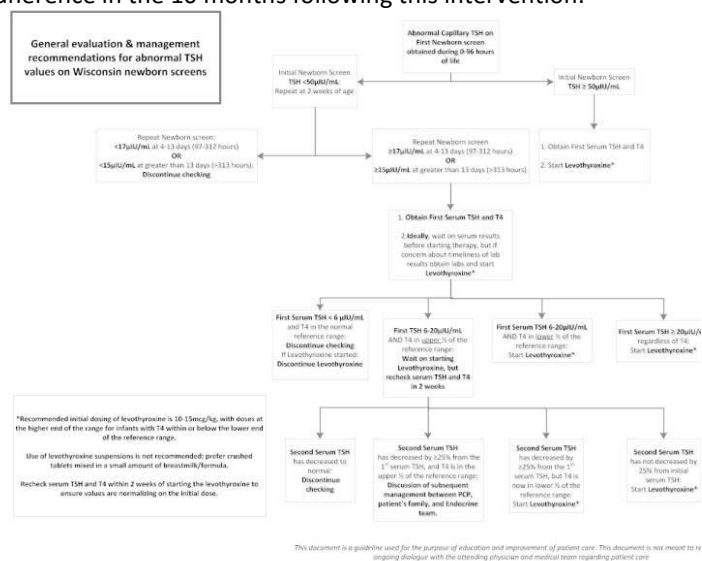
**Objective:** To establish practice variance in the management of infants with primary CH seen in our academic group practice, to create consensus guidelines, and to monitor adherence to the guidelines.

**Methods:** We created a survey based on international (ESPE)/national (AAP) guidelines to establish practice variance in diagnosis and management of primary CH within the pediatric endocrinology section at Children's Hospital of Wisconsin. We presented the ESPE and AAP guidelines, and survey results to the 12 providers, arrived at an algorithm incorporating the consensus guidelines, and monitored

compliance to the agreed upon algorithm. Results from Nov 2016 through Feb 2017 are presented here, but monitoring will continue for 10 months after guideline implementation.

**Results:** There was a wide variance in the TSH threshold for starting thyroxine when the ft4 levels were in the normal range. A lower ft4 or an increasing TSH led to earlier LT4 therapy, but with remaining practice variance. For example: were no ft4 value provided, at day of life (DOL) 14, half of respondents would start LT4 at varying TSH thresholds (5-20mIU/mL), but 25% would only start LT4 at DOL 30 if TSH >10mIU/mL. Furthermore, provider methods to determine initial LT4 dosing varied: by weight (4), by TSH (4), by TSH+Weight (3), and by TSH+DOL (1). If LT4 were begun, 2 providers rechecked labs in 1 week, 4 in 2 weeks, 2 in 3-4 weeks, and 4 in 4 weeks. If LT4 was not started, 7 providers rechecked labs in 1-2 weeks, 2 in 4 weeks, and 3 varied based on ft4 and TSH. Compliance with the algorithm was 100 % (10/10).

**Conclusions:** Significant practice variance existed in the criteria for initiating therapy, in monitoring patients with or without therapy, and in initial dosage calculations. Discussion of this variance, combined with a discussion of published guidelines, allowed practice members to accept a common algorithm for management of primary CH. We will monitor adherence in the 10 months following this intervention.



P1-1411

## ANALYSIS OF MUTATIONS IN HUMAN GROWTH HORMONE FOR INTERACTION WITH GROWTH HORMONE BINDING PROTEIN AND STRUCTURAL STABILITY USING PURIFIED PROTEINS EXPRESSED IN E. COLI.

Shaheena Parween, PhD; Maria C Miletta, PhD; Andree Eblé, Technician Diploma; Amit V. Pandey, PhD, University Children's Hospital Bern,, Bern, Switzerland

**Objectives:** Human growth hormone acts via binding to two molecules of growth hormone receptor (GHR) which dimerize and start signaling pathways for downstream effects. Mutations in GH1 gene cause isolated growth hormone

deficiency (IGHD) by affecting production, secretion and stability of growth hormone as well as its binding to GHR. The P59L mutant of GH1 had been shown earlier to be associated with IGHD, and GH-secretion studies had showed a moderate difference in secretion between GH-P59L and wt-GH. Most studies reporting IGHD have focused on defects in transcription or secretion of GH protein due to mutations in GH1 gene. Study of protein interactions between hormone and its receptor requires purified proteins to confirm the differences in binding affinities due to mutations.

**Methods:** We have adopted the analysis of GH1 gene mutations by recombinant production of mutant human GH proteins in bacteria and purifying the proteins by chromatographic methods. Purified GH variants were separated using SDS-PAGE and analyzed by western blotting to confirm their identity with anti-GH antibodies. Purified proteins were further analyzed by receptor binding and conformational stability assays using ELISA, Fast proteolysis and fluorescence spectroscopy.

**Results:** Computational analysis showed that P59 residue is close to first GH binding site of GHR. In silico mutagenesis and molecular dynamics simulations indicated a defective binding of GH-P59L to the GHR. Binding affinity of purified WT GH was found to be 10 fold higher than GH-P59L mutant, providing a definitive link between biochemical assays and known phenotype of the reported patient. Analysis of WT and P59L GH stability by FASTpp assay using thermolysin at different temperatures to study protein degradation revealed no major differences, confirming that IGHD due to P59L mutation in GH1 is due to reduced binding of GH protein with GHR.

**Conclusions:** Advanced protein chemistry and computational analysis methods can be used to characterize the molecular basis of defects in GH1 gene causing IGHD. Use of purified recombinant proteins allowed us to use advanced biophysical and biochemical methods for analysis of mutations in human growth hormone.

P1-1412

## REDUCING TIME TO TREATMENT OF DIABETIC KETOACIDOSIS IN THE EMERGENCY DEPARTMENT SETTING

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**Objectives:** Background: Timely treatment of diabetic ketoacidosis (DKA) is vital to avoid morbidities and mortality. The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends immediate fluid resuscitation and insulin administration within 1-2 hours of starting fluid replacement. Our institution has had a DKA-specific pathway and order set for use in the Emergency Department (ED) since 2006 and 2011, respectively. However, chart review in 2013 revealed significant delays in treatment for many patients. This led us to pursue a quality improvement (QI)

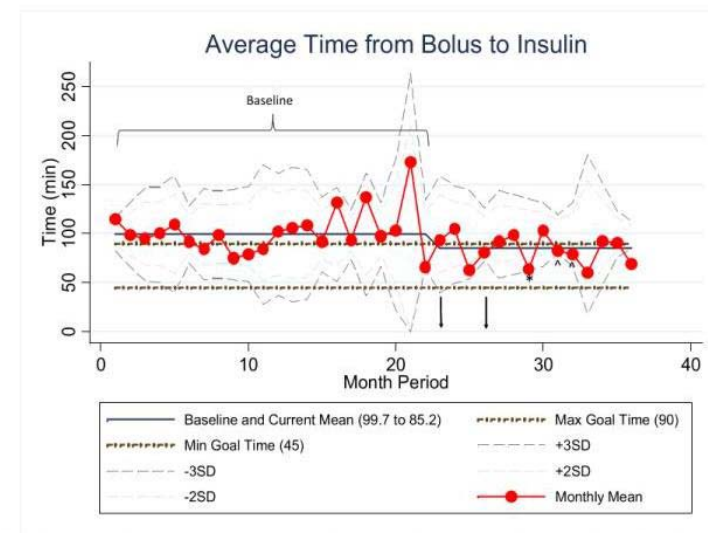
project to reduce treatment variability and optimize timing for all patients.

**Problem statement:** Patients in DKA who present to the ED at our institution do not uniformly receive fluid and insulin therapy within the recommended timeframes, potentially leading to increased risk of complications and morbidities due to treatment delay.

**Methods:** Our QI project began in 2013 and remains ongoing. The project meets criteria for QI activity, outlined by our hospital's Institutional Review Board. Data for all non-transported patients with type 1 diabetes mellitus who presented to the ED with DKA were tracked and analyzed through January 2017 (n=291). Tests of change included order set and pathway modifications, a nursing flowsheet, and feedback to providers. Median times for several metrics were compared across three time periods (T1-T3) based on tests of change.

**Results:** Median time to insulin administration after fluid bolus decreased from 96 minutes [range 0-356] in T1 to 75 minutes [range 20-210] in T3 (p=0.003). Median time from ED arrival to insulin infusion also decreased significantly (168 [range 19-446] minutes in T1 vs 146 [range 32-354] minutes in T3, p=0.02). Time from ED arrival to fluid bolus remained unchanged (median 55 minutes [range 2-352] in T1 and 54 minutes [range 8-296] in T3, p=0.8).

**Conclusions:** After several tests of change, time to insulin administration for patients who presented to the ED with DKA decreased significantly. Total time to insulin administration after arrival to the ED remained high at approximately 2.5 hours, likely related to the unchanged time from arrival to fluid resuscitation, which will be the next focus of intervention.



P1-1413

## DIABETES ACTION PLAN: A REFRIGERATOR MAGNET THAT SAVES LIVES (AND \$\$\$)

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**Objectives:** Quality improvement project to increase subjective comfort and objective awareness of managing diabetes-related situations via an easy visual tool.

**Methods:** At our practice, there were 189 DKA admissions in ~800 patients (US NEWS) with established type 1 diabetes (T1D) from 1/2013 to 4/2016.

A Diabetes Action Plan (DAP) was created using established guidelines after 5 families of children with T1D identified specific gaps. The DAP has green, yellow, and red zones related to the severity of signs and symptoms with interventions.

**PDSA1:** 20 families completed a pre-intervention survey and were given a DAP, followed 4 weeks later by a post-intervention survey to assess their comfort and knowledge in managing diabetes during illness and hypoglycemia.

**PDSA2:** Feedback from PDSA1 led to separate DAPs for pump and injection users. Families of 12 patients using insulin pump (PDSA2P) and 18 patients using insulin injections (PDSA2I) were enrolled.

**PDSA3:** Different-sized DAP magnets (with feedback incorporated) are being given to all patients. DKA admissions in established patients will be followed to assess change in incidence.

**Results:** Patients were 4 to 21 years of age (mean 13+/-4.3) and at 5.4 years (+/-3.9) from diagnosis. Most families completed the post-intervention survey (19 of 20 in PDSA1, 10 of 12 in PDSA2P, and 14 of 18 in PDSA2I) with 79% of caregivers in PDSA1, 80% in PDSA2P and 100% in PDSA2I actively using the Action Plan. Many caregivers reported improvement in perceived diabetes control. Overall, 42% of caregivers had an increase in comfort-scores in managing sick days and ketones. Initially, only 5% in PDSA1, 25% in PDSA2P, and 0% in PDSA2I listed all 3 critical steps in managing diabetes with fever. However, on post-intervention survey, 47.3% in PDSA1 (P=0.005), 70% in PDSA2P (P=0.1) and 35% in PDSA2I (P=0.07) listed all 3. For management of persistent vomiting, the percentage of families with the correct answer improved from 45 to 85% in PDSA1 (P=0.008), 17 to 70% in PDSA2P (P=0.05), and from 56 to 100% in PDSA2I (P=0.04). There was significant improvement in objective awareness about managing hypoglycemia.

**Conclusions:** A refrigerator magnet with a tailored diabetes action plan is an inexpensive way to improve diabetes management.

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the DSD list and 12 variants came from the SF-1-related gene list. With these data, we then constructed a scheme of the oligogenic hits identified in the SF1 patients against the genetic landscape of currently known gene interactions involved in male sex determination and differentiation.

**Conclusions:** WES analysis reveals that the broad phenotype in heterozygous *NR5A1* 46,XY DSD subjects may be explained by an oligogenic mode of inheritance. Finding a hit in one (known) DSD gene in an affected individual may not exclude additional disease-causing variants.

P1-1502

# GONADOTROPIN REPLACEMENT FOR INDUCTION OF PUBERTY IN ADOLESCENTS WITH HYPOGONADOTROPIC HYPOGONADISM

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**Background:** Patients with congenital hypogonadotropic hypogonadism (CHH) have a poor prognosis of fertility despite of substitutional testosterone and human chorionic gonadotropin (hCG) therapy. One potential reason for this is deficient proliferation of immature Sertoli cells before and during puberty due to the absence of FSH stimulation.

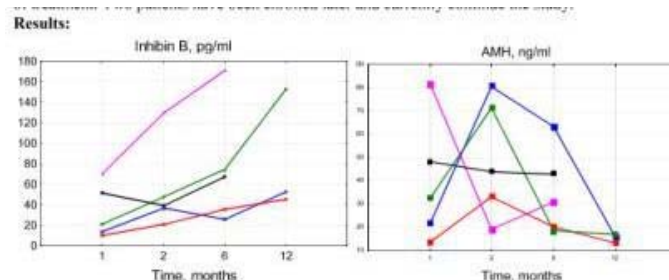
**Objective and hypotheses:** To study the effects of recombinant human FSH (rFSH) and hCG therapy on testicular function and pubertal development in adolescents with CHH.

**Methods:** We included five adolescence and young adult males 15.7 [15.5; 15.9] yrs. of age with CHH. The diagnosis was confirmed by genetic testing in four patients (*GNRHR*p.R262Q/*FGFR1* p.V248M, *FGF8* p.P26L, *FGFR1* p.Y99C/*SPRY4* p.C209Y, *FGFR1* p.P366L). The bone age by the time of treatment initiation was 13.5 yrs. in all patients. Patients were treated with 37.5 U/w of r-hFSH ((Pregnyl; Merck Sharp & Dohme.) and 500 U/w of hCG (Gonal-F, Merck Serono S.A.) once a week for the first six months. The doses of medications were increased (rFSH to 75 U/w and hCG to 1000 U/w) for the next six months. The patients were examined at 2, 6 and 12 months of treatment. Two patients have been enrolled later and currently continue the study.

**Results:** Tanner stage progressed from 1 [1;2] to 2 [2;3] in all patients, but there were no bone age acceleration. Testicular volume significantly enlarged from 0.45 [0.3; 0.7] to 0.7 [0.3; 0.9] P < .05) in all but one patient. Inhibin B level increased from 15.7 [15.5; 15.9] to 52.5 [45.5; 153.3] pg/ml during the treatment.

**Conclusions:** We showed efficiency of combined hCG and rFSH therapy for induction of puberty and Sertoli cell proliferation in patients with congenital hypogonadotropic hypogonadism.

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P1-1503

# ANTI MULLERIAN HORMONE FOR DIAGNOSIS OF POLYCYSTIC OVARY SYNDROME IN ADOLESCENTS AND YOUNG ADULTS FROM INDIA

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**Objectives:** To assess the diagnostic value of anti Mullerian hormone (AMH) for polycystic ovary syndrome (PCOS) in adolescents and young adults and whether AMH can replace polycystic ovarian morphology (PCOM) on ultrasound in the present Rotterdam criteria

**Methods:** A prospective observational study where 123 young women <23 years of age and at least 2 years post menarchal with complaints of hirsutism, menstrual irregularities (MA) or infertility were recruited between Jan 2015 to Dec 2016. AMH was assayed using generation II assay and transabdominal ultrasound was done by a single observer in the follicular phase.

**Results:** Of the 123 patients, 115 (93.5%) had MA, 78 (63.4 %) had PCOM and 89(72.4%) had hyperandrogenemia (HA) (36 clinical, 84 biochemical while 29 had both). The mean age was  $20.2 \pm 2.4$  years and mean BMI was  $24.9 \text{ kg/m}^2$ . According to Rotterdam criteria, 104 (84.6%) patients were diagnosed as PCOS. The mean AMH was significantly higher in PCOS ( $10.1 \pm 4.7 \text{ ng/ml}$ ) as compared to non PCOS patients ( $4.0 \pm 3.7 \text{ ng/ml}$ ) ( $p = <0.05$ ). AMH levels positively correlated with ovarian volume (OV) ( $R = 0.354$   $p = <0.01$ ), number of follicles in one section ( $R = 0.379$   $p = <0.01$ ) and total testosterone (T) ( $R = 0.212$   $p = <0.01$ ). The diagnostic power of AMH was derived from ROC curve. The area under curve (AUC) was 0.881 (95% CI- 0.782-0.980), multiple threshold values of AMH at various levels of sensitivity and specificity were analysed and a level of 5.9 ng/ml had sensitivity of 83.3% and specificity of 84.2%. When PCOM was replaced by this AMH value in Rotterdam criteria 105 (85.4%) patients were diagnosed with PCOS (AMH-ROTTERDAM), a positive predictive value of 96.2% and a negative predictive value of 88.2%, proportion of patients diagnosed as PCOS same as in the original Rotterdam criteria. AUC for T was 0.759 (95% CI- 0.626-0.893), for OV was 0.892 (95% CI- 0.831-0.953) and for follicles per one section was 0.867 (95% CI- 0.794-0.940). The phenotype with PCOM had significantly higher AMH level compared to others.

**Conclusions:** AMH can be a surrogate marker for PCOM and is useful for diagnosis of PCOS especially in girls where transvaginal ultrasound is not possible because of varied reasons. AMH reflects the severity of the disease with highest levels seen in patients with all components of the syndrome

P1-1504

#### **UNDERSTANDING THE NEEDS OF PROFESSIONALS WHO PROVIDE PSYCHOSOCIAL CARE FOR CHILDREN AND ADULTS WITH DSD**

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**Objectives:** Investigation of facilities for psychosocial care that is provided to children, adolescents and adults with DSD

**Methods:** International survey among 93 providers of psychosocial care, identified through clinicians of DSDnet, I-DSD Registry, Pediatric Psychology Network and EuroPsi

**Results:** Forty-six respondents (49%) from 22 different countries completed the survey. Respondents were trained in different disciplines, from psychiatry to religious workers. All respondents had obtained at least a bachelor's degree and 76% of them had attended a specific course on DSD. Almost all respondents (87%) were collaborating with a team of professionals specialized in DSD care, most of them were based in hospital-based expert teams (78%). Most referrals for psychosocial counseling came from pediatric endocrinologists (76%), gynecologists (39%) and pediatric urologists (37%); psychological counseling was most frequently provided to parents (74%), followed by children (39%), adolescents (37%) and adults (11%) and was most frequently focused on education (52%), coping and acceptance of DSD (54%), the atypical body (39%) and genitalia (41%), decisions on genital surgery (33%), problems in making love and sexual intercourse (29%), disclosure (28%) and coping and acceptance of infertility (11%). Respondents most frequently observed DSD related confusion about gender (54%), acceptance of cross gender behavior (50%), anxiety (43%), sadness and depression (38%).

**Conclusions:** Most DSD related psychosocial care is provided to parents, Parental support is important, as comprehension

and acceptance is conditional to become affectionate caretakers. Although it may be more difficult for youngsters to communicate about their condition and treatment, children and adolescents should be stimulated to bring up the issues that are important for them. Clinicians and parents should be aware that parental and patients' interests may not correspond completely. Psychosocial management should also include transition and adult care.

P1-1505

#### **OVARIAN FOLLICULAR CELL AMH PRODUCTION IS TRANSIENTLY AFFECTED IN MOST OF THE GIRLS WITH ACUTE LYMPHOBLASTIC LEUKEMIA AND LYMPHOBLASTIC LYMPHOMA RECEIVING CHEMOTHERAPY**

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**Objectives:** Improvements in the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LL) have increased survival. Concern has therefore arisen over the long-term effects that chemotherapy in childhood may have on ovarian function. The main objective was evaluate small ovarian follicle status in girls.

**Methods:** We measured serum AMH in a prospective cohort. Main outcome measure was the prevalence rate of decrease in serum AMH after each phase of chemotherapy, every 6 months during maintenance and 1 year after treatment completion. Secondly, gonadotropin and estradiol levels were analyzed. Results of continuous variables are expressed as medians (range).

**Results:** Thirty-four girls were included; 31 with ALL (4 standard-, 19 medium- and 8 high-risk ALL) and 3 with LL. At diagnosis, age was 5.9 yr (0.2-15.7), 24 were prepubertal and 10 pubertal. Follow-up was 1.1 yr (0.25- 3.5). Decreased serum AMH was observed in 29/34 (85%) patients. In 8



patients (23.5%) decreased AMH was seen at diagnosis, and in 21 cases during chemotherapy treatment. Out of the 29 patients that presented low AMH levels, 19 (65.5%) recovered normal serum AMH: 9 (47.4%) during intravenous chemotherapy, 8 (42.1%) during maintenance and 2 (10.5%) after the end of treatment. No difference in the proportion of patients with decreased AMH was found between patients with high risk LLA (84.7%) and with standard or medium risk ALL (87.5%).

LH was increased in 9 patients (5 prepubertal and 4 pubertal) and FSH in 10 patients (7 prepubertal and 3 pubertal). In all cases, gonadotrophins increased transiently and mildly. Estradiol was not informative.

**Conclusions:** These preliminary results suggests that most girls with ALL or LL suffered a transient dysfunction of small ovarian follicles during chemotherapy, with recovery in approximately two-thirds of the cases.

Table 1. Median Serum AMH (range) in girls with ALL or LL during and after chemotherapy

	Basal	Post 1A	Post 1B	Post F1P1I	Pre Mant	6 mo. Mant	End of treatment	12 mo after e of treatm
n	34	26	32	24	21	16	9	6
AMH pmol/L	12.5 (2.5-80)	9.3 (2.5-59)	7.8 (2.5-48)	2.5 (2.5-24)	4 (2.5-22)	9.5 (2.5-64)	17 (3-29)	20 (5-26)

P1-1506

### TEACHING 1ST YEAR MEDICAL STUDENTS ABOUT COMPLETE ANDROGEN INSENSITIVITY SYNDROME: CURRICULUM METHODS TO TEACH ABOUT DIFFERENCES IN SEX DEVELOPMENT

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**Objectives:** To address the lack of Lesbian, Gay, Bisexual, Transgender (LGBT) and individuals born with Differences in Sex Development (DSD) in medical education, the University of Louisville School of Medicine initiated the *eQuality* project to promote mastery of the skills, knowledge, and attitudes required for excellent care for patients within the LGBT and DSD communities. Under the umbrella of *eQuality*, we created and implemented a problem-based learning (PBL) case, DSD specific lecture, and DSD patient panel as a means for medical students to understand and address both the medical and psychosocial factors that affect individuals born with DSD and their families.

**Methods:** One hundred and fifty-five 1st year medical students were required to participate in the DSD specific lecture, DSD patient panel experience, and DSD PBL. The PBL case presents a teenager with complete androgen insensitivity syndrome (CAIS) and focuses on sex, gender identity, gender expression, and sexual orientation. Students were asked to complete a 10 question multiple choice knowledge pre-test and post-test. Efficacy of the curriculum was evaluated by answering 3 open-ended questions regarding comprehension, competence, attitudes and barriers to acquisition and implementation of knowledge.

**Results:** The post-test average score was 20% higher than the pre-test. The post-test (n=155) had a range of 90% to 99% of students answering each question correctly, whereas the range for the pre-test (n=144) was from 29% to 94%. Average number of correct answers on the pre-test and post-test were 7.2 and 9.1 respectively. Seventy-nine percent of students said that the session changed their knowledge and competence regarding individuals born with a DSD. However, 13% of students said there are barriers that will prevent them from implementing their gained knowledge. Barriers cited included societal views and religion.

**Conclusions:** Based on the assessments and students’ comments, learning was markedly increased through the specific DSD curriculum. Despite this clear increase in knowledge, societal views or personal barriers, such as religion, challenge some students and might prevent them from implementing their newly gained knowledge.

P1-1507

### EXOME RESULTS IN UNDIAGNOSED 46,XY DISORDER OF SEX DEVELOPMENT CASES WITH TARGETED NEXT-GENERATION SEQUENCING.

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**Objectives:** To investigate new genes responsible in subjects that were previously undiagnosed with targeted next-generation sequencing (TNGS) with whole exome sequencing analysis.

**Methods:** Six patients, who were diagnosed as 46,XY DSD without mutations detected by TNGS (56 known genes were scanned) and whose family had consanguinity, were considered for the study. Exome sequencing was performed on the DNA specimens collected from patients and their parents with the “Illumina Nextseq 500”. Candidate genes were determined by filtering obtained results on the “Illumina Variant Studio” program. Verifications were conducted for every candidate gene. Found variations were evaluated on “in-silico” modelling programs.

**Results:** Mutations were detected in 3 of 6 cases in conducted analysis. 2 of the detected genes are newly identified with this study. In one case, a homozygous c.332delC (p. L112YfsX2) mutation was detected on the CCDC60 gene. In another case, homozygous c.36\_41dupGGAGGC (p.Ala14\_Glu15insGluAla) mutation was detected on the ZNF653 gene. Heterozygous mutations of the same genes were detected in subjects’ parents. In detailed analysis, mutations on these genes that are expressed in testicles were thought to be possibly responsible for causing 46,XY DSD. In the third subject, the homozygous c. 1460dupG (p.C487WfsX13) mutation on the AMHR2 gene was detected in whole exome analysis, which was not detected in TNGS despite it was on the panel. Because this gene was on top of

another gene, it was not detected due to a bioinformatic error in TNGS study.

**Conclusions:** In our study, two new genes which may be responsible for 46,XY DSD were detected first time in literature. Functional studies of the genes were planned.

P1-1508

#### ETIOLOGICAL STRUCTURE DISORDERS OF SEX DEVELOPMENT

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**Objectives:** To study structure disorders of sex development (DSD) by one center.

**Methods:** It was included 248 patients with diagnosis DSD at birth to 18 years. It was conducted: cytogenetic, molecular cytogenetic and molecular genetic studies, structural evaluation of the external and internal genitalia, histology of gonads removed, hormonal research in mini-puberty and puberty, basal and stimulated by human chorionic gonadotropin hormone measurements in neutral period.

**Results:** The structure of patients with DSD by karyotyping showed 46, ?Y DSD – 48% (120/248), 46, ?? DSD – 38% (93/248), 14% (35/248) – sex chromosome DSD. A definitive diagnosis was received in 65% (162/248) of children with DSD. In groups 46, ?X DSD and sex chromosome DSD diagnosis is established in 100% of cases. Sex chromosome DSD include the following variants: mosaicism 45,X/46,XY in 65% (23/35) cases, Klinefelter syndrome – 23% (8/35), Turner syndrome – 6% (2/35), chimeric – 6% (2/35). 46, ?X DSD consisted of congenital adrenal hyperplasia in 91% (85/93) and testicular DSD in 9% (8/93) patients.

Final diagnosis in the group of 46,XY DSD was established in 28% (33/120) and 10% (12/120) of diagnosis confirmed by molecular genetic study: disorders of gonadal (testicular) development - 61% (20/33), disorders in androgen synthesis or action - 30% (10/33), persistent Mullerian duct syndrome - 9% (3/33). Disorders of gonadal development include complete gonadal dysgenesis in 10% (2/20) cases; in 75% (15/20) of cases – partial gonadal dysgenesis; in 15% (3/20) – gonadal regression. Disorders in androgen synthesis or action presented by androgen insensitivity in 90% (9/10) and 10% (1/10) - 17-hydroxysteroid dehydrogenase deficiency. While 6% (7/120) of patients had heterozygous mutations in the genes *FOXF2*, *ZFPM2*, *ESR2*, *LHX1*, *ZFPM2*, *DHCR7*, *LHCGR1*, pathological significance of today is not known.

**Conclusions:** Only 65% of patients with DSD had a verified variant of nosological pathology at that in groups 46, ?X DSD and sex chromosome DSD by all patients. While in the group of patients with karyotype 46, XY only every third had nosological diagnosis therefore diagnostic algorithm should be optimized in this group.

P1-1509

#### MOLECULAR AND CELLULAR CHARACTERIZATION OF PATIENTS WITH 46,XX TESTICULAR AND OVOTESTICULAR DISORDERS OF SEX DEVELOPMENT

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**Objectives:** The aim of this study is to characterize a cohort of 46,XX-SRY negative (in lymphocyte and gonad DNA) testicular (T) and ovotesticular (OT) disorders of sex development (DSD) patients (P) followed in a tertiary hospital.

**Methods:** We collected 17 well characterized families with 46,XX T and OT DSD. For the study design, the patients were divided in two groups: isolated DSD (n=13) and syndromic DSD (n=4), mainly based on the presence of additional anomalies, dysmorphic features and intellectual disability. All patients were confirmed to be SRY-negative by PCR assay. Copy number variations (CNVs) were studied by whole genome CGH+SNP microarray in four patients with syndromic DSD. Direct sequencing of gene-candidates and CNVs in *SRY*, *SOX9*, *NROB1*, *NR5A1* and *WNT4* were assayed by MLPA in all patients. Genetic variants were searched by whole exome sequencing (WES). Deleterious variants were established by *in silico* tools. In gonadal tissues, *RSPO1* genetic variants were studied by Sanger and CNVs by same MLPA assay as in genomic DNA. Expression of *HSD3B2* and *CYP17A1* was analyzed by immunohistochemical (IHC) staining in gonadal tissues.

**Results:** Clinically significant chromosomal alterations were detected in two out of four with syndromic DSD. A complex deletion/duplication rearrangement involving the short arm of chromosome 12, a loss in copy number in the 9q31.2 region as well as multiple contiguous stretches of homozygosity were identified in the child of related parents (coefficient of consanguinity of 1/8). The second patient was found to carry an ~11.2 Mb deletion in 1p chromosome, containing multiple genes implicated into ovarian development. WES did not identify alterations in any genes that are known to induce testicular differentiation. IHC in gonad tissue was studied in 2 P (P1 and P2) evaluated at the

age of 1 and 3 months respectively. Histological studies showed dysgenetic testes in P1 and ovotestes in P2. IHC revealed minimal expression of CYP17A1 in interstitial cells and mild expression of HSD3B2 in Sertoli cells.

**Conclusions:** Diagnosis of patients with 46,XX DSD remains to be a challenge. We propose that the ectopic expression of steroidogenic enzymes may be due to a switch in cell fate lineage in the bipotential gonad resulting in abnormal gonadal differentiation.

P1-1510

# SEVERE CASE OF TESTOTOXICOSIS IN AN INFANT WITH NODULAR LEYDIG CELL HYPERPLASIA DUE TO LHCGR GENE ACTIVATING MUTATION

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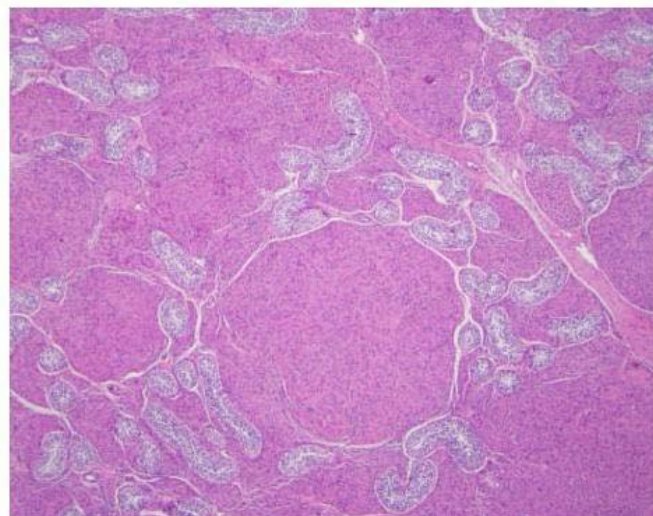
**Objectives:** To describe a case of a 9-month-old male with extremely elevated levels of testosterone, diagnosed with testotoxicosis due to an activating *LHCGR* gene mutations.

**Methods:** At 9 months of age he appeared large for age with coarse facial features and low pitched voice. The scrotum appeared to be rugated and slightly enlarged for age with bilateral testicular volumes of 4 mls, along with pubic hair Tanner stage III. The penile length was 6.5 cm with a girth of 2.5 cm. Testosterone levels were elevated at 1383 ng/dl and 17 OH-progesterone (OHP) levels of 507 ng/dl, undetectable  $\beta$ -HCG, AFP levels, undetectable ultrasensitive LH and FSH levels. He was started on an androgen receptor blocker Bicalutamide 25 mg and Anastrozole 1 mg daily. He continued to have erections along with progression of secondary sex characteristics and testosterone levels rose further up to 1542ng/dl. Testicular ultrasounds showed progressive heterogeneity and nodularity in both testicles. He underwent right orchiectomy at 1 years of age.

**Results:** Pathology after the right radical orchiectomy was consistent with diffuse nodular Leydig Cell Hyperplasia. After his right radical orchiectomy he continued to go through a growth spurt with testosterone levels increasing to maximum of 2177 ng/dl and clinical symptoms to refractory to medical therapy. He underwent left orchiectomy which revealed diffuse, small nodular aggregates of medium sized polygonal cells with abundant, granular, eosinophilic cytoplasm with interspersed seminiferous tubules consistent with Leydig cell hyperplasia (see Fig). Bone age at 10 months of age was 8 years. CT scan of the chest and abdomen was negative. Normal MRI of the Brain and Pituitary gland. Genetic testing revealed 1732G->C mutation was noted on the *LHCGR* gene resulting in a p.Asp578His amino acid change of the sixth transmembrane part of the receptor.

**Conclusions:** We report a severe case of testotoxicosis presenting at a very early age refractory to medical management and nodular changes in testis. He required

sequential and eventual bilateral orchiectomy. The mutation found in this case has only been previously reported to be somatic in 3 boys with benign nodular adenoma with testotoxicosis. In contrast our patient had diffuse nodular lesions and a genomic DNA 1732G->C mutation.



P1-1511

# A RARE CASE OF TURNER SYNDROME WITH A SPECIAL KARYOTYPE: A CASE REPORT AND REVIEW OF LITERATURE

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**Objectives:** Reported an extremely rare case of Turner syndrome with a special karyotype of 46, X, rea (X) (qter-->q22.3::p11.23-->qter).

**Methods:** with the development of HTS and aCGH technology, and its comprehensive application combined with G banding analysis and FISH to conduct a more sophisticated study in derived chromosome.

**Results:** The female patients had some typical characteristics of Turner syndrome, including short stature, cubitus valgus, left toe brachydactyilia, underdeveloped breasts and so on. The ultrasound examination showed a small-sized uterus and bilateral ovaries in patients. Oral glucose tolerance test (OGTT) presented impaired glucose tolerance. Growth hormone stimulation assay revealed growth hormone deficiency. G-banding chromosome analysis indicated normal 46, XX. And FISH with locus specific probed for sex chromosome further confirmed 100% XX. Unexpectedly, high-throughput sequencing indicated an abnormal female karyotype. There were a 45.04 Mb deletion in Xp22.33p11.23, a 47.16 Mb repeated fragment in Xq22.3q28, and a 0.68 Mb repeated fragment in 3p12.3.

**Conclusions:** with the development of HTS and aCGH technology, and its comprehensive application combined with G banding analysis and FISH, it is promising to conduct a more sophisticated study in derived chromosome, which will allow for a detailed elucidation on the association between the genotype and phenotype.

P1-1512

#### **A TRICKY TRIAD: XY FEMALE WITH TRISOMY 21 AND PARTIAL TRISOMY 22**

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**Objectives:** We describe a 5 year old XY phenotypic female patient with trisomy 21 and 22 q11.21 duplication initially evaluated at birth. To our knowledge, this combination has not been previously described in the literature.

**Methods:** At birth, the patient was noted to have normal female external genitalia and features of trisomy 21. Chromosomal analysis revealed 47 XY trisomy 21 with partial trisomy 22 (duplication of 22 q11.21). SRY gene probe was positive and no mutations were noted in the complete coding region. Pelvic ultrasound showed a normal uterus, uterine cervix and vaginal canal. No gonads were noted. FSH was 46.9 IU/L, LH was 6.6 IU/L, and estradiol was 31 pg/mL (11 days of age).

MRI revealed two oval structures at the junction of the pelvis and inguinal area. Total inhibin 40pg/mL, anti-Müllerian hormone < 0.08ng/mL. Baseline dihydrotestosterone was 6.5pg/mL (0-49.9). Further baseline testing specimens were lost.

After a three day HCG stimulation test, the testosterone was <1ng/dL and dihydrotestosterone <2.5pg/mL. Ultrasound at three years of age showed bilateral soft inguinal masses identified as lymph nodes. Uterus and vaginal canal were again confirmed, and no gonads identified.

She has above-average functioning for a patient with trisomy 21. On the Down's syndrome growth chart, weight is in the 25th percentile and height is on the 30th percentile.

The patient appears phenotypically female and to date identifies as female.

**Results:** We describe a unique case with multiple chromosomal anomalies including trisomy 21, partial trisomy 22 involving duplication of 22q11.21, and XY karyotype with female phenotype. To date, an etiology for the disorder of sexual differentiation is not yet established as no mutation in the SRY gene has been noted.

**Conclusions:** To our knowledge no patient has been described with Trisomy 21 and 22 q11.21 duplication with or without a disorder of sexual differentiation with XY female phenotype. Further testing to include whole genome sequencing is necessary to elucidate the DSD etiology and monitoring for gonadoblastoma is necessary. Ongoing evaluation for significant effects of trisomy 22 and 21 will also be performed.

P1-1513

#### **CLINICAL FINDINGS OF A NOVEL CYP19A1 (AROMATASE) C.1206\_1263+106DEL (P.H402RFSX4) MUTATION CAUSING VIRILIZATION OF A 46,XX NEWBORN**

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**Objectives:** P450 aromatase (CYP19A1) converts androgens to estrogens. CYP19A1 gene mutations cause aromatase deficiency. It is very rare entity. As a result of intrauterine exposure to increased androgens, girls are born with virilization. However, serum androgens returned rapidly to normal after delivery in some cases. Also, ovarian cysts may be developing due to increased LH stimulation. Hirsutism, deep voice and acne formation are seen in mother during pregnancy. Baby girl with novel CYP19A1 gene mutation was presented here.

**Methods:** A baby girl born after 36 weeks gestation was referred to evaluation of genital ambiguity. Her parents were first cousin. Hirsutism in the mother beginning second trimester was reported. She also had symptoms similar acromegaly such as growth in hands, feet and nose, increased IGF-1 level, elevated liver enzyme during last trimester. Although IGF-1 and liver enzyme convert to the normal, mother's physical appearance did not change.

**Results:** At the admission, baby's clinical examination revealed clitoromegaly. Karyotype was 46, XX. Laboratory examination revealed LH 0.29 mIU/mL, FSH 16.18 mIU/mL, Estradiol <10 pg/mL, Total testosterone 0.31 ng/mL, 1.4 androstenedione 4.35 ng/mL, DHEAS 239.1ug/dL. Congenital adrenal hyperplasia was ruled out by ACTH stimulation test. Although uterus was prepubertal size, no follicles were seen in both hypoplastic ovaries. To confirm the clinical diagnosis, genetic study was performed.

Genetic analysis revealed a homozygous c.

1206\_1263+106del (p.H402RfsX4) mutation in the CYP19A1 gene. This large deletion was predicted to be deleterious by in silico analysis softwares.

**Conclusions:** c.1206\_1263+106del (p.H402RfsX4) is a novel CYP19A1 mutation may causes a virilization and hypoplastic ovaries in a 46, XX newborn.

P1-1514

#### **FAMILIAL CASE OF 46,XY DISORDER OF SEX DEVELOPMENT DUE TO NOVEL MUTATION IN MAP3K1 GENE**

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# A RARE CAUSE OF PREPUBERTAL GYNECOMASTIA

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**Objectives:** Prepubertal gynecomastia is a rare condition; some cases are due to excessive aromatase activity or estrogen producing adrenal or testicular tumors. Nearly 5% of the patients with testicular mass present with gynecomastia. Sertoli cell tumors (SCTs) account for 2% of prepubertal testicular tumors. SCTs are sporadic in 60% of the reported cases, while the remaining is a component of Peutz-Jeghers syndrome and Carney complex. We here report a case of testicular tumor which presented with prepubertal gynecomastia.

## Methods: Case Description:

A 6-year-old boy was referred to pediatric endocrinology clinic because of progressive bilateral breast enlargement for the last two years. There were no perioral lesions, no history of a chronic disease, intestinal symptoms, medication, or a familial disorder. Height was 120 cm (>75th centile for age), weight was 25 kg (>75th centile for age), and physical examination revealed bilateral gynecomastia (Tanner Stage-3), no axillary or pubic hair, stretched penile length was 6 × 1.5 cm, and left testis was 6 mL and left testis was 2 mL. Bone age was advanced (7 years). Serum estrogen was 30 pg/ml, serum FSH was 0.5 mIU/ml and serum LH was 0.2 mIU/ml. Testicular ultrasonography and magnetic resonance imaging exhibited a 15 × 15 × 20 mm cystic lesion in the left testis. Left high inguinal orchiectomy was done.

**Results:** Histopathological investigation revealed a SCT with strong inhibin positivity. Gynecomastia regressed at the end of three months following the operation.

**Conclusions:** Progression of gynecomastia in a boy with increase in growth velocity, advanced bone age, increase in testicular volume should raise the suspicion of SCTs.

P1-1516

# PHENOTYPE-GENOTYPE CORRELATION IN NR5A1 GENE REMAINS ELUSIVE: HETEROZYGOSIS FOR P.D293N MUTATION ALSO LEADS DSD PHENOTYPE

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**Objectives:** We report on a patient with XY partial gonadal dysgenesis (PGD) with a heterozygous mutation that had already been described in homozygous patients from a family with different phenotypes.

**Methods:** Our patient was referred with 14 days of age due to sex ambiguity. He had a 1.5-cm phallus, penoscrotal hypospadias, and both gonads were in the labioscrotal folds.

**Objectives:** Male sex determination depends on the expression of *SRY* on the Y chromosome that induces the development of the undifferentiated gonads in testis. Mutations in *MAP3K1* are associated with 46, XY disorder of sex development (DSD). *MAP3K1* and mitogen-activated protein kinase (MAPK) signaling pathway determine normal development of the testis. The absence of the p38a and p38b MAPK isoforms results in XY sex-reversal that is associated with reduction in *SRY* levels. Sex-reversal is associated with a failure to transcriptionally upregulate *SRY* and with a delay in *SRY* expression. Few cases of familial and sporadic 46,XY DSD due to mutation in *MAP3K1* gene have been reported.

**Methods:** We report maternal half sisters with 46,XY DSD (Picture 1).

**Results:** Both patients have been raised as female. 17-year-old patient had clitoral hypertrophy, urogenital sinus, Tanner stage 2, primary amenorrhea, hypergonadotropic hypogonadism (Tab.1). Karyotype 46,XY was determined. Hypoplastic uterus, gonads (right size 20 x 10 mm and left size 7 x 14 mm) were found by MRI. 13.5-year-old patient had normal female external genitalia, Tanner stage 1, hypergonadotropic hypogonadism, karyotype 46,XY. Hypoplastic uterus was found by MRI, ovaries were not defined. The diagnostic laparoscopy in both patients was performed. Bilateral gonadoblastoma with the transformation in dysgerminoma on the right side in 17-year-old patient and ovotesticular gonadal dysgenesis in 13.5-year-old patient were revealed by histological examination. The heterozygous mutation p.C691R in the *MAP3K1* gene was detected in maternal half sisters by parallel sequencing (platform Ion Torrent).

**Conclusions:** We identified the heterozygous mutation in *MAP3K1* gene responsible for familial case of 46,XY DSD. This mutation was not previously described. Variable phenotype in siblings with the same mutation in the *MAP3K1* gene could be seen.

Picture 1. Pedigree of maternal half sisters with 46,XY DSD

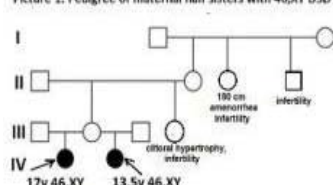


Table 1. Clinical and Laboratory data of patients with 46,XY DSD

	Age	External genitalia	Height SDS	Tanner stage	FSH, U/l	LH, U/l	Ts, nmol/l	17-OHP, nmol/l
Patient 1	17 y	clitoral hypertrophy, urogenital sinus	164.3 cm +0.35	2	104 (19-117)	88 (2.6-12)	3.11 (0.1-2.7)	3.6
Patient 2	13.5 y	Normal female genitalia	155.9 cm -0.64	1	137 (19-117)	39.9 (2.6-12)	0.653 (0.1-2.7)	4.4

**Conclusions:** We identified the heterozygous mutation in *MAP3K1* gene responsible for familial case of 46,XY DSD. This mutation was not previously described. Variable phenotype in siblings with the same mutation in the *MAP3K1* gene could be seen.

Karyotype was 46,XY. At 6 weeks of age he had normal FSH, DHEA and androstenedione, whereas LH, 17-OH-progesterone and testosterone were elevated, slightly elevated and low, respectively. ACTH test resulted normal but there was no response to hCH test performed at 7 months. Antimüllerian hormone was also low. He received a male sex assignment and underwent hypospadias repair. He had a right streak gonad and a left dysgenetic testis, leading to the diagnosis of XY PGD. Spontaneous puberty started at 12 years and progressed normally. At 16 years he had high FSH and LH but normal testosterone. Whole exome sequencing was performed to search for pathogenic mutations in genes involved in testis differentiation.

**Results:** Whole exome sequencing revealed heterozygosity of the c.877G>A transition within exon 5 of *NR5A1*. This change leads to p.D293N mutation that had already been described in four homozygous members of a family: one with XY PGD, one with XX complete gonadal dysgenesis (CGD) and two with XY CGD. Heterozygous members of the family were phenotypically normal. The mother of the present patient was born in the same little town where that family originated.

**Conclusions:** To our knowledge, this is the first p.D293N heterozygous individual to present DSD. The recessive inheritance for this mutation concluded on basis of that family pattern and on the relatively high level of residual activity of the mutated SF-1 is no longer appropriated. SF-1 acts in a dose-dependent manner and regulates many other genes involved in sex differentiation process, which could explain the broad spectrum of phenotypes caused by the same mutation. The present case illustrates the difficulty in establishing an appropriate phenotype-genotype correlation and highlights the importance of genetic knowledge for the correlation of *NR5A1* mutations with clinical phenotypes. (Fapesp: 2015/04763-4)

P1-1517

# A MUTATION IN WT1 (WILMS' TUMOR SUPPRESSOR 1) ASSOCIATED WITH 46,XX TESTICULAR DSD

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**Objectives:** 46,XX DSD (Disorder of Sex Development) includes individuals with ovotestes (ovotesticular DSD (OTDSD)) or testes (testicular DSD (TDSD)). Most individuals with 46,XX TDSD carry the *SRY* gene. However, our understanding of the molecular causes of TDSD and OTDSD remains incomplete. Recently, using exome sequencing we and others have identified a recurrent missense mutation in *NR5A1* associated with 46,XX TDSD/OTDSD. Here, using a similar approach we identified a novel and de novo missense mutation of the *WT1* gene in a case of 46,XX TDSD.

**Methods:** The boy of Egyptian origin presented with male external genitalia, dysgenetic testis, microcephaly and a small uterus. Kidney function was normal. The DNA of the boy and

his parents was exome sequenced. Pathogenic mutations were confirmed by Sanger sequencing. Transient gene expression assays and protein-protein interaction studies were performed to show the effect of the mutation on the biological activity of the *WT1* protein.

**Results:** The 46,XX boy lacked the *SRY* gene in DNA from peripheral blood and testis tissue. Array CGH indicated normal ploidy. Exome sequencing identified a *de novo* missense mutation of a highly conserved arginine residue in the fourth zinc-finger of *WT1* (p.Arg495Gly). This mutation was absent from all public databases and an in-house panel of 300 ancestry-matched controls. Transient gene expression assays and protein-protein interaction studies showed that the mutant *WT1* protein abnormally regulated/interacted with genes/proteins involved in both male and female gonadal development. More interestingly, in the *in-vitro* conditions, the mutation altered the transcriptome of granulosa cells to resemble that of Sertoli cells. These data are strongly in favour of the *WT1* mutation being responsible for the development of testis in this 46,XX boy.

**Conclusions:** Mutations in *WT1* have been previously reported in anomalies of testis formation in 46,XY individuals. This is the first time that a mutation in *WT1*, has been identified associated with 46,XX TDSD. This raises the intriguing possibility that specific mutations in *WT1* may be associated with testis formation in 46,XX chromosomal context in a similar manner to the recurrent p.R92W mutation of *NR5A1*.

P1-1518

# PARTIAL ANDROGEN INSENSITIVITY SYNDROME IN A FAMILY WITH A DEEP INTRONIC MUTATION CREATING AN ALTERNATIVE SPLICE ACCEPTOR SITE IN THE AR GENE

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**Background:** Partial androgen insensitivity syndrome (PAIS) is a rare endocrine disorder caused by compromised responsiveness to androgens. However, androgen receptor gene (*AR*) mutations on the coding regions and their splice sites have been identified only in < 25% of patients with PAIS. Here, we report a novel deep intronic mutation in the *AR* gene that created an alternative splice acceptor site in a family with PAIS.

**Methods: Patients:** We encountered a Japanese family in which the proband and his two nephews PAIS-compatible phenotype including undermasculinized genitalia, sufficient



androgen production, and hypergonadotropinism. The two obligatory carrier females and their non-consanguineous husbands were clinically normal.

**Results: Molecular studies:** We sequentially performed Sanger sequencing of *AR*, *NR5A1*, and *MAMLD1*, and whole-exome sequencing, yet identifying no pathologic sequence variant on the coding regions and their splice sites. However, since the same allele of CAG repeat length polymorphism on exon 1 of *AR* was shown to be co-segregated with the PAIS phenotype, we carefully re-examined the non-coding sequences of *AR* using the whole-exome sequencing data, identifying a deep intronic substitution at intron 6 (c.2450-42G>A) creating the "AG" splice acceptor motif in the affected individuals and the carriers. Furthermore, we performed sequencing analysis for RT-PCR products obtained with primers on exons 5 and 8 before and after treatment of cycloheximide (CHX), an inhibitor for nonsense mediated mRNA decay (NMD), identifying a mutant mRNA with retention of a 40-bp intronic segment and a premature termination on exon 7 that satisfied the condition for NMD after CHX treatment, as well as a wildtype mRNA that remained constant before and after CHX treatment.

**Conclusions:** We identified a *de novo* deep intronic mutation (c.2450-42G>A) creating an alternative splice acceptor site in a family with PAIS. Notably, while this mutation produced mutant mRNA subject to NMD, wildtype mRNA was also generated. It is inferred, therefore that the deep intronic mutation has resulted in a production of reduced, but not abolished, amount of wildtype AR protein, leading to the development of PAIS.

P1-1519

#### AN UNUSUAL CASE OF AMBIGUOUS GENITALIA: URETHRAL DUPLICATION WITH SALT WASTING IN A NEWBORN

*Massiel Sarmiento, MD; John H Makari, MD; Rebecca Riba-Wolman, MD, University of Connecticut School of Medicine, Farmington, CT, United States*

**Objectives:** Congenital Adrenal Hyperplasia (CAH) has an incidence of 1:10,000-20,000 births with the majority due to 21-hydroxylase deficiency. Virilization and mineralocorticoid deficiency in a 46,XX infant is a medical emergency most commonly due to CAH. Here, we present an unusual case of urethral duplication with obstructive uropathy and UTI presenting as salt wasting in a female with genital ambiguity.

**Methods:** A one day old full term infant presented with ambiguous genitalia after an uncomplicated pregnancy without maternal virilization. Initial exam by a multidisciplinary team for disorders of sexual differentiation revealed: 2 cm phallic structure, introitus with protruding cystic structure, nonpalpable gonads, increased anogenital ratio and urination from perineal urethra. Ultrasound showed normal uterus, ovaries and bladder; tiny cortical cysts in right kidney. Initial labs showed mild acidosis, random cortisol 3.5 mcg/dL, karyotype 46,XX, negative FISH for Y. ACTH stimulation test was performed; patient was presumptively started on hydrocortisone (HC), fludrocortisone (FC) and

sodium (NaCl). Due to persistent hyponatremia, NaCl and FC were held. By day of life 12, hyponatremia (Na 129), hyperkalemia (K 7.4) and acidosis (CO<sub>2</sub> 14) developed on HC treatment.

**Results:** A voiding cystourethrogram was done with concern for urethral duplication. It identified an anterior urethra filling a diverticular structure, with the appearance of a phallus, and a normal perineal urethra. E.coli urosepsis was diagnosed and treated. ACTH stimulation, microarray and whole exome sequencing were normal. Patient uneventfully weaned off all medications, as metabolic derangements were transient.

**Conclusions:** Female urethral duplication is rare (<40 cases reported to date). Fewer than 10 have been associated with genital ambiguity. Urethral duplication with obstructive uropathy and UTI can present with electrolyte disturbances due to mineralocorticoid resistance; however, the combination with genital ambiguity was described once in the last 40 years. Suspicion for CAH **must** be high in an infant with salt wasting and virilization, but urethral duplication with clitoral enlargement and mineralocorticoid resistance is a rare diagnosis with a similar presentation.

P1-1520

#### THE ROLE OF A NEXT GENERATION SEQUENCING PANEL IN THE DIAGNOSTIC PATHWAY IN DISORDERS OF SEX DEVELOPMENT

*Emma Webb, PhD, University of Birmingham, Birmingham, United Kingdom; Lowri A Hughes, MD; S Allen, PhD; Trevor Cole, PhD; Julie Reed, PsyD; N D Drinkall, PhD; H Chandran, MD; L Mccarthy, MD; Jeremy Kirk, MD, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, United Kingdom; Nils Krone, PhD, University of Sheffield, Sheffield, United Kingdom*

**Objectives:** To highlight how advances in genomic medicine change clinical management of individuals with disorders of sex development (DSD).

**Methods:** N/A

**Results:** Patient 1 presented at birth with proximal penoscrotal hypospadias, micropenis, partial bifid scrotum and no palpable gonads. Initial hyponatraemia (128mmol/L) quickly resolved with low dose sodium supplements. Urinalysis was normal. Karyotype was 46,XY, cortisol peak to synacthen stimulation was normal and baseline testosterone low (1.3nmol/L). Following review at the multidisciplinary DSD clinic laparoscopy was planned to locate the gonads and clonal sequencing using a custom designed TruSeq amplicon panel covering 31 genes associated with DSD performed. A pathogenic WT1 mutation was identified. Urgent USS pelvis identified a heterogeneous lesion in the left kidney, On biopsy diffuse mesangial sclerosis was identified. The patient went on to have a left nephrectomy and chemotherapy for Wilms tumour aged 3 months.

Patient 2 had genetics performed as part of investigation for her right sided diaphragmatic hernia and motor delay aged 2 years; karyotype was 46,XY. She has normal external female genitalia. Baseline and hCG stimulated testosterone were

undetectable. She was reviewed in the DSD clinic prior to the development of the DSD gene panel. USS pelvis aged 3 years showed a rudimentary uterus, possible right ovary and “bright” kidneys. Following review at the multidisciplinary DSD clinic aged 4 years targeted WT1 screening was performed in view of her diaphragmatic hernia and echogenic kidneys. A pathogenic WT1 mutation was identified. Aged 5 years she had excision of a left streak gonad and a right gonadoblastoma.

**Conclusions:** These cases highlight the value of targeted sequencing panels in achieving an early diagnosis in children with DSD. Children with WT1 mutations are at significant risk of malignancy as well as renal failure and benefit from regular clinical assessment. If the DSD panel had been available at the time patient 2 was first seen in the DSD clinic her WT1 mutation may have been identified several years earlier and she may not have developed a gonadoblastoma. In our clinical practice, we have therefore introduced NGS analysis at an early stage of our clinical pathway to enable timely personalised medicine delivery.

P1-1522

#### A NOVEL SYNDROMIC FORM OF 46,XX DSD IS CAUSED BY FRAMESHIFT MUTATIONS IN THE NUCLEAR RECEPTOR NR2F2 (COUP-TFII)

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**Objectives:** Disorders of sex development (DSD) are a group of rare complex orphan diseases of errors of gonadal development and hormone synthesis or action. This includes testis formation on a 46,XX background (46,XX testicular or ovotesticular DSD). Most non-syndromic 46,XX (ovo)testicular DSD patients carry the SRY gene or have rearrangements involving different SOX gene loci. However, the vast majority of SRY-negative 46,XX (ovo)testicular DSD cases do not have a molecular diagnosis. Unbiased genomic approaches, such as exome sequencing should reveal new gene mutations causing 46,XX (ovo)testicular DSD.

**Methods:** We performed whole exome sequencing on 2 cases of a novel syndromic form of 46,XX DSD at a coverage of x50. Sanger sequencing of the NR2F2 gene was performed on a

further case of 46,XX DSD with the same somatic anomalies as well as ancestry-matched controls and non-syndromic cases of 46,XX DSD.

**Results:** Three individuals presented with variable expression of congenital heart disease, eyelid anomalies and variable masculinization of the external genitalia. Two cases were suspected (ovo)testicular DSD, and gonad histology of the third case revealed an ovotestis. Analysis of datasets revealed, in all three cases, novel frameshift mutations in the NR2F2 genes that are predicted to generate downstream premature stop codons. In two cases the mutations were *de novo*. These mutations are specific for this DSD phenotype since they are absent from all public databases, ancestry-matched in-house controls and 67 cases of non-syndromic 46,XX (ovo)testicular DSD. Consistent with the phenotype, NR2F2 was found to be expressed in the pre-granulosa cells in the human foetal ovary immediately before the expression of FOXL2 could be detected.

**Conclusions:** Specific frameshift mutations involving the nuclear receptor NR2F2 are responsible for a novel syndromic form of 46,XX DSD.

#### POSTER SESSION 1

Thursday, September 14, 2017, 5:45-6:45pm

#### P1 - Syndromes

P1-1600 – P1-1615

P1-1600

#### THE GENOTYPIC AND PHENOTYPIC DIVERSITY OF MOSAIC TURNER SYNDROME (TS)

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**Objectives:** TS is a heterogeneous disorder that benefits from a multidisciplinary approach to screen & provide treatment for its associated endocrine, cardiac, renal, audiological, & autoimmune features. We sought to identify the prevalence of these comorbidities in our patients with mosaic TS.

**Methods:** The records of 40 patients (38 children & adolescents & 2 adults) who presented for evaluation between 8 weeks & 42 years of age to genetics and/or endocrine clinic were reviewed, to determine their clinical course. All patients had varying mosaic TS karyotypes that lacked Y chromosomal material (3-96% monosomy X).

**Results:** Twenty-five percent (10/40) of patients had been diagnosed prenatally via chorionic villus sampling or amniocentesis. Seventy-one percent (27/38) were below the third percentile for height on the standard curve upon initial presentation, while the remaining 29% fell between the 5<sup>th</sup> and 75<sup>th</sup> percentile. Final adult heights were documented in fifteen patients, & ranged from 134.6-167 cm. Three

patients (7.5%) had severe congenital heart disease requiring surgery, while 19% had bicuspid aortic valves on echocardiogram. Otitis media (OM), myringotomy tube placement, and/or hearing deficits were documented in 47.5%. Thirty-one (77.5%) were noted to have neurocognitive concerns including developmental delays, ADHD, anxiety, autism spectrum disorders, and difficulties in school. Genitourinary anomalies were rare; one patient had a horseshoe kidney, another had a duplicated collecting system, & a third had a bicornuate uterus and septated cervix. Twenty-five patients (62.5%) received growth hormone therapy. Fifteen percent were being treated for hypothyroidism, while other autoimmune diseases were less common (one patient each had been diagnosed with celiac disease, type 1 diabetes, & inflammatory bowel disease). Forty-four percent of teenage females (11/25) had ovarian failure. Nine patients (22.5%) were obese, & two had undergone weight loss surgeries.

**Conclusions:** Short stature, cardiovascular anomalies, neurosensory hearing loss, OM, developmental & psychiatric issues, ovarian failure, hypothyroidism, & obesity were the most prevalent comorbidities in our cohort of patients with mosaic TS. There was no correlation between phenotype & monosomy X percentage.

P1-1601

#### AMBULATORY BLOOD PRESSURE IN YOUNG WOMEN WITH TURNER SYNDROME

*Line Cleemann, MD; Sara Christensen, MD; Kirsten Holm, MD; Gitte Salskov, Nurse, Nordsjaellands Hospital, Hilleroed, Denmark; Claus H Gravholt, Professor, Aarhus University Hospital, Aarhus, Denmark*

**Objectives:** Evaluation of 24-hour blood pressure (BP), pulse and night:day BP ratio in a group of young women with Turner syndrome (TS).

**Methods:** 20 patients with TS (age  $22.9 \pm 2.3$  (mean  $\pm$  SD) years) and a control group of 12 healthy age-matched young women (age  $23.11 \pm 2.2$  (mean  $\pm$  SD) were investigated by 24-hour ambulatory blood pressure in a cross-sectional setting as part of a prospective interventional trial. 30 % (n=6) of the TS patients had a former cardiac disease of which four had bicuspid aortic valves. No participants, TS or controls, were treated with antihypertensive medication.

**Results:** The 24-hour ambulatory systolic BP was similar among TS and controls (median 112 vs 109 mmHg,  $p = 0.70$ ), while 24-hour ambulatory diastolic BP (median 70 vs 64 mmHg,  $p = 0.01$ ) and pulse (median 75 vs 66,  $p = 0.01$ ) were significantly increased in TS. Day diastolic BP was higher in TS (median 75 vs 70 mmHg,  $p = 0.08$ ) however not statistically significant. Day pulse also was higher in TS (median 79 vs. 67 bpm,  $p = 0.03$ ) whereas day systolic BP was comparable. Night diastolic BP (TS vs C: median 61 vs 52 mmHg,  $p < 0.0005$ ) and pulse (TS vs C: median 67 vs 55 bpm,  $p = 0.02$ ) were significantly higher in TS compared to controls. There was no difference in night systolic BP (TS vs C: median 99 vs 98 mmHg,  $p = 1.00$ ). In TS, diastolic night:day ratio was

insignificantly higher (TS vs C: median 0.81 vs 0.78,  $p = 0.08$ ), while systolic night:day was comparable (TS vs C: median 0.85 vs 0.89,  $p = 0.07$ ). No differences in systolic and diastolic BP or pulse, day or night, or in night:day BP ratios were found between TS patients with or without former cardiac disease.

**Conclusions:** Already in late adolescence and early adulthood diastolic BP is increased and a significant non-dipping pattern in diastolic night BP and increased diastolic night:day ratio was present among TS. It implies that continuously and regular follow-up of BP in young adulthood and perhaps even before is important in order to reduce the increased cardiac morbidity and mortality associated with TS. It remains an enigma why BP becomes dysregulated early in life in TS.

P1-1602

#### EXERCISE CAPACITY IN ADOLESCENTS WITH 47,XXY/KLINEFELTER SYNDROME

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**Objectives:** Adult males with Klinefelter syndrome (KS) have lower exercise capacity, greater adiposity, and a higher prevalence of cardiovascular mortality than men without KS. Our objective is to evaluate whether cardiometabolic impairments exist in adolescents with KS compared to healthy male controls of similar age, body mass index (BMI) and pubertal status.

**Methods:** Males 12-18 years of age with non-mosaic 47,XXY were compared to healthy, sedentary male controls of similar BMI and pubertal stage. All participants underwent a physical exam, fasting morning blood draw, full body dual energy x-ray absorptiometry for body composition, and a graded exercise test to peak oxygen consumption ( $VO_2$  peak) using an upright bicycle ergometer. Insulin sensitivity was calculated from fasting insulin and glucose using the homeostatic model assessment.

**Results:** The mean age of the 28 participants (14 KS, 14 controls) was  $14.3 \pm 1.5$  years. The mean BMI was  $20.8 \pm 3.9$  kg/m<sup>2</sup> and median pubic hair Tanner stage was 4 (range 2-5), with no differences between groups.  $VO_2$  peak for KS was  $31.6 \pm 8.3$  ml/kg/min compared to controls whose peak  $VO_2$  was  $42.4 \pm 8.4$  ml/kg/min ( $p=0.002$ ). There were no differences in peak heart rate or respiratory exchange ratio. Percent body fat was greater in KS ( $26.4 \pm 8.2\%$  versus  $18.1 \pm 9.9\%$ ,  $p=0.025$ ); for any given BMI, males with KS had 10.0% higher body fat. After adjusting for differences in lean body mass,  $VO_2$  peak was still significantly lower in KS ( $44.5 \pm 7.9$  ml/lean kg/min versus  $54.8 \pm 7.6$  ml/lean kg/min,  $p=0.002$ ).  $VO_2$  peak strongly correlated with body fat percentage ( $r=0.78$ ,  $p<0.001$ ) and insulin sensitivity ( $r=0.53$ ,

p=0.005). Hematocrit and total testosterone were similar between groups and did not correlate with VO<sub>2</sub> peak.

**Conclusions:** Adolescent males with KS have impaired exercise capacity and greater body fat compared to sedentary males of similar age, BMI, and pubertal stage. Adolescent males with KS appear to be at greater cardiometabolic risk than their peers despite not being overweight or obese. Possibilities underlying these differences may include impairments delivering substrate to muscle or energy metabolism within muscle, and additional research into these mechanisms is underway.

**Table 1. Comparison of cardiometabolic outcomes between adolescent boys with and without Klinefelter Syndrome / 47,XXY.**

	XXY (n=14)	Controls (n=14)	p-value
Age	13.9 ± 1.6	14.7 ± 1.3	0.15
BMI	20.8 ± 4.0	20.9 ± 3.9	0.94
BMI%	57.4 ± 31.3	51.1 ± 31.1	0.60
%BF by DXA	26.4 ± 8.2	18.1 ± 9.9	<b>0.025</b>
HbA1C	5.40 ± 0.23	5.06 ± 0.38	<b>0.008</b>
Fasting glucose	87.9 ± 6.1	82.5 ± 7.0	0.059
Fasting insulin	14.5 ± 12.5	9.3 ± 7.3	0.13
HOMA-IR	3.2 ± 3.0	1.9 ± 1.4	0.12
Hematocrit	44.4 ± 3.0	45.9 ± 3.8	0.25
Total Testosterone	484 ± 283	404 ± 248	0.45
<b>Graded Exercise Testing</b>			
RER	1.17 ± 0.10	1.18 ± 0.07	0.69
Peak HR	181 ± 11	187 ± 10	0.11
VO <sub>2</sub> peak (ml/min)	1935 ± 352	2511 ± 631	<b>0.006</b>
VO <sub>2</sub> peak (ml/kg/min)	31.6 ± 8.3	42.4 ± 8.4	<b>0.002</b>
VO <sub>2</sub> peak (ml/lean kg/min)	44.5 ± 7.9	54.8 ± 7.6	<b>0.002</b>

Comparisons were completed with a two-sided t-test or Mann Whitney test as appropriate.

BMI = body mass index, BF = body fat, DXA = dual energy x-ray absorptiometry, HbA1C = hemoglobin A1C, HOMA-IR = homeostatic model assessment of insulin resistance, RER = respiratory exchange ratio, HR = heart rate, VO<sub>2</sub> = oxygen consumption.

P1-1603

#### CLINICAL AND BIOCHEMICAL PROFILE OF PEDIATRIC PATIENTS WITH CUSHING SYNDROME AT THE UNIVERSITY OF THE PHILIPPINES – PHILIPPINE GENERAL HOSPITAL

Sharon B. Gawigawen, MD; Lorna R. Abad, MD, University of the Philippines- Philippine General Hospital, Manila, Philippines

**Objectives:** This study aimed to describe the clinical and biochemical profiles of pediatric patients diagnosed with endogenous Cushing syndrome, to identify the etiologies, and to determine the treatment outcome in these patients.

**Methods:** A retrospective chart review of pediatric patients with endogenous Cushing syndrome seen at a tertiary hospital from January 2006 to December 2015.

**Results:** There were 12 cases (4 Cushing's disease, 4 adrenal sources, 4 ectopic ACTH producing tumors) of endogenous Cushing syndrome in this study. The age range was from 1.6 to 18.4 years old (mean age= 12.65 years). Slight female predominance was noted. The most commonly reported clinical features were moon facies (100%), buffalo hump (100%), weight gain (92%), easy fatigability (83%) and short stature (58%). The co- morbidities noted were hypertension (83%), hypokalemia (83%), hypocalcemia (58%), dyslipidemia

(33%) and osteopenia (8%). Majority had loss of diurnal variation in serum cortisol and elevated 24 hour urinary free cortisol. Ectopic ACTH producing tumors exhibited the highest serum cortisol levels. Only 8 (67%) cases underwent tumor resection. Disease recurrence was noted in 3 cases. Two patients went into remission and 2 had residual hypertension. Two cases of ectopic ACTH producing tumors and 1 case of Cushing's disease died due to sepsis.

**Conclusions:** The main etiologies of pediatric endogenous Cushing syndrome are pituitary, adrenal and ectopic sources. In childhood, lack of height gain consistent with the weight gain is the most common presentation in Cushing syndrome. Diagnosis is confirmed by biochemical and imaging studies. Surgical resection remains to be the definitive treatment modality. Early and correct diagnosis of Cushing syndrome leads to prompt treatment thereby decreasing morbidity and most importantly death.

P1-1604

#### SCREENING AND PREVELANCE OF THYROID DISEASE IN DIGEORGE SYNDROME

Seema Jain, MD, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, United States; Andrea Balazs, MD, Baylor College of Medicine/Texas Children's Hospital, Houston, TX, United States

**Objectives:** To evaluate the prevalence and screening rates of thyroid disease in DGS patients at Texas Children's Hospital (TCH)/Baylor College of Medicine (BCM). Thyroid disease has been sporadically described in patients with DiGeorge Syndrome (DGS). Hypothyroidism occurs in 0.7-20% of patients and is a treatable cause of short stature and intellectual disability. Hyperthyroidism occurs in 1.6-5% of patients, which is higher than the general population. The prevalence of thyroid disease in DGS patients at TCH/BCM has not been previously reported, also previous studies have not described provider rate of adherence to current screening recommendations.

**Methods:** This is a descriptive cross sectional study, performed via retrospective chart review. EMR system was utilized to identify patients with ICD codes of: DiGeorge Syndrome, 22q11 deletion, Velocardiofacial syndrome. Patients included in the study were seen at our institution from 2001-2016, aged 0 to 28 years old and carried a diagnosis of complete or partial DGS based on clinical features and/or genetic testing.

**Results:** A total of 307 patients were identified, of which 17 were excluded as they did not meet diagnostic or age criteria. Our final sample size consisted of 290 patients. Of these patients 68% (n= 197) had screening thyroid tests ordered by multiple specialties. Of the screened patients 75% (n =147) had normal screens, and 25% (n=50) had abnormal screens. 96% (n= 48) of patients with abnormal screens were identified as having a degree of hypothyroidism and 4% (n=2) with hyperthyroidism. Autoimmunity was the most common identified etiology of thyroid disease. Other identified etiologies included: thyroid dysgenesis, subclinical

hypothyroidism and sick euthyroid syndrome. Of note, subclinical hypothyroidism occurred commonly in our patients with spontaneous resolution over time.

**Conclusions:** The majority of DGS patients at our institution are being screened for thyroid disease, however our screening is sub-optimal at 68%. Thyroid disease occurred at a higher prevalence than previously described, with a predominance of hypothyroidism. Screening for thyroid disease identified multiple patients with overt thyroid disease, which otherwise may have been missed.

P1-1605

#### SCHOOL PERFORMANCE OF GIRLS WITH TURNER SYNDROME: A TRANSCULTURAL ASSESSMENT

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**Objectives:** Girls with Turner syndrome (TS) have specific cognitive phenotype that may cause selective learning difficulties. We aimed to analyse the real-life school performance of TS girls in primary school.

**Methods:** Forty-four Czech (age 7-27 years; median 14) and 50 Egyptian TS girls (age 7-18 years; median 13) agreed to participate. The karyotypes were 45,X (CZ:23; EG:20), 46,XiXq (CZ:1; EG:10), 45,X/46,XX (CZ:5; EG:12), 45,X/47,XXX (CZ:2), 45,X/46,XiXq (CZ:4; EG:3), 45,X/46,XdelX (CZ:4; EG:2), 45,X/46,XrX (CZ:1; EG:2), and 45,X/46,XY (CZ:4; EG:1). All TS girls were in long-term endocrine follow-up and attended a governmental primary school.

Parents of Czech participants retrospectively collected school testimonials from classes 1-9 (ages 6 to 15 years) of the TS girl and of her two sisters (if available) and/or age-matched female schoolmates. In Egypt, the parents collected the recent school testimonial only. Finally, the control groups included 30 patients' sisters and 47 schoolmates from Czechia and 65 patients' sisters and 35 schoolmates from Egypt. The Czech school grading system is based on a 5-grade scale, "1" being excellent and "5" unsatisfactory. In Egypt, school results were converted into a similar scale.

**Results:** In the study cohort with longitudinal data (Czechia), school results were similar in TS girls and their sisters/peers during the first two classes. In classes 3 to 5, TS girls performed slightly worse (mean grade 1.61) if compared to controls (mean grade 1.49) in principal teaching subjects (maths, native language and 1st foreign language;  $p=0.055$ ) but not in other subjects. In classes 6 to 9, TS girls performed slightly worse in maths only (class 6-7, mean grade 2.21 vs. 1.94,  $p=0.054$ ; class 8-9, mean grade 2.41 vs. 2.08,  $p=0.057$ ). In the cross-sectional study in Egypt, TS girls' results were similar to their sisters and peers in all subjects except maths

(TS: mean grade 3.58; controls: 3.19;  $p=0.014$ ). In pooled results from three principal teaching subjects, TS girls performed just slightly worse than controls (3.11 vs. 2.92;  $p=0.043$ ).

**Conclusions:** The differences in school results between girls with Turner syndrome and their unaffected sisters and female schoolmates are minor and have no substantial impact on their general school performance.

P1-1606

#### KARYOTYPE PHENOTYPE CORRELATION IN PATIENTS WITH TURNER SYNDROME.

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**Objectives:** To identify associations between karyotype, phenotype and gonadal function in patients with Turner syndrome.

**Methods:** This study was part of the DSD life study ([www.dsd-life.eu](http://www.dsd-life.eu)). We evaluated the different karyotypes and compared these with the age of diagnosis, dysmorphic features, FSH at diagnosis, spontaneous puberty, puberty induction and cardiac/renal involvement (bicuspid aortic valve (BAV), coarctation of the aorta (COA) and horseshoe kidney (HK)). Median (min-max) was used to describe baseline characteristics and associations between phenotype and karyotype were analysed using different parametric and non-parametric tests. A  $p$ -value  $< 0.05$  was considered statistically significant.

**Results:** Information on 328 patients with TS (median 28 (15-73) years) was available. Participants had a karyotype of monosomy 45X (47%), mosaicism 45X/46XX (10%), karyotype with isochromosome (19%) or other karyotype (25%). The peak age of diagnosis was in infancy and at the age of 10-11 years. Patients with a monosomy 45X were more frequently diagnosed during infancy compared to patients with other karyotypes. Besides, the median age (median 10 (0-61) years) at diagnosis was lower in this patient group (median 10 (0-61) versus median 11 (0-53) years;  $p=0.02$ ). Patients with a monosomy 45X had significantly more dysmorphic features ( $p<0.0001$ ), BAV ( $p=0.006$ ) and COA ( $p=0.002$ ) compared to the other karyotypes. No associations with HK were found. Levels of FSH at diagnosis in girls (median 23 (0-289) U/L) were higher in patients with 45X monosomy ( $p=0.01$ ). 27% of the women had a history of spontaneous puberty, this was more common in women with a 45X/46XX mosaicism ( $p<0.0001$ ) than in women with a monosomy 45X ( $p<0.0001$ ).

**Conclusions:** These results show that the clinical signs of TS are more severe in patients with monosomy 45X. Adequate prediction of the clinical phenotype is important for the

personalized follow-up of patients. Despite the more severe features in monosomy 45X, the median age of diagnosis is only slightly lower compared to patients with other karyotypes, which suggests opportunities for improvement.

P1-1607

THE BEHAVIOR OF VITAMIN D IN PRADER-WILLI SYNDROME

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**Objectives:** The aim of this study was to evaluate the vitamin D profile in pediatric patients with the diagnosis of Prader-Willi Syndrome (PWS) and then compare these to exogenous obese adolescents.

**Methods:** Fifty five patients with PWS were included. Age, body mass index (BMI), sex, somatropin use, type of genetic mutation and season were described and correlated to vitamin D levels. The comparative analyses was between 19 PWS obese adolescents (PWSOA) and 79 exogenous obese adolescents (EOA) at the same age, gender, BMI and season that the sample was collected.

**Results:** There was no difference between vitamin D levels according to age (p 0.155), sex (p 0.581), somatropin use (p 0.098), seasonality (p 0.), type of mutation (p 0.602) or BMI (p 0.111) in patients with PWS.

The majority of PWS patients were vitamin D sufficient and comparing then to exogenous obese adolescents we found higher levels of vitamin D in PWSOA group (19.5±5.3 vs 27.1±10.7, p<0.001).

**Conclusions:** PWS obese adolescents presents with higher levels of vitamin D in comparison to exogenous obese adolescents.

PLEASE SEE TABLE IN NEXT COLUMN

Variable (n)	Vitamin D insufficiency % <sup>a</sup>	Vitamin D sufficiency % <sup>b</sup>	p value <sup>c</sup>
Age			0.155
< 10 years old (30)	13.3	86.7	
> 10 years old (25)	28.0	78.0	
Gender			0.581
Male (29)	20.7	79.3	
Female (26)	19.2	80.8	
BMI			0.111
Eutrophic (9)	0.0	100.0	
Overweight/obese (46)	76.1	21.9	
Mutation Type			0.602
Dissomy (21)	28.6	71.4	
Deletion (20)	15.0	85.0	
rHGH use			0.098
Yes (32)	87.5	12.5	
No (23)	69.6	30.4	

<sup>a</sup> Vitamin D levels < 20ng/mL; <sup>b</sup> Vitamin D > 20 ng/mL; <sup>c</sup> p value for comparing vitamin D insufficiency and sufficiency in PWS- Chi-square

Variable (mean)	EOA (n= 79) <sup>a</sup>	PWSOA(n=19) <sup>b</sup>	p value <sup>c</sup>
Age	14.0 ±2,3	15.2±3,1	0.07
BMI	3.6±0.7	4.07±1.4	0.08
High/Low UV incidence	-	-	<b>0.56<sup>d</sup></b>
Vitamin D	19.5±5.3	27.1±10.7	<b>&lt;0.001</b>

<sup>a</sup> Obese Adolescents Patient; <sup>b</sup> Prader Willi Obese Adolescents; <sup>c</sup> p value for comparing EOA vs PWSOA <sup>d</sup>Chi-square

P1-1608

MC ALBRIGHT SYNDROME: CLINICAL, HORMONAL AND MOLECULAR STUDIES

Julio C. Soto , MD, UNIVERSIDAD DE CHILE, SANTIAGO, Chile; Fernando J. Cassorla , MD; Maria I. Hernandez , MD, UNIVERSIDAD DE CHILE, SANTIAGO, Chile

**Objectives:** The Mc Albright syndrome (MAS) is a rare disease, characterized by the clinical triad of precocious puberty (PP), café-au-lait skin spots and fibrous dysplasia of bone (FD).

Our objective was to perform a complete characterization of all patients with MAS evaluated at our Hospital between 2008-2016.

**Methods:** We evaluated the symptoms at onset, the clinical phenotype and, hormonal function, as well as the molecular studies, the age at menarche and menstrual function following menarche in these patients.

**Results:** The study population consisted of thirteen patients, 11 girls and 2 boys. The average age at the onset of symptoms was 3,8 ± 4.0 years and the age at diagnosis 5.2±4.6 years.

The main reason for initial consultation was vaginal bleeding in 5 cases, premature thelarche in 4 patients and gait alteration in both boys. The most common clinical criterion was the presence of café-au-lait skin spots and precocious puberty in 11 patients, followed by fibrous dysplasia of bone in 4 cases. Other hormonal disorders were present in two patients with hyperprolactinemia, and additional hypersecretion of growth hormone in one patient. It is important to mention that both boys with MAS had normal puberty. The mean average age of menarche was 11 years



and 11 months and the range was from 10 7/12 to 17 years. Following at least 2 years after menarche, 4 out of 11 cases showed abnormal uterine bleeding.

Molecular study was performed in ten patients and was positive in 4 cases in DNA obtained from leukocytes. Three cases of precocious puberty progressed to secondary central precocious puberty and received GnRh analogs. Other treatments used were aromatase inhibitors and estrogen receptor blockers in 3 patients.

**Conclusions:** MAS is a heterogeneous entity. The main symptoms at diagnosis were thelarche and vaginal bleeding. Age at menarche was in the normal range, but abnormal uterine bleeding was observed in 4 out of 11 girls following menarche, suggesting that reproductive function may be compromised in some of these patients.

N	sex	Current age	Symptoms Onset age	Age at diagnoses	café-au-lait skin spots	PP	FD	Other Hormonal disturbances	Age at menarche	Menses cycles
1	F	14 años 4 meses	8 months	2 years and 2 months	(+)	(+)	(-)	(-)	11 years and 9 months	Normal
2	F	16 years and 2 months	7 months	1 years and 5 months	(+)	(+)	(-)	(-)	11 years and 5 months	Normal
3	F	18 years and 9 months	9 months	6 years and 5 months	(+)	(+)	(-)	(-)	10 years and 8 months	Abnormal uterine bleeding (AUB)
4	F	13 years and 1 month	3 years and 1 month	5 years and 1 month	(+)	(-)	(-)	(-)	10 years and 7 months	AUB
5	F	15 years and 3 months	7 years	7 years and 4 months	(+)	(+)	(-)	(-)	11 years and 7 months	Normal
6	M	14 years and 2 months	1 year and 7 months	1 year and 7 months	(+)	(+)	(+)	(-)		
7	F	20 years and 5 months	14 years and 4 months	17 years and 6 months	(+)	(-)	(+)	(+) prolactin	17 years	Normal
8	F	16 years and 1 month	2 years	2 years	(+)	(+)	(-)	(+) prolactin and GH	11 years and 8 months	AUB
9	M	16 years and 9 months	3 years	7 years and 8 months	(+)	(-)	(+)	(-)		
10	F	9 years 4 months	13 months	14 months	(+)	(+)	(-)	(-)	(-)	
11	F	5 years and 2 months	2 years and 7 months	2 years and 7 months	(+)	(+)	(-)	(-)	(-)	
12	F	12 years and 11 months	8 years and 9 months	9 years	(+)	(+)	(-)	(-)	No information provided	
13	F	15 years and 4 months	3 years and 5 months	3 years and 8 months	(+)	(-)	(+)	(-)	11 years and 2 months	AUB

P1-1609

# INCREASED AORTIC DIAMETERS IN NORMOTENSIVE CHILDREN AND ADOLESCENTS WITH TURNER SYNDROME WITH EMPHASIS ON ASSOCIATIONS WITH B-TYPE NATRIURETIC PEPTIDE AND INSULIN-LIKE GROWTH FACTOR1

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**Objectives:** Turner Syndrome(TS)is associated with increased aortic diameters(ADs)in studies performed mostly in adulthood.Factors contributing to increasedADs inTSremain nebulous.B-type natriuretic peptide(BNP)is one of the transcriptional targets of the"short stature homeobox"gene,which is responsible for some of the phenotypic features ofTSowing to its haploinsufficiency.BNPand atrialNP(ANP)are novel cardiovascular risk(CVR) biomarkers.We assessedADs at predefined9anatomic positions in young,normotensive patients withTS.Associations between increased ADs and traditionalCVR biomarkers,natriuretic peptides and cardiac imaging findings were examined after adjusting for well-established confounders of vascular disease.

**Methods:** In this prospective,cross-sectional study,48patients(mean age:12.3 yr(range 6.6yr-21.3yr)withTSand34 healthy peers were compared with respect to body mass index(BMI),systolic blood pressure(SBP) and diastolicBP(DBP) measurements,homeostasis model assessment-insulin resistance(HOMA-IR),plasma lipids,high sensitivity C-reactive protein(hs-CRP),plasma aldosterone/renin ratio(PRA),IGF1standard deviation score(SDS)and cardiacMRIfindings.The differences in ADs between patients withTSand healthy controls were examined with respect to putatively influential factors using multivariate regression analyses.

**Results:** Patients withTShad higherBMIthan controls as expected( $p<0.001$ ).SBPandDBPwere comparable.TSpatients had higher hsCRP,BNPandANP.HOMA-IR,plasma lipidsandIGF1SDSwere comparable between the patients and controls( $p>0.05$ ).ADs at3of the9predefined positions were significantly higher inTSpatients than in controls( $p<0.05$ ).Multivariate regression analyses of the putatively influential factors(i.e.age,SBP,DBP, hs-CRP,BNP,ANP,PRA,IGF1SDS)on the body surfacearea-adjustedADs revealed an independent significant association of logBNPandIGF1SDSwith these findings.In case of the descending aorta(positions 8and9)only logBNPremained explanatory( $p<0.01$ ).When controls were also included in the analyses,logBNPremained explanatory for the differences in ADs.

**Conclusions:** Our findings emphasize the need for longitudinal studies onADs in patients withTSas related to the potential influence ofGH-IGF1axis andBNPon the increase inADs.

P1-1610

# METRELEPTIN THERAPY IN A PATIENT WITH CONGENITAL GENERALIZED LIPODYSTROPHY TYPE 4

Claudia Boettcher, MD, Justus Liebig University Giessen, Giessen, Germany; Anne Schänzer, MD, Justus Liebig University, Giessen, Germany; Clemens Kamrath, MD, Justus Liebig University Giessen, Giessen, Germany; Eva Richter, MD; Klaus-Peter Zimmer, MD; Stefan A Wudy, PhD; Andreas Hahn, MD, Justus Liebig University, Giessen, Germany

**Objectives:** Congenital generalized lipodystrophies (CGL) are rare autosomal recessive disorders characterized by near total loss of subcutaneous adipose tissue accompanied by metabolic and hepatic disturbances. CGL type 4, caused by mutations in the PTFR (Cavin 1) gene, is characterized by deficiency of caveolae in different tissues, and a peculiar form of myopathy.

**Methods:** We report for the first time a patient with a homozygous PTFR mutation treated with the synthetic leptin-analogue Metreleptin.

**Results:** The girl is the first child of healthy consanguineous Pakistani parents. Failure to thrive, slowly progressive muscle weakness, and joint pain setting after the age of 2 years were reported. At age 14 years height was 131 cm [ $<P3$ ], weight was 36 kg [ $<P3$ ], and Tanner Stage was B3, P4. Clinical examination displayed proximal muscle weakness despite bulky muscles, painless muscle mounding elicited by percussion, contractures of the ankles, prominent veins due to lack of body fat, and hepatomegaly with protuberant abdomen and a small umbilical hernia. Creatine kinase levels were elevated and electromyography displayed myopathic changes. Muscle biopsy showed increased endomysial fibrosis and loss of expression of PTRF, and caveolin 1 and 2. Malignant cardiac arrhythmias, dens axis dysplasia, and gastrointestinal dysfunction were further features. Blood work showed (insulin resistant) diabetes mellitus ( $HbA_{1c}$  9.3%) and hypertriglyceridemia. After genetic confirmation of CGL4, Metreleptin treatment was started. Over two weeks, blood sugar levels decreased significantly. The insulin dosage could be tapered down and was finally stopped. In combination with dietary measures, hypertriglyceridemia nearly normalized, and liver size decreased substantially. By contrast, skeletal muscle and cardiac dysfunction remained unchanged

**Conclusions:** These observations suggest that Metreleptin therapy improves metabolic control, hypertriglyceridemia, and hepatomegaly in CGL4, but that it has no positive effects on skeletal myopathy and cardiac function.

P1-1611

#### **SAFETY AND EFFICACY OF DIAZOXIDE CHOLINE CONTROLLED-RELEASE TABLET IN PATIENTS WITH PRADER-WILLI SYNDROME**

Virginia Kimonis, MD; June-Anne Gold, MD; Abhilasha Surampalli, MD; Marie Wencel, , University of California Irvine School of Medicine, Irvine, CA, United States

**Objectives:** The objective of the study was to evaluate the safety and efficacy of diazoxide choline controlled-release tablets (DCCR) in subjects with Prader-Willi syndrome (PWS).

**Methods:** The study enrolled overweight and obese, male and female subjects between 10 and 22 years old with genetically-confirmed PWS and utilized a randomized withdrawal design. Subjects were titrated open-label on DCCR and treated through 10 weeks. Subjects who showed reductions in hyperphagia or increased energy expenditure during the open-label phase were designated Responders,

enrolled in the 4-week double-blind, placebo-controlled phase, and randomized either to continue DCCR treatment or receive placebo. Hyperphagia and behaviors were measured using questionnaires.

**Results:** Thirteen subjects were enrolled in the study. Eleven subjects completed open-label treatment. All were designated Responders and randomized into the double-blind phase. Data was analyzed for both phases of the study. There were significant improvements in hyperphagia in DCCR treated subjects at the end of the open-label phase (-31.6%,  $p=0.003$ ) and in those who continued on DCCR in the double-blind phase (-29.2%,  $p=0.006$ ). There was a significant reduction in aggressive, threatening, destructive behavior at the end of the open-label phase. The effect on behavior seems to be independent of the effect on hyperphagia. Significant impacts were seen on fat mass (-3.8%,  $p=0.011$ ), lean body mass (+5.4%,  $p=0.002$ ), lean body mass/fat mass ratio (+9.8%,  $p=0.002$ ) during open-label treatment. The impacts on body composition were similar in growth hormone-treated and naive subjects. DCCR treatment significantly reduced cardiovascular risk factors. The safety profile of DCCR in PWS subjects was consistent with prior studies. The most common adverse events included peripheral edema, which was responsive to dose reduction and diuretics, and transient hyperglycemia which led to the discontinuation of one subject. A second subject was withdrawn due to a pre-existing psychiatric illness.

**Conclusions:** DCCR treatment of adolescent and adult PWS patients addressed a number of the highest priority unmet needs in the disease. DCCR may represent an important new therapeutic option for PWS.

P1-1612

#### **WHAT ABOUT FSH IN TURNER SYNDROME ?**

Baz Ouidad, PhD; Semrouni Mourad, Professor, University of Algiers, Algiers, Algeria; Samia Sakher, Physician's Assistant, Medical, Algiers, Algeria

**Objectives:** Girls with TS have a biphasic pattern of gonadotrophin levels with high FSH and LH serum levels during childhood and at the time of expected puberty, in subjects with monosomy 45,X0 respect to those with mosaicism. Otherwise high FSH circulating levels have been associated with bone loss.

The aim of this study is to evaluate the FSH level in young girls and adolescents with TURNER syndrome according to the age and to the karyotype and to their BMD.

**Methods:** A total of 67 girls with TURNER syndrome confirmed by karyotype, follows in our hospital between 2010 to 2013, with age range at diagnostic between 3 year to 18 years. mean age was 13 + 4 years. FSH level, pelvic ultrasonography, and BMD were performed.

**Results:** 67 patients with a karyotype distribution of: 31% of the girls with monosomy, 40% with mosaisme, 17 % with mosaisme and structural abnormalities and 12% with structural abnormalities alone. The average FSH of all patients was 55 + 44 ui/ml, according to the Karyotype the

patients with mosaisme have the lowest rate (average FSH 36 ui/ml). There was no significant difference between other subgroup. The BMD performed in 2/3 of the patients before and after puberty in some cases. The BMD was low in 75% of cases, between the 25% normal BMD 50% were patients with mosaisme.

**Conclusions:** Our study demonstrate a low bone density in girls and young women with TS, before and after puberty induction. The high FSH level appears to be the determining factor in fragility of bone and the factor of maintaining this fragility also in Turner patients. The Patients with mosaic due to their lower FSH levels have better bone strength.

P1-1613

#### IS RUBINSTEIN-TAYBI SYNDROME RELEVANT TO RBFOX1?

*Ying Weng, PhD, Huzhong University of Science and Technology, Wuhan, China; Xiaoping Luo, MD, Huazhong University of Science and Technology, Wuhan, China*

**Objectives:** RBFOX1 could be another account of Rubinstein-Taybi syndrome (RSTS).

**Methods:** A patient showed typical RSTS phenotype, including broad thumbs and toes, craniofacial abnormalities, and growth deficiency, was analyzed by chromosomal microarray (CMA).

**Results:** A de novo deletion of 274kb at 16p13.3 (6,665,696-6,939,296) was found. The deletion contains only one gene RBFOX1 which was known as coding RBFOX proteins that regulate RNA splicing events.

**Conclusions:** We believe this deletion is causative reason to the patient's clinical manifestation and RBFOX1 could be another account of RSTS.

P1-1615

#### THE TREATMENT OF PRECOCIOUS PUBERTY IN A MCCUNE-ALBRIGHT SYNDROME PATIENT USING CHINESE MEDICINAL HERBS COMBINED WITH MEGESTROL ACETATE: A CASE REPORT

*Jian Yu, PhD, Children's Hospital of Fudan University, Fudan University, Minhang District, Shanghai, China; Wen Sun, DO; Yonghong Wang, MD, Children's Hospital of Fudan University, Shanghai, China*

**Objectives:** We describe a girl onset MAS using Chinese medicinal herbs combined with megestrol acetate treatment and aim to provide a new option for the treatment of children with this rare form of precocious puberty.

**Methods: Case presentation:** A 4-year-old girl was presented to the outpatient clinic in June 2009 with 4 months history of repeated vaginal bleeding. The vaginal bleeding was irregular and lasted for 3 to 4 days every time. Gynecological pharmaceuticals, past history of major diseases and trauma surgery were denied. Birth history was normal. Her parents were non-consanguineous marriage, and her brother showed no similar symptoms. **Physical examinations:** Ht 114 cm, Wt 20 kg, well-nourished, the breasts development was Tanner

stage ? with a little darkened areola. There were no pubic hairs, no labia-pigmentation. Hormones levels: Thyroid hormones, adrenal hormones, HCG, PRL, and AFP were normal. The  $E_2$  was 17.29 pg/ml. GnRH stimulation test were negative. **Ultrasonography:** Uterus  $21.4 \times 12.5 \times 15.5 \text{ mm}^3$ , intermediate type, endometrial line visible; left ovary  $21.8 \times 8.9 \times 12.0 \text{ mm}^3$ ; left ovarian follicle  $3.0 \text{ mm}^3$ ; right ovary  $17.1 \times 6.6 \times 9.6 \text{ mm}^3$ ; right ovarian follicle  $1.0 \text{ mm}^3$ .

**X ray:** 1. bone age was 7 years old; 2. multiple bone changes of the left tibia, suggesting the fibrous dysplasia of bone. CT scan: multiple bone changes in the skull.

**Gene sequencing:** the peripheral blood samples of the girl, her parents and her little brother were screened with NimbleGen 2.0 probe sequence capture array of Roche. The activating mutation of *GNAS* wasn't detected in any of the four peripheral blood samples.

**Results:** We applied megestrol acetate combined with a TCM receipt to control the girl's premature symptoms. After 2 months, the breast stages reduced to Tanner 2, and events of vaginal bleeding reduced to only 1 to twice / year. The girl's BA and the fibrous dysplasia showed no progressive advancement. Up to August 2016, she was 154.5 cm in height with the bone age of 13 years old.

**Conclusions:** The combination therapy of Chinese medicinal herbs plus megestrol acetate in treating precocious puberty in a McCune-Albright syndrome is an alternative option, which not only modulates the premature sexual development but also keeps the growth potential for the children.

#### POSTER SESSION 1

Thursday, September 14, 2017, 5:45-6:45pm

##### P1 - Thyroid

##### P1-1700 – P1-1727

P1-1700

#### INTELLECTUAL OUTCOME IN CHILDREN WITH SUBCLINICAL HYPOTHYROIDISM: EFFECTS OF TWO YEARS OF LEVOTHYROXINE TREATMENT

*Sara Alfano, MD; Miriam Polizzi, MD; Raffaella Di Mase, MD; Carla Ungaro, MD; Nicola Improda, MD; Donatella Capalbo, PhD; Carmela Bravaccio, PhD, University of Naples, Federico II, Naples, Italy; Mariacarolina Salerno, MD, University of Naples Federico II, Naples, Italy*

**Objectives:** To evaluate the intellectual outcome of children with subclinical hypothyroidism (SH) before and after 2 years of treatment with levothyroxine (L-T4).

**Methods:** Thirty-five children (18 males and 17 females) aged  $8.8 \pm 0.5$  years with persistent, idiopathic and mild SH (TSH serum levels between 4.5 and 10 mIU/L) were enrolled in the study. Thirty-five age- and sex-matched healthy children were enrolled as controls.

Twenty-one SH subjects underwent a 2 year-course of L-T4 therapy (SH-group 1), whereas 14 SH children refused any treatment (SH-group 2).

Intellectual quotient (IQ) was evaluated through the Wechsler Intelligence Scale-revised for children in all subjects at study entry and after two years of therapy in SH-group 1 and after two years of clinical observation in SH-group 2.

**Results:** At baseline, no significant differences were observed between SH children and controls as regards to verbal (VIQ, 98.9±2.4 vs 92.5±3.8), performance (PIQ, 100.9±1.7 vs 102.9±2.9), and full-scale (FSIQ, 99.8±2.0 vs 100.6±3.0) IQs. Moreover, IQs at baseline were comparable between SH-group 1 and SH-group 2 (VIQ 100.8±3.0 vs 96.1±4.2; PIQ 102.2±2.3 vs 99.0±2.6; FSIQ 101.5±2.6 vs 97.2±3.0, respectively).

Two years of L-T4 treatment in SH-group 1 were associated with a normalization in TSH values as compared to baseline (6.2±0.2 vs 3.2±0.4 mIU/L,  $p < 0.0001$ ) but not with an improvement in IQ scores (VIQ 100.3±3.5, PIQ 105.9±3.0, FSIQ 103.7±3.3) as compared to both baseline and untreated SH-group 2 IQ values (VIQ 96.9±3.9, PIQ 99.3±2.6, FSIQ 97.5±2.9).

**Conclusions:** Our data suggest that persistent, mild SH in children is not associated with intellectual impairment and that a 2 year-course of L-T4 treatment does not induce any significant improvement in IQ scores.

P1-1701

#### MANUFACTURERS' REFERENCE INTERVALS FOR FREE THYROXINE ARE NOT IDEAL FOR CHILDREN ON THYROXINE REPLACEMENT THERAPY AND TARGET RANGES NEED TO BE ASSAY-SPECIFIC

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**Objectives:** We aimed to determine the physiologically correct free thyroxine (FT4) target range in children on thyroxine for primary hypothyroidism to guide optimal therapy for all children on thyroxine including those with central hypothyroidism. There are biases among current FT4 assays as reflected by the manufacturers' reference intervals. Therefore, we postulate that the ideal FT4 target range for children on thyroxine therapy would also be assay-specific.

**Methods:** Patients with primary hypothyroidism were prospectively recruited. Patient samples with thyroid-stimulating hormone (TSH) in the normal range (0.4-4.0 mIU/L) on Beckman Coulter Dxl were included for analysis. Samples were measured on four other instruments (Siemens Centaur, Roche Cobas, Abbott Architect, Ortho Vitros). FT4 ranges (median (2.5th-97.5th)) were calculated. The results were compared to the manufacturers' quoted reference intervals (e.g. Dxl: FT4, 7.9-14.4 pmol/L).

**Results:** Results from thirty-two patients aged from 2 to 18 years were analysed. In the thyroxine-treated group (congenital hypothyroidism (n=24) and autoimmune hypothyroidism (n=8)), FT4 was 14.3 pmol/L (11.5-17.3) on Dxl, FT4 was 18.5 pmol/L on Centaur.

**Conclusions:** This study suggests that target FT4 in children on thyroxine should be well above the manufacturer's quoted reference interval. In thyroxine-treated hypothyroidism with normal TSH, FT4 levels vary as much as 30% among the different assays. Therefore, target FT4 ranges should also be assay-specific.

P1-1702

#### NEXT GENERATION SEQUENCING PANEL FOR THE SYNDROMES OF REDUCED SENSITIVITY TO THYROID HORMONE

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**Objectives:** Patients with syndromes of reduced sensitivity to thyroid hormone (THR) present with elevated thyroid hormone levels and normal or elevated levels of TSH. After exclusion of laboratory artefacts, about 80% of the patients presenting biological THR have been shown to harbor mutations in the thyroid hormone receptor  $\beta$  gene (*THRB*). Other genes have recently been implicated in THR: thyroid hormone receptor  $\alpha$  gene *THRA*, thyroid hormone cell membrane transport (MCT8) and enzyme reducing the intracellular metabolism generating T3 from T4 (SECISBP2). Finally, about 15% of the patients with THR have no identified pathogenic variant. We report here the results of the molecular studies for thyroid hormone receptivity within our center for rare diseases of hormonal receptivity.

**Methods:** 556 patients were addressed to our referral center for suspicion of THR. Thyroid hormone receptor  $\beta$  gene (*THRB*) has been sequenced in all, and 48 genes have been tested by NGS for 8 selected patients. Complete thyroid hormonal status (T4L, T3L and TSH) was known for 211 patients. We have standardized the results by relating the values to the upper standards.

**Results:** We have found 78 different *RTHB* genetic variants (several of them newly reported). Patients with *RTHB* mutation had levels of FT4 and FT3 significantly higher than patients without variant of *RTHB* (FT4  $1.62 \pm 0.57$  vs.  $1.31 \pm 0.42$  the upper limit; FT3  $1.45 \pm 0.5$  vs.  $1.26 \pm 0.59$  the upper limit,  $p < 0.01$ ). We sequenced 48 genes by NGS in 8 selected patients without *RTHB* mutation (these patients had the highest FT4 and FT3 levels). One patient had heterozygous albumin variant reported to cause familial dysalbuminemic hyperthyroxinemia (FDH). Five patients had variants in genes responsible for hypothyroidism, therefore unlikely involved in the biological THR. No variants were found in 2 patients.

**Conclusions:** In our population of suspected THR, we found RTHB mutation in 48% patients. The sequencing of 48 genes by NGS for 8 patients with potential RTH has identified one dysalbuminemic hyperthyroxinemia.

P1-1703

**CENTRAL HYPOTHYROIDISM IN KLINEFELTER SYNDROME**

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**Objectives:** Increasing evidence suggestive of tertiary/secondary thyroid dysfunction in males with Klinefelter Syndrome (KS) has been recently reported. Our objective was to determine the prevalence of central hypothyroidism in our pediatric/adolescent patients with KS. We aimed to describe our population of KS children including presentation, symptoms, laboratory studies, relation to testosterone therapy and response to treatment with levothyroxine.

**Methods:** A retrospective chart review utilizing diagnosis code of Klinefelter Syndrome collected over the last five years from our clinic. Initial free T4, TSH and in some cases Total T3 and Reverse T3 were collected. Body Mass Index, testosterone levels, fasting lipid profiles, cortisol levels with 1 mcg ACTH stimulation and brain MRI results were analyzed.

**Results:** We identified four patients with KS followed in our clinic. All patients were obese. Of the four patients, three had central hypothyroidism. Central hypothyroidism was defined by low free T4 (using dialysis equilibrium assay) with an inappropriately normal TSH. Mean free T4 at presentation was 0.75 +/- 0.2. At presentation of central hypothyroidism, all subjects were not on testosterone therapy. Other pituitary deficiencies were not indentified. Mean peak cortisol with ACTH stimulation testing was 22.6 +/- 0.3. indicating a normal hypothalamic-pituitary-adrenal axis. There were no differences in metabolic parameters, brain/pituitary MRI or association with testosterone therapy.

**Conclusions:** Our cohort of children/adolescents with KS have a high prevalence of central hypothyroidism consistent with recent studies evaluating thyroid dysfunction in this population. The impact of puberty, testosterone treatment and other metabolic correlations should be further explored in the future. A suggested mechanism is a decrease or change in set point of thyrotroph control of thyroid function or differences in deiodinase activity. Patients with Klinefelter Syndrome should be monitored closely for evidence of central hypothyroidism.

P1-1704

**MATERNAL HYPOTHYROIDISM IN PREGNACY AND IMPACT ON THE MENTAL DEVELOPMENT OF THEIR CHILDREN**

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**Objectives:** Maternal hypothyroidism (MH) in the first trimester (1T) of pregnancy can affect mental development in the offspring. It's unclear which level of TSH determines this situation. In 2011 ATA guidelines the upper reference limit for TSH concentration in the 1T of pregnancy was defined as 2.5 mU/L. 2017 ATA guidelines defined MH as a TSH concentration elevated beyond of the upper limit of pregnancy-specific reference range. In this study our objective were to assess whether or not there is a relationship between TSH maternal levels in 1T with their children's intelligence quotient (IQ) and evaluate if the presence of MH in 1T determines a lower IQ

**Methods:** Thyroid function (FT4, FT3 and TSH), TPO-Ab and iodine urinary concentration (UIC) were analyzed in 2104 pregnant in 1T. We determined the 95th and 97th percentiles for TSH (4.2 mU/L and 5.5 mU/L) and the 10th percentile for FT4 (14.1 pmol/L). Maternal subgroups were created considering different upper cut-off of TSH. In 352 randomly children IQ (WISC-IV) was assessed at 7 years. Mean IQ results were compared between maternal TSH subgroups

**Results:** TSH median was 1.28 mU/L (0.00-295). TSH was ≥ 2.5 mU/L in 15% of pregnant, ≥ p95 in 5%, and ≥ p97 in 3%. In these subgroups differences in TPO-ab positives and in the FT4 were found. In children differences in IQ were found considering TSH levels.

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No correlation was found between IQ and levels of TSH, FT4, TPO or UIC in 1T.

**Conclusions:**

- We found a relationship between TSH≥2.5 mU/ml and lower perceptual score in children. No others relation were found.
- TSH ≥ 2.5 mU/L in 1T was related with TPO-ab positives and hypothyroxinemia but not with UIC.

2104 pregnant	n	UIC (µg/L)	FT4 (pmol/L)	FT3 (pmol/L)	FT4<p10 (%) <sup>1</sup>	TPO (%) <sup>1</sup>
TSH<2.5 mU/ml	322	109.9	16.1	5.9	16	83
TSH<2.5 mU/ml	1972	111	17.4	5.9	8	69
TSH<p95	107	108.9	15.6 <sup>2</sup>	5.8	27.6	78.5
TSH<p95	1997	110.6	17.3 <sup>2</sup>	5.9	9	15.3
TSH<p97	65	95.7	14.8 <sup>2</sup>	5.7	21.5	78.5
TSH<p97	2039	111.3	17.3 <sup>2</sup>	5.9	8.8	16.7

Chi-cuadrado: p<0.000; <sup>2</sup> T-student: p<0.000

352 children	n	Verbal	Perceptual	Working memory	Processing speech	Total
TSH<2.5 mU/ml	54	102.8	102.5 <sup>1,2</sup>	103.5	107.5	104.1
TSH<2.5 mU/ml	298	104.4	108.0 <sup>1,2</sup>	103.8	106.7	106.7
TSH<p95	22	103.4	101.1 <sup>1</sup>	104.1	107.2	103.9
TSH<p95	330	104.1	107.6 <sup>1</sup>	103.8	106.8	106.5
TSH<p97	16	104.0	101.7	103.4	108.7	104.7
TSH<p97	336	104.1	107.4	103.8	106.7	106.5

<sup>1</sup> T-student: p<0.003; <sup>2</sup> U-Mann-Whitney

**BENIGN THYROID NODULES IN PEDIATRIC PATIENTS: FOLLOW UP AND OUTCOMES**

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**Objectives:** We aim to determine the optimal time interval for repeat evaluation of a cytologically benign thyroid nodule in a pediatric patient. Thyroid nodules in pediatric patients are typically evaluated following the American Thyroid Association guidelines for adults, as no specific guidelines for re-evaluation of benign pediatric thyroid nodules exist despite well-characterized differences between thyroid nodules in adults and children.

**Methods:** This is a retrospective chart review of patients <19 years of age at Rhode Island Hospital from 2003-2013 with the ICD-9 diagnosis code for thyroid nodule. We identified patients with an initially benign thyroid nodule by fine needle aspiration (FNA) cytology. Data collected included thyroid ultrasounds with nodule characteristics, FNA biopsy results, follow up data, and treatment.

**Results:** We identified 43 patients with benign thyroid nodule cytology on initial FNA. Average age at diagnosis was 15.6 years, and there was female predominance with 91% female. Initial ultrasound findings showed the following: average nodule size 2.4 cm (largest dimension); 12% of patients with >1 nodule; 9% calcifications; 33% hyperemia; 28% hypoechoic nodules; and 7% lymphadenopathy. Follow up ultrasound was done in 40% of patients and repeat FNA in 7%. First follow up ultrasound occurred at an average of 15 months after the initial ultrasound, and ultrasounds were followed for an average of 28 months. Four patients had nodules with significant growth over time (>20% increase in largest diameter). One patient with papillary thyroid carcinoma on final pathology had initially decreasing nodule size, then subsequent increase in nodule size after 4.5 years. Thyroid nodules were surgically removed in 33% with final pathology showing benign cytology in 4 patients, follicular adenoma in 8 patients, and papillary thyroid carcinoma in 2 patients.

**Conclusions:** The majority of patients with benign thyroid nodules did not have an increase in nodule size after 1 year of follow up, including one patient who was subsequently found to have papillary thyroid carcinoma. We recommend follow up ultrasound at 1 year after initial presentation in pediatric patients with benign thyroid nodule cytology.

PLEASE SEE TABLE IN NEXT COLUMN

Table 1. Ultrasound findings

	All Patients	Benign	Follicular Adenoma	Papillary thyroid carcinoma
Number of patients	43	33	8	2
Size of largest nodule (largest dimension)				
Average (cm)	2.4	2.3	3.2	2.8
Range	0.6-4.7	0.6-4.7	1.9-4.4	2.5-3
<1cm	4 (9%)	4 (12%)	0 (0%)	0 (0%)
1-1.9cm	11 (26%)	10 (30%)	1 (13%)	0 (0%)
2-2.9cm	8 (19%)	7 (21%)	0 (0%)	1 (50%)
3-3.9cm	10 (23%)	7 (21%)	2 (25%)	1 (50%)
>4cm	4 (9%)	3 (9%)	1 (13%)	0 (0%)
Data not available	6 (14%)	2 (6%)	4 (50%)	0 (0%)
Number of nodules				
1	27 (63%)	23 (70%)	4 (50%)	0 (0%)
2	7 (16%)	6 (18%)	0 (0%)	1 (50%)
3	2 (5%)	1 (3%)	0 (0%)	1 (50%)
4	2 (5%)	2 (6%)	0 (0%)	0 (0%)
5	1 (2%)	1 (3%)	0 (0%)	0 (0%)
Data not available	4 (9%)	0 (0%)	4 (50%)	0 (0%)
Laterality (largest nodule)				
Right	23 (54%)	18 (55%)	3 (38%)	2 (100%)
Left	16 (37%)	13 (39%)	3 (38%)	0 (0%)
Isthmus	2 (5%)	2 (6%)	0 (0%)	0 (0%)
Data not available	2 (5%)	0 (0%)	2 (25%)	0 (0%)
Cystic Component				
Yes	26 (60%)	22 (67%)	3 (38%)	1 (50%)
No	13 (30%)	11 (33%)	1 (13%)	1 (50%)
Data not available	4 (9%)	0 (0%)	4 (50%)	0 (0%)
Calcifications				
Yes	4 (9%)	2 (6%)	1 (13%)	1 (50%)
No	35 (81%)	31 (94%)	3 (38%)	1 (50%)
Data not available	4 (9%)	0 (0%)	4 (50%)	0 (0%)
Hyperemia				
Yes	14 (33%)	12 (36%)	1 (13%)	1 (50%)
No	25 (58%)	21 (64%)	3 (38%)	1 (50%)
Data not available	4 (9%)	0 (0%)	4 (50%)	0 (0%)
Hypoechoic				
Yes	12 (28%)	11 (33%)	1 (13%)	0 (0%)
No	27 (63%)	22 (67%)	3 (38%)	2 (100%)
Data not available	4 (9%)	0 (0%)	4 (50%)	0 (0%)
Lymphadenopathy				
Yes	3 (7%)	3 (9%)	0 (0%)	0 (0%)
No	36 (84%)	30 (91%)	4 (50%)	2 (100%)
Data not available	4 (9%)	0 (0%)	4 (50%)	0 (0%)

P1-1706

**LOW VALUE OF THYROID TESTING IN THE INPATIENT SETTING**

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**Objectives:** Thyroid function testing (TFT) is often done in hospitalized patients even when symptoms do not suggest hyperthyroidism or hypothyroidism. Our aim was to assess how frequently these tests fell outside the norm and how often they added value to ongoing medical care.

**Methods:** TFTs on all admissions from July 2015 to June 2016 were retrospectively reviewed with focus on abnormal results.

**Results:** Out of 20,907 admissions, 1202 patients (5.7%) had TFTs done; 251 had TSH only whereas 951 had TSH + FT4 n=907, FT3 n=404, T4 n=64, and T3 n=10. We defined high TSH as >5 mIU/ml and high free T4 as >2 ng/dl. It was discovered that the high number of FT3 tests was largely due to inpatient psychiatry ordering FT4, FT3 and TSH routinely. We noted 205/1202 (17%) of TFTs to be abnormal. Of those, 84 (40.9%) had TSH >5 of whom only 6 had TSH >15; 58 (28%) with mildly low TSH (0.1-0.5) and normal FT4; 25 (12%) with normal TSH and high FT4; 8 (3.9%) with inconsistent findings



of high TSH and FT4; 3 (1%) with normal TSH and low FT4 and 4 (1.9%) with TSH5, but only 1 had a TSH>10.

Our chart review found that 81% had no documented reason for the testing. Thyroid testing was most useful in patients who were already receiving thyroid hormone replacement, and those on medications like amiodarone and lithium. We found that only 13 patients (1% of all TFTs) needed treatment or alteration in the thyroid dose. Six were on thyroid medications, 1 was post thyroidectomy, 2 had abnormal NBS, 2 had trisomy 21, 1 was on heparin and 1 had goiter. In none of these patients was the hospital course altered due to TFTs.

**Conclusions:** While this review of inpatient thyroid testing revealed many abnormal results, the lack of any relation to the reason for the admission or to the course of their illness suggests such testing be mainly limited to situations with high risk of abnormal findings. These should include patients already on thyroid medications, exposed to amiodarone, undergoing evaluation for possible hypopituitarism, or with new onset type 1 diabetes. As a result of our review, inpatient psychiatry agreed to discontinue routine ordering of FT4, FT3 and TSH.

P1-1707

#### THE CLINICAL PREDICTIVE FACTORS FOR DIFFERENTIATION TRANSIENT CONGENITAL HYPOTHYROIDISM FROM CONGENITAL HYPOTHYROIDISM PATIENTS

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**Objectives:** The NST(neonatal screening test) with TSH(thyroid-stimulating hormone) screening has become standard in many part of the world. Nowadays, mild and transient forms of CH were increasing.The aim of this study was to recognize differences between transient CH(TCH) from permanentCH(PCH). Whether their clinical characteristics, laboratory tests and imaging studies might be possible as predictive factors for prognosis.

**Methods:** We performed retrospective reviews, using database of pediatric department of Bundang Jesaeng General Hospital, Daejin Medical Center, Korea from Jan. 1998 to Feb. 2016. We collected the data about sex, birth weight, gestational age, age at diagnosis and treatment, and treatment duration of each patient. We measured TSH, free thyroxine(FT4), total triiodothyronine(TT3) level at diagnosis and treatment, at one, two and three months after onset of treatment. The doses of medication of start, one, two and three years were recorded. Thyroid scan(Tc<sup>99m</sup> scintigraphy), thyroid ultrasonography reports were described. SPSS 21 was used for the statistical analyses of the data.

**Results:** Among the 282 neonates included in the analysis, 51(26 male, 25 female) were diagnosed with congenital hypothyroidism. 27(18 male, 9 female) out of 51 were identified as TCH. Serum TSH levels measured at the time of diagnosis were significantly different between two groups. Those of PCH group (mean TSH 150.49 IU/mL) were higher

than of TCH group (mean TSH 30.29IU/mL) (p=0.001). FT4, TT3 levels measured at the time of diagnosis also had significant differences between two groups. There were significant difference between the two groups both in the FT4 level measured at two months later from start of treatment. FT4 in PCH group were higher (p=0.034). Treatment doses required between two groups had significant difference in only after 2 years of therapy. Thyroid USG was normal in 53.3% of patients with PCH compared with TCH group, in which all patients were normal. Except athyroid patients of PCH group, thyroid sizes of both groups were not comparable.

**Conclusions:** According to these data, we may consider initial measurements of Serum TSH, FT4, T3, and the dose of 2years as predictive factors in categorizing TCH from PCH. The size of thyroid from Tc<sup>99m</sup> scintigraphy can't differentiate TCH from PCH.

P1-1708

#### CLINICAL COURSE AND CHARACTERISTICS OF HYPOTHYROIDISM IN INFANTS WITH CONGENITAL HEART DISEASE

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**Objectives:** To identify the frequency, clinical course, and risk factors of hypothyroidism in infants with congenital heart disease.

**Methods:** Medical records of 59 patients (25 males, 3~98 days of age) with congenital heart anomalies who underwent thyroid function tests within 100 days after birth at Seoul National University Hospital, Seoul, Korea between January 2007 and July 2016 were reviewed. Data were collected on gestational age, birth weight, congenital heart disease, serum free thyroxine (fT4) and thyroid stimulating hormone (TSH) levels, and medication known to affect thyroid function test results such as dopamine, dobutamine, amiodarone, steroid, and furosemide. Patient histories were also reviewed for previous exposure to iodine contrast media (cardiac CT, MRI, catheterization, iodine dressing before and after surgery) and mechanical ventilator care.

**Results:** Mean birth weight was 2.9kg, mean gestational age was 38 weeks, and mean follow-up duration was 1,860 days. The serum TSH levels of the 15 patients (25.4%) increased to 5~10uIU/mL and normalized afterwards without thyroid medication. Nineteen patients (32.2%) started levothyroxine treatment. (Eighteen patients had serum TSH levels exceeded 10uIU/mL and one patient had serum fT4 level below 0.7ng/dL.) Of 42 patients followed up until 3 years of age, 11 started levothyroxine treatment and of these, 9 continued with levothyroxine treatment past 3 years of age. The group that needed levothyroxine treatment had a lower birth weight (2.6 vs. 3.0kg, P=0.017) and higher rates of iodine contrast media exposure (55.6% vs. 27.8%, P=0.006) and

surgery (80% vs. 27.8%,  $P=0.033$ ) than the group for which levothyroxine treatment was unnecessary.

**Conclusions:** About one third of infants with congenital heart disease started levothyroxine treatment within 100 days of birth. This is a higher incidence than the incidence of the total population including healthy infants. Further prospective studies on the incidence and risk factors of transient and permanent hypothyroidism in congenital heart disease patients are needed.

P1-1709

## THE RELATIONSHIP BETWEEN NON-ALCOHOLIC FATTY LIVER DISEASE AND PEDIATRIC CONGENITAL HYPOTHYROIDISM PATIENTS

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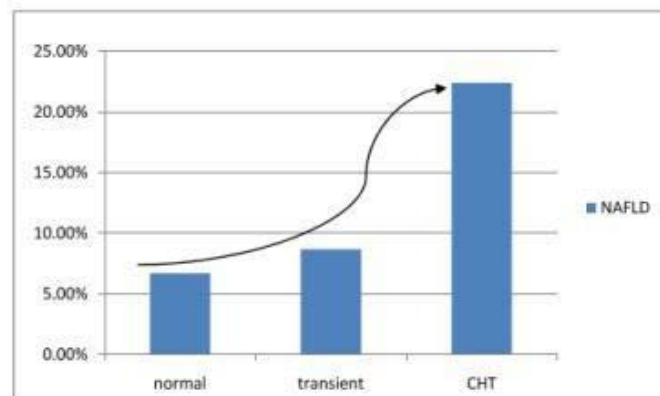
**Objectives:** Previous studies have shown hypothyroidism is independently associated with non-alcoholic fatty liver disease in adult populations but few studies examined their relationship in pediatric populations. The aim of this study was to compare the prevalence of non-alcoholic fatty liver disease in pediatric congenital hypothyroidism patients under long term levothyroxine treatment with the age-matched controls.

**Methods:** Patients diagnosed congenital hypothyroidism through newborn screen with follow up and treatment at our clinics and aged 6 to 25 were enrolled as congenital hypothyroidism group ( $n=58$ ) from the year of 2013 to 2014. Age-matched controls were selected from normal subjects ( $n=30$ ) and transient hypothyroidism patients without medication after the age of three ( $n=46$ ). Laboratory data including thyroid function, liver function and metabolic profiles were checked. Abdominal echo was performed by a single experienced gastrointestinal specialist who was blinded to the clinical and laboratory data at our institution. Non-alcoholic fatty liver disease was diagnosed based on the four known criteria (Hepato-renal echo contrast, liver brightness, deep attenuation, and vascular blurring). Variables that were statistically significant by univariate analysis were added to a multiple regression model to identify independent predictors of the presence of non-alcoholic fatty liver disease.

**Results:** There was no difference in characteristics between normal, transient and congenital hypothyroidism group, except for age, T3, T4, and fasting glucose ( $p<0.05$ ). The prevalence of non-alcoholic fatty liver disease did not differ significantly between control, transient and congenital hypothyroidism group (6.7%, 8.69%, 22.4%,  $p=0.056$ ), but we still found a trend between them ( $X^2_{\text{linear by linear}}=4.9$ ,  $p=0.027$ ). Multivariate regression analysis, after adjustment for age, obesity status, T3, T4, fasting glucose and known risk factors, showed that congenital hypothyroidism patients under

treatments were significantly associated with non-alcoholic fatty liver disease ( $\beta$ -coefficient=3.52,  $p<0.05$ ).

**Conclusions:** Patients with congenital hypothyroidism had higher chance of developing non-alcoholic fatty liver disease, which might be due to fluctuating thyroid function even under medication use.



**Figure 1.** The prevalence of NAFLD in control/transient/CHT groups. The prevalence of non-alcoholic fatty liver disease in these three groups were 6.7%, 8.69%, 22.4%, respectively, which did not differ significantly ( $p=0.056$ ), but there is a trend between them ( $X^2_{\text{linear by linear}}=4.9$ ,  $p=0.027$ ).

P1-1710

## IODINE STATUS IN HEALTHY CHILDREN WITH UNEXPLAINED SUBCLINICAL HYPOTHYROIDISM

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**Objectives:** Subclinical hypothyroidism (SCH) is a common condition among children with an even higher prevalence among obese individuals. The most common cause of SCH is autoimmune thyroiditis. Nonetheless the etiology is unknown in a large number of subjects, identification of the cause in those individuals is key to determine the appropriate therapy. The 2007-2008 National Health and Nutrition Examination Survey (NHANES) reported that the prevalence of iodine insufficiency in children and adolescents 6-19 years of age is between 17-23.7%. This could be explained by the fact that approximately 70% of the dietary salt is derived from processed food, which is made mostly with non-iodized salt. In addition to processed foods, studies indicate that many iodized salt containers do not meet the standard iodine content. We have been conducting a long term study to define the clinical characteristics of subjects with SCH. Here we present new data from this study.

**Methods:** This was a prospective study that enrolled children ages 6-19 years with unexplained SCH from a single Pediatric Endocrinology clinic. 24 hour urine for iodine and creatinine was used to determine iodine status.

**Results:** 17 subjects (8 males and 9 females) were enrolled into the study. Mean age was 10.8 years with a standard deviation (S.D) of 3.6 years. All subjects had a normal FT4 ( $1.15\pm0.18$  ng/dl) and an elevated TSH ( $6.89\pm1.28$  mIU/L). The majority of subjects (56%) with SCH were either overweight (16%) or obese (40%). 24% ( $N=6$ ) of the subjects

had iodine deficiency (urinary iodine 300 mcg/L). The relationship between iodine status and weight was not significant.

**Conclusions:** The prevalence of iodine deficiency in our cohort (24%) was greater than that of general pediatric population (20%). However, there was no significant relationship between weight and iodine status. Nonetheless, the large number of subjects with SCH who were either overweight or obese suggests that diet plays a role in the etiology of SCH.

P1-1711

#### THE RELATIONSHIP BETWEEN THYROID DISORDERS AND HORMONAL AND METABOLIC FEATURES OF POLYCYSTIC OVARY SYNDROME IN ADOLESCENT GIRLS

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**Objectives:** The coexistence of hypothyroidism and autoimmune thyroiditis (AIT) with polycystic ovary syndrome (PCOS) was reported in recent years. Many possible pathophysiological mechanisms are suggested to be the cause of this relationship.

The aim of the study was to investigate the thyroid function, ultrasonographic features and thyroid autoimmunity in adolescent girls with PCOS as well as to assess their relationship to metabolic and hormonal profile.

**Methods:** Seventy nine adolescent girls with diagnosis of PCOS (study group - SG) (chronological age:  $16.9 \pm 1.5$  y, age of menarche:  $12.0 \pm 2.0$  y, BMI:  $25.4 \pm 8.3$  kg/m<sup>2</sup>) and 35 regularly menstruating girls (chronological age:  $17.0 \pm 1.8$  y, age of menarche:  $12.0 \pm 2.0$  y, BMI:  $22.3 \pm 6.2$  kg/m<sup>2</sup>) (control group – CG) were recruited to the study. In all participants metabolic and hormonal tests were done and ultrasound of pelvis was performed. Thyroid function and morphology were evaluated by measurement of thyroid stimulating hormone (TSH), free thyroxine (fT<sub>4</sub>), antiperoxidase antibodies (anti-TPO Ab), antithyroglobulin antibodies (anti-Tg Ab) and ultrasound of the thyroid gland.

**Results:** AIT was diagnosed in 15 (19%) girls with PCOS and 5 (11%) girls from CG. In 8 (10.2%) girls from SG and in 3 (8.6%) from CG levothyroxine treatment was introduced by the family doctor and subclinical hypothyroidism was detected in 5 (6.3%) girls with PCOS and one (2.9%) from CG. In the SG AIT correlated positively with fasting glucose level ( $r_v=0.36$ ,  $p=0.01$ ) and HOMA-IR ( $r_v=0.29$ ,  $p=0.04$ ) as well as negatively with testosterone ( $r_v=-0.29$ ,  $p=0.004$ ) and androstenedione concentration ( $r_v=-0.27$ ,  $p=0.05$ ). Moreover volume of the thyroid correlated positively with anti-TPO Ab ( $r=0.47$ ,  $p=0.03$ ) and with LH concentration ( $r=0.36$ ,  $p=0.04$ ). No significant associations were found between TSH and fT<sub>4</sub>, BMI, hormones level and volume and pattern of the ovaries.

**Conclusions:** The study does not confirm the significant relationship between PCOS and thyroid disturbances in adolescent girls, however indicates some possible reciprocal

interaction between thyroid function and hormonal and metabolic features related to PCOS.

P1-1712

#### CASE REPORT: CHALLENGES IN CLINICAL MANAGEMENT OF A 16 YEAR OLD BOY WITH MULTIPLE ENDOCRINE NEOPLASIA 2A

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**Objectives:** Multiple Endocrine Neoplasia 2a (MEN2a) is characterized by medullary thyroid carcinoma (MTC), primary hyperparathyroidism and pheochromocytoma. The underlying pathology is a mutation in the RET proto-oncogene on chromosome 10q11.2. After molecular genetic diagnosis in an index patient, offspring should be examined for the at-risk mutation; if present early thyroidectomy is to be performed to prevent early metastasizing MTC. We report of a family where delay is caused by emotional reluctance to adhere to the recommendations.

**Methods:** We present a 16 year old adolescent, whose father was diagnosed with MTC and consecutively MEN2a due to a moderate-risk mutation of the RET gene (10q11.2; pCys618Gly).

**Results:** The family was initially reluctant to receive the recommended genetic counselling and to have their children's risks assessed. Thereby delayed molecular genetic analysis revealed that both children were carriers of the mutation. Again, the family was hesitant to agree on suggested preventative thyroid surgery, whereby thyroidectomy could be performed 7 months after the diagnosis had been established in the father. Histological work-up revealed an already existing MTC in situ (1.5mm, pT1a N0 M0), although the preoperative assessment had not shown any signs of an already existing neoplasia. Postoperatively, persistent iatrogenic hypoparathyroidism occurred due to accidental resection of a parathyroid gland and complicated the clinical course.

**Conclusions:** This case illustrates yet again the importance of timely preventative measures for offspring once the diagnosis of MEN 2A has been established in an index patient. It also demonstrates the difficulties of a multidisciplinary team to reach and assist a family that takes a sceptical view towards guidance faced with a complex medical constellation. It finally is a reminder that persistent iatrogenic hypoparathyroidism following total thyroidectomy may be rare, but when present can be a cumbersome consequence and impair quality of life; therefore appropriate preoperative counselling is essential.

### IS MEDULLARY THYROID CANCER IN SIBLING POSSIBLE WHEN THE RET IS NEGATIVE. TO TREAT OR NOT TO TREAT IS THE QUESTION!

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**Objectives:** Introduction - Medullary thyroid Cancer (MTC) is the 3rd most common cancer. Since its description in 1961, great progress has been made about its genetic linkage and family inheritance. We present an interesting and challenging case of medullary thyroid cancer.

**Methods:** Case report

**Results:** Case Discussion – Case 1–13 year old African American female presented to the ENT clinic for evaluation of a neck mass around the trachea with multiple hard lymph nodes. No family history of thyroid cancer except paternal uncle had thyroid cancer. Biopsy showed MTC. Underwent Surgery and removal of mass followed by a tracheostomy. Pathology confirmed MTC. Thyroid Radioactive Imaging showed lung metastasis. Genetic testing showed positive RET proto Oncogene mutation C.2753 T>C Met 918Thr which confirm MEN 2B. PTH and Calcitonin were elevated. No other family members affected with thyroid, neuroendocrine tumors, calcium abnormality. All family members were negative for RET proto Oncogene mutations. On chart review, three years ago she had a thyroid nodule, FNA showed benign follicular nodule. She was lost to follow up and presented with outlying ED with neck mass.

Case II – Identical twin to case I, seen in clinic for genetic evaluation after sister's diagnosis. She was otherwise healthy except for being obese (BMI > 95%ile) on metformin and Oral Contraceptive Pills. PMH was significant for precocious puberty needing GnRH implant. Case II was incidentally found to have a thyroid nodule on imaging. PTH, Calcium, Calcitonin were normal. Given the high risk because of family history a FNA was obtained which showed benign follicular nodule.

**Conclusions:** Conclusion – Current guidelines recommend Total thyroidectomy to patients with a family history of MTC at age 5 years, or earlier if RET-positive and based on the detection of elevated serum Calcitonin levels. There are no set guidelines for RET-Negative members with Thyroid Nodules. After discussion with the parent, mother elected to do a prophylactic thyroidectomy. Surgery is planned for summer of 2017. Immuno-histochemical and pathological analysis of anatomical tissue sample will give more information about management of the RET Oncogene negative but thyroid nodule positive siblings.

### CASE REPORT: PATIENT OF 14 YEARS OLD WITH THYROID AUTOIMMUNITY DISEASE AND RESISTANCE TO THYROID HORMONES

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**Objectives:** Resistance to thyroid hormone is a disorder characterized by decreased tissue responsiveness to thyroid hormones. This syndrome affects 1 of 40000 live births. In contrast, autoimmune thyroid disease has a high prevalence in the general population and the coexistence of resistance to thyroid hormone and autoimmune thyroid disease was thought to be coincidental. Gavin et al. proposed that this correlation could be associated to the chronic TSH stimulation over the intrathyroidal lymphocytes leading to thyroid damage.

**Methods:** N/A

**Results:** We describe a 14 years old girl who presents with a history of asthenia, adinamia, and short stature with growth detention since 9 years old. Initially she was diagnosed with hypothyroidism in a particular center, where she had a determination of TSH in 100. It was determined a short stature of 127,5cm (Z score -4.9), a weight of 30.6kg, keeping a symmetric growing, considering a midparental height of 161cm and a bone age of 11 years old. She had increased plasma free T4, free T3 at the upper limits with unsuppressed TSH in many determinations despite the therapy with levothyroxine, and her adequate adherence. Anti TPO and anti TG antibodies were positive, compatible with thyroid autoimmunity disease. The thyroid ultrasonography showed a heterogeneous pattern. In order to exclude a TSH secreting pituitary tumor we made a T3 suppression test, where pharmacologic doses of T3 cause significant TSH suppression in patients with pituitary resistance but fail to reduce TSH levels in patients with TSH secreting adenomas. In this case we observed a reduction in TSH levels after the administration of liothyronine. As part of the approach, we determined anti T3 and anti T4 antibodies, those ones were positive.

**Conclusions:** The coexistence of thyroid autoimmune disease and resistance to thyroid hormone is intriguing given their

different epidemiological and etiological features. However there are some studies reporting an odds ratio of 2.36 in relation to healthy people. It is important consider the possibility of a resistance to thyroid hormone in patient diagnosed with thyroid autoimmune disease with reduce sensitivity to levothyroxine.

Date	TSH	T4T	T4L	T3T	T3L	AC TG	AC TPO	IGF1
30.06.16	42	9.8		116		528	51.8	
10.10.16	> 75	8.6	5.6					266
02.01.17	> 75	9.2	> 6	110	5.9		9	
13.01.17	1.92	8.1	5.8	> 600	33.6	406	93.9	

P1-1715

CENTRAL HYPOTHYROIDISM IN A BOY CAUSED BY A LARGE DELETION IN THE IGSF1 GENE: DESCRIPTION OF THE PUBERTAL TIMING

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**Objectives:** The X-linked IGSF1 deficiency syndrome is mainly characterized by central hypothyroidism and adult macroorchidism. The first mutations in *IGSF1* have been described in 2012. We report a new mutation in *IGSF1* in a French male patient and describe the pubertal timing.

**Methods:** Case description

**Results:** The boy was born at 40 weeks, with birth weight 3740 g (+0.8SD), length 52 cm (+1SD), and head circumference 35 cm (0SD). He had been treated with hCG for undescended testes at the neonatal period. Psychomotor development was normal. During the first years, growth was normal (+1.5 SD, target height +1.7 SD), and BMI increased to 20.4 kg/m<sup>2</sup> (+3SD) at the age of 5 years. Because of overweight, thyroid function was assessed and showed central hypothyroidism with prolactin deficiency: TSH 2.4 mUI/L (N 0.1-4.5), free T4 9.5 pmol/L (N 12-21), PRL pituitary gland. Despite the excess weight, a progressive decrease in growth velocity was observed from the age of 7, and at 12 years, height was +0.4SD. A GH deficiency was diagnosed (IGF-1 179 ng/mL, GH peak to ITT 3UI/L), and he received rhGH for 2.5 years. Regarding gonadal function, excess testicular enlargement was observed from the age of 11 (testis volume was in contrast with the lack of pubic hair). Puberty is described in the table below. Adult height is 191.4cm (+2.9DS), and BMI 31.4 kg/m<sup>2</sup>. Sequencing of the TRH, TRH receptor, PROP-1, PIT-1, LHX3 genes were normal. A large deletion in the IGSF1 gene was found, encompassing the exons 10 to 20 of the gene.

Age (yrs)	Pubic hair	Testes (L x l; mm)	FSH (UI/L)	LH (UI/L)	T (nmol/L)	AMH (ng/ml)	INHB (pg/mL)
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11 years	1	25 x 12	2.2	0.2	0.97	95.38	39
13 years	1	30 x 20	7.1	1	2.5	54.9	187
14 years	3	40 x 20	5.7	0.7	2.46	5.60	107
15 years	4	50 x 30	10.3	2.5	14.21	5.18	112
16 years	5	55 x 35	10.3	3.5	22.6	5.74	95
18 years	5	60 x 45	6.6	3.1	17.4	6.16	114

**Conclusions:** IGSF1 gene deletion is associated with central hypothyroidism. Macroorchidism in the boy was observed at the onset of puberty. Despite enlarged testes, inhibin B concentrations were close to the lower normal limit, whereas testosterone production was normal.

P1-1716

UNILATERAL PROPTOSIS AS A RARE PRESENTATION OF EUTHYROID GRAVE'S DISEASE

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**Objectives:** Grave’s disease (GD) is the most common cause of hyperthyroidism in children. Grave’s ophthalmopathy (GO) as the only presenting symptom of GD in children is uncommon. Most cases of GO are seen in children who are hyperthyroid at presentation. Euthyroid GD is extremely uncommon; incidence is between 1-8% of all cases of GD. The diagnosis of euthyroid GO is often delayed as it is a rare initial presentation of GD and imaging can be difficult to interpret without experienced radiologists.

**Methods:** A 7 year old previously healthy female presented with proptosis of her right eye. Proptosis was present for 2 months and was worsening with time. She reported no pain, visual changes, erythema, dry eye or visual field defects. Family history was negative for autoimmune disorders. Review of systems was negative for signs of hyperthyroidism. Her weight and height were at the 70th percentile and BMI at the 80th percentile. Vitals signs showed: heart rate of 76 BPM, blood pressure of 116/66, respirations of 24 breaths/min, temperature of 36.8 °C. Physical exam was significant for right eye proptosis and a normal thyroid exam; no other significant findings.

**Results:** MRI of the orbits showed increased signal and minor induration of the right inferior rectus/superior rectus muscle of the right eye consistent with GO. Laboratory evaluation is shown in Table 1. Thyroid US was normal with no goiter, thyroiditis or nodules. Patient was given one dose of IV methylprednisolone initially. Her proptosis did not improve so she was started on 20 mg daily of prednisone for 2 weeks again without improvement in symptoms.

**Conclusions:** Unilateral proptosis is a rare presentation for GD. However, case reports of patients with proven Grave's disease have shown that unilateral eye disease can be more common in patients with euthyroid GD. It is an important consideration on the differential diagnosis of a patient with unilateral proptosis as delays in diagnosis are common, especially in euthyroid patients. These patients are at risk for eventually developing hyperthyroidism, which has been shown previously to put patients at risk for worsening eye disease. These patients should be closely monitored over time to ensure treatment is enacted quickly once they become hyperthyroid.

Table 1- Laboratory Evaluation

	At Presentation	1 month Follow Up
TSH (Normal: 0.6-4.14 mIU/L)	1.04	1.130
Free T4 (Normal: 0.8-2.0 ng/dL)	1.5	n/a
Thyroxine (Normal: 4.5-10 ug/dL)	n/a	9.2
T3 (Normal: 90-260 ng/dL)	153	143
TSI (Normal: < 122%)	266	212
TPO Antibody (Normal: < 9 IU/mL)	480	n/a
Thyroglobulin Antibody (Normal: < or = 1 IU/mL)	19	n/a

P1-1717

#### A 12.5 YEAR OLD GIRL WITH UNUSUAL PRESENTATION OF HASHIMOTO'S DISEASE AND THYROID-ASSOCIATED OPHTHALMOPATHY

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**Objectives:** Hashimoto thyroiditis in majority of children presents with thyromegaly, hypothyroidism and elevated levels of thyroid antibodies. Grave's disease (GD) manifests with goiter, hyperthyroidism and ophthalmopathy. Hashitoxicosis is very rare in children and might overlap clinically with GD, but differs with shorter clinical course and absence of ophthalmopathy.

**Methods:** A 12.5 year old girl presented with 6 year history of tachycardia, frequent stools and severe right eye myopia (-6.8), but without significant weight loss. Bilateral ophthalmopathy and tremor persisted in the last year before establishment of the diagnosis. She was thin (-1.55 SDS) and tall (0.15 SDS) with BMI 13.79 (-2.72 SDS). Diagnostic assessment of our patient was achieved by analysis of clinical features, auxology parameters, biochemical work up and ultrasound examination of the heart and the thyroid gland.

**Results:** Hormone analyses revealed: extremely elevated levels of thyroxine (>300 ng/dl), thyroperoxidase antibodies (anti-TPOb), (>1000 IU/ml) and suppressed thyroid stimulating hormone (<0.04 uIU/ml). Ultrasound of the

thyroid gland showed diffuse inhomogeneous and hypoechoic enlarged pattern. ECG revealed tachycardia (120/min) with incomplete right bundle branch block. Cardiac ultrasound was uneventful. After 107 days of treatment with anti-thyroid drug and  $\beta$ -blocker she became euthyroid with heart beat within normal range for her age and sex. Ophthalmopathy nearly completely resolved in both eyes.

**Conclusions:** Herein we present a rare condition in 12.5 year old girl. She had Hashimoto's disease associated with hyperthyroidism, significantly elevated levels of anti-TPOb, followed by thyroid enlargement, typical ultrasound findings and thyroid-associated ophthalmopathy. Early recognition, adequate treatment and follow up, might influence its improvement and outcome.

P1-1718

#### YOUNG PATIENT WITH UNUSUAL COURSE OF AUTOIMMUNE THYROID DISEASE (CONVERSION FROM HYPOTHYROIDISM TO HYPERTHYROIDISM) PRECLUDED BY NECK TRAUMA.

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##### Objectives:

Autoimmune thyroid disease is a well known cause of acquired hypothyroidism and hyperthyroidism. It is not uncommon that patients who initially present with hyperthyroidism convert to hypothyroidism. The opposite conversion from hypothyroidism to hyperthyroidism is rarely seen.

**Objectives is** to describe a young child who initially presented with hypothyroidism following neck trauma that converted to hyperthyroidism

##### Methods:

5 years old Hispanic girl presented with history of neck trauma and goiter. Initial thyroid function tests showed elevated TSH at 146 UIU/ml and low normal fT4= 0.9 ug/dl. Thyroid ultrasound showed thyromegaly with hyperemic thyroid gland and few small hyperechoic nodules in left thyroid lobe. In 3 weeks without treatment TSH went down to 14.5 UIU/ml, TPO, thyroglobulin antibodies were positive. She was started on levothyroxine 25 mcg daily. Within 6 weeks child developed clinical signs of hyperthyroidism (tachycardia, eye proptosis, lid lag, bruit over thyroid), TSH became suppressed < 0.005 UIU/ml, fT4 and tT3 became elevated 5.15 pg/ml and 459 ng/dl. Levothyroxine was stopped; methimazole, atenolol were started. TSI (thyroid stimulatory immunoglobulin) antibodies was elevated at 670% and Thyrotropin receptor blocking antibodies were elevated at 8.68 IU/L. In 1 month on small dose of methimazole 5 mg PO daily fT4 and T3 normalized. This patient is continue to be followed at present time.

##### Results:

This is the case report of rare conversion of autoimmune hypothyroidism to hyperthyroidism in young child. Highlights of this case are rapid clinical and biochemical conversion from hypothyroidism to hyperthyroidism, presence of all thyroid



antibodies and possible precipitating factor such as neck trauma.

**Conclusions:**

The prevalence of stimulatory or blocking antibodies to TSH receptors as well as other thyroid autoantibodies determine the stage of autoimmune thyroid disease - hypothyroidism versus hyperthyroidism. Clinicians maybe missing some cases of hypothyroidism prior to developing hyperthyroidism and need to be aware about this conversion at any stage of autoimmune thyroid disease. There is also a concern about trauma to thyroid gland triggering autoimmune process.

P1-1719

**PAPILLARY THYROID CARCINOMA PRESENTING AS CERVICAL LYMPHADENOPATHY WITHOUT EVIDENCE OF PRIMARY THYROID SOURCE**

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**Objectives:** Rarely papillary thyroid cancer (PTC) presents as isolated cervical lymphadenopathy representing metastatic PTC with a small (micro) primary in the thyroid gland. Primary PTC in a lymph node without evidence of a primary source in the thyroid is distinctly unusual.

**Methods:** A six year old girl presented with a palpable latero-cervical neck mass, progressing in size. She underwent lymph node excision, reported by Pathology as PTC. Thyroid ultrasound and non-contrast CT of the neck and chest did not reveal a primary focus in the thyroid. Full body PET scan showed multiple lateral cervical lymph nodes and a small oval mass density at the thoracic inlet. Patient was clinically and biologically euthyroid, with absent thyroid autoimmunity.

**Results:** Patient underwent total thyroidectomy and bilateral neck dissection. Focal metastases of PTC were found in three more lymph nodes, but no primary primary tumor was identified inside the thyroid gland. I131 whole body scan after treatment revealed an area of uptake in the neck. She had RAI therapy. Will continue on lifelong thyroid supplementation and will be followed by assessing thyroglobulin levels and by radionuclide scanning.

**Conclusions:** As a primary tumor source could not be found in the thyroid itself, we consider the possibility that this tumor originated from ectopic thyroid tissue in the lymph nodes. Embriology explains thyroid inclusions in cervical lymph nodes (found in 4.7% of unselected autopsies). PTC has been reported to originate from other ectopic thyroid tissue such as thyroglossal duct cysts.

Rare cases of PTC presenting as isolated lateral lymphadenopathy without evidence of primary thyroid focus were reported in adults. This presentation has not been documented in the pediatric literature.

P1-1720

**A CASE OF GRAVES' DISEASE ASSOCIATED WITH IMMUNE THROMBOCYTOPENIA.**

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**Objectives:** The association between thrombocytopenia and autoimmune thyroid disease is an uncommon but well-recognized condition in the adult patient. Although both autoimmune disorders may be associated with other immune-mediated disorders, the pathogenesis of immune thrombocytopenia (ITP) in patients with Graves' disease (GD) is unclear, and this combined condition is also rare. Here we report a case of ITP accompanied by GD.

**Methods:** A 13-year-old girl presented with a 3-month history of anorexia, increased perspiration, fatigue, and weight loss. Antecedent infection and drug exposure were absent. She denied a history of liver disease. Her family history was negative for endocrine abnormalities, autoimmune diseases and coagulopathies.

**Results:** On the initial physical examination, she was afebrile, her heart rate was regular at 144bpm, blood pressure was 124/76mmHg. Palpation of her neck revealed a painless, diffuse and firm goiter with bruit. Results of her neurological examination were normal except for tremor of hands. Very mild exophthalmos was noted. Spleen was not enlarged. Results of laboratory evaluation revealed normal red and white blood cell counts with normal differential count. The platelet count was 41,000/ $\mu$ L on admission, which fell to 30,000/ $\mu$ L five days later. Thyroid function tests showed suppressed basal TSH level of less than 0.01 $\mu$ IU/mL, elevated free T3 level of over 30pg/mL and free T4 level of 4.06ng/dL. Thyroid antibody levels were elevated at 62.6IU/L for TSH receptor antibody, 2329% for thyroid stimulating antibody, 126.1IU/mL for anti-thyroperoxidase antibody. In addition, elevated level of platelet-associated IgG (PAIgG) was detected. Improvement in thyroid function with methimazole (MMI) led to the spontaneous recovery of the platelet count (>200,000/ $\mu$ L) with negative conversion of PAIgG.

Two years later, the mild recurrence of hyperthyroidism under the MMI maintenance therapy did not cause the second thrombocytopenia.

**Conclusions:** In this case, both hyperthyroidism and ITP show a good control under MMI therapy. It suggests that correction of hyperthyroidism may be beneficial to the control of an imbalance in the immune system which impairs not only thyroid but also the platelet.

P1-1721

**NON-THYROIDAL ILLNESS - NOT SO RARE IN PEDIATRICS**

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**Objectives:** Non-thyroidal illness (NTI) defines a particular thyroid biological profile in critically ill patients.

We report 4 cases of NTI in a setting of severe hypoalbuminemia.

**Methods:** The first child, a 9-month-old boy, presented with a celiac crisis and altered thyroid function.

The second child, a 4-year-old boy presented severe anemia and cavernous transformation of the portal vein. The hepatic and thyroid function were abnormal, with hypoalbuminemia.

The third child, a 18-month-old boy, presented with failure to thrive. The biological picture showed a celiac disease and thyroid dysfunction.

The 4th child, a 18-year-old girl presents a severe nephrotic syndrome secondary to a parvovirus B19 infection in a setting of sickle cell disease. Persistent hypoalbuminemia induced an abnormal thyroid profile.

**Results:** In the first case, the biology confirmed the celiac disease, with tissue transglutaminase antibody (tTG) IgA class at 128 U/l and anti gliadin antibody (AGA) at 142 U/l. The albumin is at 19 g/l (normal range 25 - 45) with thyroxine (T4) level at 5 pg/ml (normal range 8 to 17) and thyroid releasing hormone (TSH) at 1,13 mUI/l (normal range 0,3 - 3,5). 10 days later, the albumine level and thyroid function returned to normal.

For the second case, the hemoglobine was 1,8 g/dl, the albumine at 22 g/l, the T4 at 5,6 pg/ml with TSH at 2 mUI/l. The T4 level amelioration followed albumine level increasing during the first 10 days of management.

In the third case, the thyroid profile with T4 at 4,9 pg/ml and TSH at 1,76 mUI/l was available before the confirmation of celiac disease (tTG IgA class at 200 U/ml and AGA at 89 U/l, albuminemia at 13 g/l).

In the 4th case, the persistent nephrotic syndrome with heavy proteinuria (urine protein/creatinine ratio > 10 g/g) and hypoalbuminemia (28 - 30 g/l) induces the thyroid dysfunction (T4 at 7 pg/ml, TSH at 3,51 mUI/l).

**Conclusions:** The common denominator is an altered thyroid profile, with low T4 and inappropriately normal TSH levels (NTI) in the setting of hypoalbuminemia. The reversal of normal thyroid function relied on correction of hypoalbuminemia.

The NTI pathogenic mechanisms are not completely understood, but they can concern hypothalamic-pituitary-thyroid feedback regulation, peripheral thyroid hormones metabolism and action.

P1-1722

#### GRAVES'S DISEASE AND HYPOCALCEMIA IN A 7-YEAR OLD FEMALE

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**Objectives:** Graves' disease is an autoimmune disorder characterized by the presence of circulating autoantibodies that stimulate the thyroid hormone receptor resulting in hyperthyroidism and goiter. The actions of thyroid hormones on bone and their effects on calcium homeostasis also result in a negative calcium balance in thyrotoxicosis. Nevertheless marked hypercalcemia is uncommon although mild hypercalcemia may be present in up to 20% of patients. The incidence of hypocalcemia is not related with the Graves disease

**Methods:** Case report

**Results:** 7-year old female presented with a history of seizures, cramps, and clinical manifestation of Hyperthyroidism, exophthalmos and goiter since she was 4 years old. The physical findings during her first visit were tachycardia, warm skin, bilateral exophthalmos, bilateral lid retraction (Right eye 5mm, Left eye 7mm), goiter and positive Chvostek and Trousseau signs (Total serum calcium 4.6 mg/dl, ionized calcium 2.3). We suspected Graves's disease and hypoparathyroidism, which were confirmed by laboratory workup detecting a TSH 0.04 uIU/ml, FT4 2.3 ng/ml, T4 16.7 ug/dl, FT3 8.6 pg/ml, T3 287 ng/dl, TSI >40 IU/l; Cortisol 18 ug/dl, C-peptide 2.4 ng/ml; PTH 4.8 pg/ml, Vitamin D 31.1 ng/dl, hypocalcemia and hyperphosphatemia.

Intravenous and oral calcium replacement and calcitriol was initiated with gradual improvement of hypocalcemia symptoms. According to past clinical history and scarce economic resources, radioactive iodine therapy was also given, with favorable response. Thyroid ultrasound showed increased gland volume hypervascularization. Cerebral CT scan with basal ganglia calcification. Bone mineral density L1-L5 z-0.3, total corporal z-1.2. Renal ultrasound within normal parameters. We did Immunology studies were reported normal. HLA and CATCH-22 mutation are pending

**Conclusions:** The association of Hypoparathyroidism and Graves' Disease is considered uncommon in pediatric age, with few reports with association in Polyglandular Syndromes, CATCH-22 and Fahr syndrome

P1-1723

#### REVERSIBLE HYPERTHYROIDISM ASSOCIATED WITH ORAL ISOTRETINOIN TREATMENT

*Areej Younes, MBBS, Nationwide Children's Hospital, Columbus, OH, United States; Eva Tsalikian, MD, University of Iowa Hospitals and Clinics, Iowa City, IA, United States*

**Objectives:** Isotretinoin is a synthetic vitamin A analogue commonly used for treatment of moderate to severe acne vulgaris. It is known that isotretinoin can affect pituitary hormone levels including the thyroid axis. Prior case reports and clinical trials have shown that treatment with isotretinoin can cause reversible hypothyroidism.

**Methods:** 16 years and 9 months old male patient presented to pediatric endocrine clinic for symptoms of headaches, insomnia, anxiety, fatigue and intermittent palpitations. Symptoms started after 2 months of being treated with

isotretinoin (60 mg daily) for acne vulgaris. On physical examination, his heart rate was 86 bpm, blood pressure 117/62, thyroid gland was not palpable, and fine hand tremor was noted. His labs revealed TSH <0.01(0.27-4.20) uIU/ml, free T4 3.13 (0.90-1.70)ng/dl, total T3 2.67 (1.0-2.10)ng/dl, TSI 90 %, (<=122%). Thyroid peroxidase and thyroglobulin antibodies were both negative. Patient was started on methimazole 10 mg orally twice daily. One month after stopping isotretinoin, labs revealed TSH of 6.53 uIU/ml, free T4 1.28 ng/dl, thus methimazole dose was decreased to 5 mg orally twice daily. Patient had poor compliance with taking the reduced methimazole dose due to lack of symptoms. He discontinued the methimazole by himself, repeat thyroid labs were within normal range (TSH 2.41 uIU/ml, free T4 1.33 ng/dl)

**Results:** Isotretinoin is an effective medication to treat acne vulgaris. Multiple studies revealed that isotretinoin can affect pituitary hormones. There are few case reports of isotretinoin induced transient hypothyroidism. The effect on the thyroid axis was described as decrease in free T3 level with no significant change on basal TSH and free T4. The mechanism underlying effect of isotretinoin on thyroid axis is unclear. To our knowledge no cases of hyperthyroidism associated with isotretinoin use have been reported in the pediatric population.

**Conclusions:** Hyperthyroidism may be associated with oral isotretinoin treatment; this association does not seem to be related to an underlying autoimmune process.

P1-1724

#### THYROID PROFILE OF PEDIATRIC PATIENTS WITH ANTITUBERCULOUS TREATMENT

*Juan P Hayes, MD; Marco A Rossell, MD; Nieves R Pinto, MD; Susana Rodriguez, MD; Bany Seoane, MD; Sandra Siacar, MD; Mireya Fuentes, MD; Natalia Mercado, MD; Alvaro G Moscoso, MD, Hospital Santa Cruz, Santa Cruz de la Sierra, Bolivia*

**Objectives:** Some patients receiving antituberculous drugs may develop thyroid disorders; hypothyroidism has been reported in patients receiving ethionamide and rifampicin. The aim of the present study is to evaluate the levels of thyroid hormones in pediatric patients diagnosed with tuberculosis at the beginning and at the end of antituberculous therapy.

**Methods:** Prospective study of patients less than 15 years of age, diagnosed with pulmonary tuberculosis, who received antituberculous therapy: Strictly Supervised Shortened Treatment (DOTS), of two phases; the first of 52 doses of isoniazid, rifampicin and pyrazinamide; the second phase of 104 doses of isoniazid and rifampicin. Plasma levels of thyrotropin (TSH), thyroxine (T4), free thyroxine (FT4), and triiodothyronine (T3) were determined at the beginning of treatment, three months after and the end of antituberculous therapy.

**Results:** We studied 19 patients who completed the DOTS. All of them were euthyroid at the beginning of

antituberculous therapy. In 3 children (15.8% of the total) the non-thyroidal illness syndrome was diagnosed (T3 levels low with normal values of the other hormones), at 3 and 6 months of treatment; 4 patients (21.0%) presented subclinical hypothyroidism (TSH levels elevated with normal values of FT4, T4 and T3), at the end of therapy; in the remaining 12 patients (63.2%), hormone levels analyzed were normal.

**Conclusions:** It is important to analyze the thyroid profile in patients receiving antituberculous treatment, since they may develop non-thyroidal illness syndrome or hypothyroidism.

P1-1725

#### NEONATAL THYROID DYSFUNCTION BORN FROM MOTHERS WITH THYROID DISEASE

*Sung Won Park, MD, Cheil General Hospital, Dankook University College of Medicine, Seoul, Korea, Republic Of*

**Objectives:** To evaluation of thyroid function in neonates born from mothers affected by thyroid disease in order to define follow-up thyroid function test is needed for these children.

**Methods:** Records were reviewed in Cheil General Hospital, from 01.01.2013 to 31.12.2015. All neonates were tested for thyroid function by measurement of thyroxine (T4) and thyroid stimulating hormone (TSH) in 3<sup>rd</sup> or 4<sup>th</sup> day.

Babies whose first results was abnormal or who were born from mothers affected by thyroid disease were tested for thyroid function repeatedly at about 2 weeks and at one month of life. Neonates who were born from women with thyroid disease and having anti-thyroglobulin (ATG) or anti-microsomal (AMA) antibodies were assigned as group I, women with hypothyroidism who did not have autoantibodies were assigned as group II.

**Results:** In group I, 13(5.7%) infants were diagnosed with compensated hypothyroidism and started levothyroxine therapy. The median age of diagnosis of hypothyroidism was 37.4 days. 17(7.5%) infants had hyperthyrotropinemia at 1st test. 46(20.7%) infants had transient hyperthyrotropinemia. The median period of normalization of TSH was 84.0 days. Especially, 7 neonates were diagnosed with hypothyroidism, despite of normal results of 1<sup>st</sup> screening test. 24 infants (7.5%) in group II had hyperthyrotropinemia at 1st test. 12 (3.8%) of them were diagnosed with compensated hypothyroidism and started levothyroxine therapy. The median age of diagnosis of hypothyroidism was 92.6 days. 69(21.7%) infants had transient hyperthyrotropinemia. The median period of normalization of TSH was 64.5 days. Especially, 56 neonates were diagnosed with hypothyroidism, despite of normal results of 1<sup>st</sup> screening test.

**Conclusions:** Transient hyperthyroxinemia above the normal reference value for age is frequently observed in the first month of life in infants born from mothers affected by thyroid disease. Persistent hyperthyrotropinemia requiring replacement therapy is observed in 5.7% of group I, 3.8% of group II. According to our experience, follow-up is recommended in these newborns between 2<sup>nd</sup> and 4<sup>th</sup> week

of life. Newborn infants born from women with thyroid disorders should be followed closely for thyroid dysfunction.

P1-1726

# A RARE CASE REPORT:CONSUMPTIVE HYPOTHYROIDISM DUE TO MULTIPLE INFANTILE HEPATIC HEMANGIOENDOTHELIOMA

*Xinran Cheng, MS/MA; Xianliang Hu, PhD; Li Yan, BS/BA; Fang Tang, MS/MA, The Chengdu Women's and Children's Central Hospital, Chengdu, China*

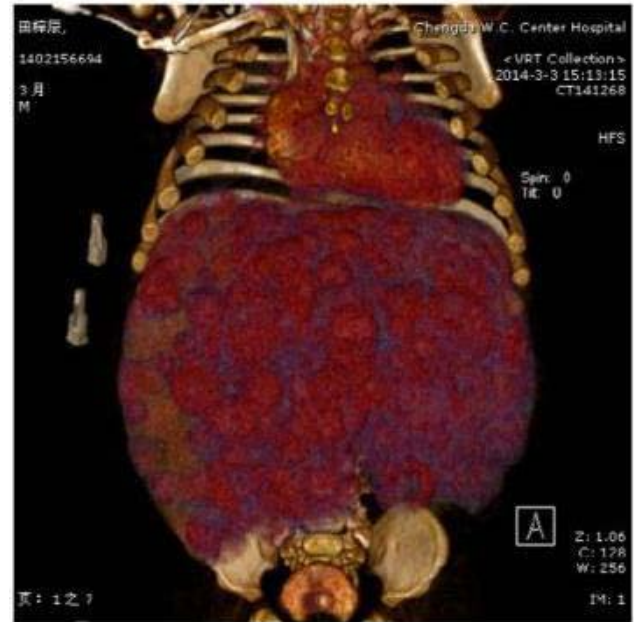
**Objectives:** A 3-month-old male patient was referred to our hospital with a diagnosis of Hepatic Hemangioendothelioma. The patient's weight was 5kg. Physical examination revealed mild abdominal distention, and an enlarged liver palpable 5 cm below the right costal margin. Blood hormone levels were: TSH 147.6  $\mu$ U/mL, T4 9  $\mu$ g/dL (3.5-17.4), fT4 0.77 ng/dL (0.89-1.76), T3 0.51 ng/mL (0.60-1.81), and fT3 1.4 pg/mL (2.3-4.2). no thyroid autoantibodies were found in the baby. Complete blood count and liver function test results were normal. Thyroid ultrasonography was normal. Abdominal ultrasonography and CT scanning showed multiple hypoechoic lesions with vascularization in both lobes of the liver, the largest being 2 cm in size. The infant had received a standard daily dose of Na L-T4 for a week after the hepatic artery was been embolised. Two weeks later, the Na L-T4 dose was increased to 20  $\mu$ g/kg daily. One month later, congestive heart failure developed during clinical follow-up. At the end of second month, Thyroid function tests were: TSH >150  $\mu$ U/mL, T4 6  $\mu$ g/dL, fT4 0.77 ng/dL, T3 0.9 ng/mL, and fT3 1.38 pg/mL. The patient's thyroid function disorder was thought to be due to the activity of the type 3 iodothyronine deiodinase expressed by the HHE, rT3 level was high. the thyroid treatment was changed to thyroxine tablets, in doses of 40mg per 3 hours, which contain T4 and T3 together. At the end of third month, The cardiac failure resolved, blood hormone levels were: TSH 1.468  $\mu$ U/mL, T4 10.3  $\mu$ g/dL, fT4 2.21 ng/dL, T3 1.19 ng/mL, and fT3 3.02 pg/mL. Repeat CT and ultrasonographic examinations showed that the hemangioendotheliomas shrank in size. Abdominal ultrasonography on the fourth month of thyroxine tablets treatment showed multiple nodular lesions with hypoechoic-heterogenous structures and ill-defined borders in the liver. At this time, blood hormone levels were: TSH 0.23  $\mu$ U/mL, T4 18.8  $\mu$ g/dL, fT4 2.48 ng/dL, T3 1.36 ng/mL, and fT3 3.51 pg/mL. Thyroid hormone replacement therapy (Thyroxine 40mg 3 times per day) was discontinued. No recurrence was found at the follow-up more than 2 years after treatment discontinuation. The patient was last seen at age 3 years. Growth and neurological development were normal and he showed no signs of thyroid deficiency.

**Methods:** -

**Results:** -

**Conclusions:** -

SEE PHOTO IN NEXT COLUMN



Picture1 Before thyroxine tablets treatment ,abdominal CT scanning three-dimensional imaging showed multiple hepatic nodules with increased signal intensity i.e. findings consistent with a diagnosis of HHE; the largest nodule was 3 cm in size .

P1-1727

# THYROID FUNCTION AND STRUCTURE IMPROVE AFTER WEIGHT LOSS IN OBESE CHILDREN

*Giorgio Radetti, MD, Marienlinik, Bolzano, Italy; Maria Rosaria Licenziati, MD; Federica Lidia Calandriello, MD; Ilaria Vetrani, MD; Gaetano De Maria, MD, Santobono-Pausilipon Hospital, Naples, Italy; Fiorenzo Lupi, MD, Regional Hospital of Bolzano, Bolzano, Italy*

**Objectives:** Thyroid function and structure are often altered in obese subjects. A raised TSH together with a thyroid echographic pattern resembling that of Hashimoto's thyroiditis have been described. The real cause is not known although the inflammatory status might play a role. The aim of this study was to verify whether the alterations in function and structure may improve after weight loss and to evaluate the role played by inflammation

**Methods:**

We examined 44 subjects (22m, 22f) at baseline and after 1 year of dieting and life style changes. Seven subjects who did not lose weight and one with anti-thyroid antibodies were excluded. The data available for the final analysis were therefore from 36 children (17m, 19f).

We evaluated: i) clinical characteristics [BMI SDS, tricipital (TS) and subscapular (SS) skinfolds, % fat mass (FM), % fat free mass (FFM), systolic (sBP) and diastolic blood (dBP) pressure, waist/hip ratio(W/H)], ii) inflammatory markers [total leucocytes and the subtypes, the neutrophil:lymphocyte ratio, HR-C-reactive protein (HR-PCR)],

iii) thyroid function (fT4, TSH) and thyroid structure (thyroid score, grade 1 to 5; grade 5=max inflammation)

**Results:** After one year, BMI SDS decreased significantly ( $2.31 \pm 0.5$  vs  $1.98 \pm 0.6$ ;  $p < 0.001$ ) as well as TS ( $27.1 \pm 4.9$  vs  $23.5 \pm 3.9$  mm;  $p < 0.001$ ), SS ( $23.6 \pm 4.2$  vs  $21.6 \pm 4.8$  mm;  $p < 0.01$ ), TS+SS ( $50.7 \pm 8.3$  vs  $45.1 \pm 8.1$  mm;  $p < 0.001$ ), %FM ( $36.3 \pm 6.3$  vs  $34.2 \pm 6.8$ ;  $p < 0.05$ ), W/H ( $0.67 \pm 0.06$  vs  $0.63 \pm 0.06$ ;  $p < 0.001$ ), systolic BP ( $106 \pm 16.4$  vs  $99.5 \pm 11.6$  mm/Hg), diastolic BP ( $63.6 \pm 11.5$  vs  $59.3 \pm 6.2$  mm/Hg;  $p < 0.05$ ), while %FFM increased significantly ( $63.7 \pm 6.3$  vs  $65.8 \pm 8.8$ ;  $p < 0.05$ ). HR-PCR decreased significantly ( $3.1 \pm 0.9$  vs  $2.6 \pm 1.1$  mg/dl;  $p < 0.01$ ) while the other inflammatory parameters did not change. fT4 remained stable, while TSH decreased significantly ( $3.83 \pm 2.1$  vs  $3.03 \pm 1.0$  mU/L;  $p < 0.05$ ) as well as the thyroid score ( $1.79 \pm 1.0$  vs  $0.76 \pm 0.9$ ;  $p < 0.0001$ ). Multiple regression analysis showed that the degree of BMI SDS reduction was the most important factor influencing the improvement in the thyroid score ( $R^2 = 0.39$ ;  $\beta = 0.62$ ;  $p < 0.001$ )

**Conclusions:** Fat excess is the most important factor negatively influencing the function and the structure of the thyroid. A significant improvement of both parameters following weight reduction supports this assumption

## POSTER SESSION 1

Thursday, September 14, 2017, 5:45-6:45pm

### P1 - Type 1 diabetes

#### P1-1800 – P1-1828

P1-1800

#### SUBCLINICAL ATHEROSCLEROSIS IS ASSOCIATED WITH VISCERAL FAT AND FATTY LIVER IN LEAN ADOLESCENTS WITH TYPE1 DIABETES

Hoda Atwa, Professor; Khaled Gad, MD; Hala Hagrasy, MD; Amany Elkelany, MD; Mona Azzam, MD, Faculty of Medicine, Suez Canal University, Ismailia, Egypt; Hassan Shora, PhD, Port Said University, Port Said, Egypt

**Objectives:** To determine whether subclinical atherosclerosis in adolescents with Type 1 diabetes is associated with fatty liver and or visceral fat.

**Methods:** The study was a case-control study performed on 110 adolescents with type 1 diabetes attending the Pediatric Diabetes Clinic at the University Hospital. Group 1 consisted of 55 adolescents with type 1 diabetes and normal carotid intima media thickness (cIMT). The second group 2 included 55 adolescents with type 1 diabetes and subclinical atherosclerosis. There was no significant difference between the two groups as regards weight, height, BMI and waist circumference. All adolescents were normotensive, normo-albuminuric and had no retinopathy. Visceral fat thickness was measured as the distance between the anterior wall of the aorta and the posterior surface of the rectus abdominis muscle. Hepatic steatosis was diagnosed based on enlarged liver size and evidence of diffuse hyper-echogenicity of liver relative to kidneys.

**Results:** The mean HbA1c was significantly higher in the increased cIMT group ( $7.376 \pm 2.668$ ) compared to the normal cIMT group ( $6.064 \pm 1.453$ ),  $p < 0.05$ . The mean visceral fat was significantly higher in adolescents with increased carotid intima media thickness ( $4.8 \pm 1.6$ ) than in the normal thickness group ( $3.9 \pm 1.4$ ),  $p < 0.05$ . Liver size was significantly larger in adolescents with increased cIMT ( $13.73 \pm 2.26$ ) than those with normal thickness ( $12.63 \pm 2.20$ ) ( $p = 0.022$ ). Carotid intima media thickness correlated with age, height, total daily insulin dose, HbA1C, visceral fat and liver size. Those correlations results were further verified by the results of the linear regression test, which showed that visceral fat and liver size are significant predictors, (with regression coefficient 0.011 and p value 0.033). Age is highly significant predictors of carotid intima media thickness, with a regression coefficient of 0.010 and a p value of 0.007).

**Conclusions:** High visceral adipose tissue in adolescents with type 1 diabetes and increased cIMT compared to control subjects. Visceral fat, age and liver size are the most fitting factors predicting c IMT.

P1-1801

#### ESTABLISHING A BASELINE FOR PATIENTS WITH TYPE 1 DIABETES WHO WEAR MEDICAL IDENTIFICATION

Kanthi Bangalore Krishna, MBBS; Malinda Wu, MD; Nafeesa Sultana, MD; Dan Hale, MD, Penn State Hershey Medical Center, Hershey, PA, United States

**Objectives:** We hypothesize that most patients using insulin who are seen at a tertiary pediatric diabetes center do not wear medical identification. We aim to increase patients' usage of medical identification through outpatient education.

**Methods:** We surveyed patients coming in for routine diabetes follow-up visits if they 1) had a medical alert and 2) were wearing it. All patients were given the survey upon arrival to clinic and patients were excluded if they were not using insulin or did not complete the pertinent questions on the survey. We also collected information about the patient's age, gender and most recent HbA1C. Patients had been routinely educated about the importance of wearing medical identification and had been provided with free medical identification bracelets prior to the initiation of the project. With the start of the project, all patients were provided a new handout reinforcing the importance of regularly wearing medical identification and information on how to obtain medical identification.

**Results:** 31% of patients surveyed wore medical identification regularly. Of patients old enough to drive, age 16-18 years, only 32% wore medical identification regularly. 53% of patients surveyed had medical identification, but only 58% of patients who had medical identification wore it regularly. Of patients who wore medical identification regularly, 57% were male. The average HgA1C of patients who regularly wore medical identification was 8.7; the average was 9.2 for patients who did not regularly wear medical identification. A sample of 150 patients of approximately 1000 type 1 diabetics who are followed in the clinic were surveyed. Of the

patients surveyed, 53% were male, 4% were 0-4 years old, 20% were 5-9 years old, 57% were 10-15 years old, and 19% were 16-18 years old.

**Conclusions:** There is little published documentation about adherence to the recommendation that patients with type 1 diabetes wear medical identification. We found that many patients own some form of identification warning of their diabetes or insulin usage such as medical alerts, but few patients are wearing it regularly. Further research needs to be done to identify how to increase the wearing of such medical identification.

P1-1802

**SERUM LEVELS OF S100B, NEURON-SPECIFIC ENOLASE (NSE) AND GLIAL FIBRILLARY ACIDIC PROTEIN (GFAP) IN PREDICTING THE DIABETIC KETOACIDOSIS-INDUCED CENTRAL NERVOUS SYSTEM DAMAGE**

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**Objectives:** Glial fibrillary acidic protein (GFAP) and S100B are synthesized by astrocytes, and neuron-specific enolase (NSE) is synthesized by neuron and neuroendocrine cells. While GFAP and NSE levels are increased in central nervous system (CNS) injuries, it has been claimed that S100B protein, which has been shown to be expressed in the body by different cells (adipocyte, myocyte, etc.) in recent years, is a more sensitive marker than NSE and GFAP in predicting CNS damage. To investigate the clinical significance of serum NSE, GFAP and S100B proteins used to predict CNS damage in patients with diabetic ketoacidosis (DKA).

**Methods:** Twenty-nine patients with moderate and severe DKA, 36 with type 1 diabetes (T1DM), and 31 healthy children were included in the multicenter study. Clinical and laboratory findings, Glasgow coma scores (GCS) and complications were recorded at admission and follow-up. In the DKA group, NSE, S100B and GFAP levels were measured at the time of diagnosis and at the 6th and 12th hours after treatment. The results were compared with the basal values of T1DM and healthy control groups. Magnetic resonance imaging was performed in the DKA group to demonstrate any CNS damage.

**Results:** The study groups were similar regarding age and sex. Diabetes duration was not different between the DKA and T1DM groups. Fourteen of the patients in the DKA group were new-onset diabetes. No clinical or radiological finding of brain edema was found in any of the cases with DKA. GFAP and NSE levels were not different between the groups

(Table1). In the DKA group, S100B protein was significantly higher than control and T1DM groups. No significant difference was found when GFAP, NSE and S100B protein levels were compared according to DKA severity [moderate (n=11) & severe (n=18)], diabetes duration [≥5 years (n=9) & <5 years (n=20)], and GCS [GCS<15 (n=7) & GCS ≥15 (n=22)].

**Conclusions:** Similar levels of NSE and GFAP, which are specific to neuronal cells, in the DKA and control groups, suggested that DKA does not cause neuronal damage in the early period. Besides, elevated levels of S100B, which is also synthesized from non-neuronal tissues, might have arisen from peripheral sources in DKA patients.

Table 1. Clinical and laboratory characteristics of the groups

	DKA (n=29)			Type 1 DM (n=30)	Control (n=35)	P
Age (year)	13 (8,1-14,5)			12,3 (11,3-14,3)	11,0 (8,5-13,4)	>0,05*
Sex(M/F)	17/12			19/11	23/12	>0,05**
Ağırlık SDS	-0,30 <sup>a</sup> (-1,1 - 0,4)			0,83 <sup>a</sup> (-0,1-1,7)	0,26 (-0,8-0,9)	<0,01*
Height SDS	-0,4 (-0,9-0,3)			0,2 <sup>b</sup> (-0,6-1,2)	-0,3 <sup>b</sup> (-1,3-0,3)	<0,05*
NSE (ng/ml)	Baseline	6th hours	12th hours	7,5 (5,5-15,7)	9,6 (5,8-14,4)	>0,05*
	7,0 (5,6-9,6)	6,7 (4,4-8,7)	7,1 (6,4-7,9)			
GFAP (ng/mL)	2,5 (2,1-2,7)	2,6 (2,2-2,9)	2,5 (2,0-2,7)	2,7 (2,3-3,0)	2,9 (2,3-3,1)	>0,05*
S-100B (pg/mL)	74,0 <sup>ab</sup> (66,2-95,1)	100 <sup>c</sup> (76,3-114,7)	83,6 <sup>d</sup> (67-105,0)	51,4 <sup>acd</sup> (45,7-58,0)	52,6 <sup>acd</sup> (45,9-64,2)	<0,01*

Data are given as median (IQR 25-75 percentile).

\*Kruskal Wallis Test (p<0,05), \*\*Chi-Square test (p<0,05), <sup>ab</sup> Mann-Whitney U test (p<0,0167)

P1-1803

**HEMOGLOBIN A1C, HOME BLOOD GLUCOSE TESTING AND SOCIAL DISADVANTAGE: METRICS OF RACIAL HEALTH DISPARITY IN YOUTH WITH TYPE 1 DIABETES**

Stuart Chalew, MD; Ricardo Gomez, MD, LSUHSC, New Orleans, LA, United States; Jodie A Kamps, PhD, Childrens Hospital, New Orleans, LA, United States; Richard Scribner, PhD; Brittany Jurgen, MS/MA; James Hempe, PhD, LSUHSC, New Orleans, New Orleans, LA, United States

**Objectives:** Black pediatric patients with type 1 diabetes (T1D) have been consistently found to have higher HbA1c than white patients. We examined the relationship of average number of home blood glucose tests performed per day (TPPD), an index of diabetes management, along with other psycho-social factors to better understand differences in HbA1c outcome.

**Methods:** Patient glucose meters were uploaded during clinic visits from youth with T1D self-identified as either black (n=33 ) or white (n=53). TPPD and mean blood glucose (MBG) were calculated for the prior 30 days. HbA1c, family income, insurance status, concentrated disadvantage (CDI), psychological depression (DSC), mother educational attainment (MEA), insulin delivery method (IDM) data was also collected. Factors potentially influencing TPPD and



HbA1c were analyzed using multiple variable linear regression modelling.

**Results:** Black patients had significantly higher HbA1c, MBG and measures of disadvantage compared to white patients. TPPD was directly correlated with HbA1c ( $r=-0.51$ ,  $p<0.0001$ ) and MBG ( $r=-0.28$ ,  $p=0.009$ ) and inversely correlated with age and CDI ( $r=-0.33$ ,  $p=0.0023$ ). In the statistical modelling race, age and IDM were all significant independent variables and accounted for 50% , ( $p<0.0001$ ) of the variance in TPPD.

Addition of gender, income level, CDI, MEA, or DSC were not significant.

**Conclusions:** TPPD is a simple, readily obtained marker of behavior closely associated with racial disparity in HbA1c. Regardless of age or IDM, TPPD was lower in black compared to white patients. Racial difference in TPPD is intricately linked with the greater social disadvantage of black patients. In light of continuing racial disparity in HbA1c outcome , innovative intervention approaches are needed to overcome obstacles to optimal management of high risk patients.

P1-1804

#### **AUTOIMMUNE COMORBIDITIES IN TYPE 1 DIABETES MELLITUS BY AGE AT DEBUT: A FOLLOW UP SINCE ONSET STUDY.**

*Maria J Chueca, MD; Diego M Peñafiel-Freire, MD; Diego M Peñafiel-Freire, MD; Sara Berrade, MD; Teodoro Dura, PhD; Maria J Goñi, PhD; Luis Forga, PhD, Complejo Hospitalario de Navarra, Pamplona, Spain*

**Objectives:** To analyze the impact of onset age Type 1 Diabetes Mellitus (DM1) over the comorbidity of other autoimmune diseases in patients diagnosed before the age of 15 years.

**Methods:** Observational retrospective follow-up study of adult patients ( $\geq 18$  years) diagnosed with DM1 before 15 years of age in our community (Navarra, Spain) since January 1990. Data from *Diabetes Registry of Navarra* were used: sex, age at debut (cutoff point in  $\geq 6$  years), thyroiditis, celiac disease, pernicious anemia and autoimmune gastritis. Statistical differences among groups were analyzed by Pearson's Chi square, binary logistic regression or Fisher's exact test were used.

**Results:** 272 patients, 55.9% male. 14% of the cohort presented early DM1 onset ( before 6 years), while the mean age of the analyzed patients was  $9.8 \pm 3.3$  years (mean $\pm$ SD). All cause autoimmune pathology, defined as positive serum antibody titer that required either treatment or nutritional changes, was found in 63 patients (23.2%) corresponding to thyroiditis (55 patients from which 16.4% were of early DM1 onset), celiac disease 7 patients (0% of early onset), pernicious anemia 2 patients (100% of early onset) and autoimmune gastritis 3 patients (100% of early onset). Binary logistic regression analysis revealed that early diabetes onset does not condition an increased risk of global autoimmune pathology ( $p 0.425$ ).

However, when studied independently, the frequencies of autoimmune gastritis and pernicious anemia differed

significantly ( $p=0.003$  and  $p=0.024$  respectively) when the DM1 onset is before 6 years.

**Conclusions:** Age at debut does not seem to influence the development of autoimmune diseases (thyroiditis, celiac, gastritis) globally throughout the evolution of DM1. However, when analyzing each pathology separately, it is observed that autoimmune gastritis and pernicious anemia are more frequent in those who undergo significantly less than 6 years. This may indicate that the pathophysiological mechanism, within the autoimmune context, does not work the same for the different autoimmune diseases studied.

P1-1805

#### **THE EFFECT OF METFORMIN AND STATIN MEDICATIONS ON SUBCLINICAL CARDIOVASCULAR OUTCOMES IN YOUTH WITH TYPE 1 DIABETES: THE SEARCH FOR DIABETES IN YOUTH STUDY**

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**Objectives:** Youth with type 1 diabetes (T1D) are at risk of subclinical cardiovascular outcomes, possibly due to insulin resistance and dyslipidemia. Using an observational cohort, we evaluated whether treatment with metformin and statin is associated with decreased odds of such outcomes.

**Methods:** SEARCH participants with T1D who had a baseline ( $9.5\pm 6.3$  months) and a follow up visit ( $7.8\pm 1.9$  years) and were treated with insulin+metformin ( $N=48$ ) or insulin+statin ( $N=40$ ) at follow up were individually matched (2:1 ratio) on age, gender, race/ethnicity, insulin sensitivity (IS, validated score including waist circumference, HbA1c and triglycerides) and non- HDL cholesterol levels measured at the baseline visit with, respectively, 96 and 80 participants treated with insulin only (reference groups). Measures of arterial stiffness [pulse wave velocity (PWV) and Augmentation Index (AI75)] and heart rate variability [the standard deviation of the NN intervals (SDNN) and the root mean square differences of NN (RMSSD)] were obtained using the Sphygmocor device at the follow up visit. Associations between cardiovascular outcomes and treatment groups were evaluated using t-tests.

**Results:** Participants on insulin+metformin were not different than the insulin-only group in their matching characteristics and outcomes: PWV ( $6.1\pm 1.2$  vs  $5.8\pm 1.2$  m/sec,  $P=0.26$ ), Aix75 ( $1.0\pm 11.1$  vs  $0.1\pm 10.6$ ,  $P=0.68$ ), median SDNN ( $52.4$  vs  $56.4$  m/sec,  $P=0.80$ ) and RMSSD ( $43.2$  vs  $48.6$ ,  $P=0.95$ ), but they had lower IS score ( $4.1\pm 1.6$  vs  $5.6\pm 2.2$ ,  $P<0.0001$ ) at the

**Objectives:** Autoantibodies in individuals with Type 1 diabetes are currently used as indicators of beta cell directed autoimmunity. However, the pathogenic role of these antibodies remains an area of controversy. We tested the ability of antibodies present in the serum of newly diagnosed individuals with Type 1 diabetes to bind live insulin producing cells generated from human embryonic stem cells

**Methods:** Serum antibody samples were collected from Insulin naïve newly diagnosed type 1 diabetes children from age 1-18 years after informed parental consent. We assessed whether antibodies present in these serum samples directly bound to live insulin producing cells with sufficient affinity to be detectable by flow cytometry. Genetically modified pluripotent stem cells, containing sequences encoding a green fluorescent protein (GFP) targeted to the INSULIN locus, were differentiated to form a single cell suspension and then incubated with patient serum samples (containing antibodies) or pooled human serum (control, sigma) at a dilution of 1: 5 and 1:20. After serum incubation, cells were labelled with APC-conjugated anti-human secondary antibodies that recognized human IgG and IgM. Samples were subjected to flow cytometric analysis using a BD Fortessa flow cytometer.

**Results:** Pilot experiments examined the potential for IgG and IgM antibodies in the sera from four newly diagnosed T1D patients to bind live INS+ cells. This analysis showed that, relative to GFP- (INS-) cells, live GFP+ (INS+) cells were not specifically bound by antibodies present in these sera.

**Conclusions:** In this preliminary study we did not observe specific binding of serum derived antibodies to in vitro derived beta cells. Our results appear to indicate that autoantibodies are not directed against antigens displayed on the surface of live beta cells and thus may not be directly involved in beta cell death. We are currently extending this study to include a larger number of patient samples.

P1-1807

## ASSOCIATION OF MATERNAL ANXIETY WITH GLYCEMIC CONTROL OF CHILDREN WITH TYPE 1 DIABETES

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follow up visit. Participants on statin+insulin were not significantly different from the insulin-only group in their matching characteristics and their outcomes: PWV ( $5.7 \pm 0.8$  vs  $5.6 \pm 1.0$  m/sec,  $P=0.55$ ), Aix75 ( $-4.1 \pm 9.9$  vs  $-2.4 \pm 12.1$ ,  $P=0.45$ ), median SDNN ( $55.1$  vs  $66.0$  m/sec,  $P=0.31$ ) and RMSSD ( $49.9$  vs  $49.5$ ,  $P=0.68$ ).

**Conclusions:** In this observational study, no association of statin or metformin use with subclinical cardiovascular outcomes was apparent. Limitations include small numbers on statins or metformin and lack of information about duration or medical decision-making around metformin or statin use. Well-designed clinical trials are needed to clarify whether insulin sensitizing therapy can ameliorate cardiovascular outcomes in T1D.

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Table 1: Baseline and follow up characteristics of youth with T1DM and their cardiovascular outcomes. Matched at baseline: group 1 with group 2 and group 3 with group 4.						
	Group 1 Insulin only	Group 2 Insulin and metformin	P value*	Group 3 Insulin only	Group 4 Insulin and statin	P value*
<b>CHARACTERISTICS AT BASELINE VISIT</b>						
Total number of subjects	N=96	N=48		N=80	N=40	
Age at visit	$12.8 \pm 3.5$	$12.9 \pm 3.9$	0.9515	$13.8 \pm 3.3$	$13.4 \pm 3.7$	0.5221
Female gender	61 (63.5)	31 (64.6)	0.9024	26 (32.5)	19 (47.5)	0.1096
Race						
Non-Hispanic White	61 (63.5)	27 (56.3)	0.3975	66 (82.5)	34 (85.0)	0.7290
Other/unk	35 (36.5)	21 (43.8)		14 (17.5)	6 (15.0)	
Insulin sensitivity score	$7.4 \pm 3.2$	$7.1 \pm 2.7$	0.5931	$9.0 \pm 3.1$	$8.8 \pm 2.9$	0.7534
Non-HDL (mg/dL)	$112.7 \pm 30.0$	$119.3 \pm 34.2$	0.2473	$128.4 \pm 24.7$	$131.2 \pm 25.6$	0.5629
LDL (mg/dL)	$93.5 \pm 23.2$	$100.3 \pm 28.0$	0.1255	$113.0 \pm 23.9$	$112.7 \pm 24.2$	0.9584
Duration of DM (months)	$11.4 \pm 6.7$	$9.6 \pm 6.2$	0.1308	$8.4 \pm 5.6$	$9.4 \pm 6.6$	0.3841
BMI z-score	$0.99 \pm 1.02$	$1.61 \pm 0.81$	0.0003	$0.61 \pm 1.09$	$0.65 \pm 0.81$	0.8059
HbA1c (%)	$8.8 \pm 2.1$	$7.6 \pm 1.5$	<0.001	$7.7 \pm 2.0$	$7.5 \pm 1.4$	0.6046
Insulin use	91 (94.8)	42 (89.4)	0.2971	79 (98.8)	39 (97.5)	1.0000
<b>CHARACTERISTICS AT FOLLOW UP VISIT</b>						
Age at visit	$19.7 \pm 4.0$	$19.4 \pm 4.3$	0.6195	$21.0 \pm 3.6$	$20.9 \pm 3.3$	0.8722
Duration of DM (years)	$7.9 \pm 1.9$	$7.3 \pm 1.8$	0.1002	$7.9 \pm 2.0$	$8.3 \pm 1.9$	0.2935
Insulin sensitivity score	$5.6 \pm 2.2$	$4.1 \pm 1.6$	<0.001	$5.9 \pm 2.1$	$5.3 \pm 1.8$	0.1253
Non-HDL (mg/dL)	$121.4 \pm 38.2$	$131.2 \pm 28.4$	0.0887	$123.9 \pm 33.4$	$134.3 \pm 39.4$	0.1365
LDL (mg/dL)	$99.8 \pm 28.8$	$106.5 \pm 25.8$	0.1775	$105.5 \pm 29.4$	$109.3 \pm 28.0$	0.5077
BMI z-score	$0.97 \pm 0.86$	$1.63 \pm 0.71$	<0.001	$0.57 \pm 1.21$	$0.85 \pm 0.75$	0.1226
HbA1c (%)	$9.3 \pm 1.7$	$9.5 \pm 1.6$	0.4983	$9.1 \pm 2.0$	$9.3 \pm 1.9$	0.5730
<b>SUBCLINICAL CARDIOVASCULAR OUTCOMES</b>						
PWV: carotid-femoral (m/sec)	$5.8 \pm 1.2$	$6.1 \pm 1.2$	0.2553	$5.6 \pm 1.0$	$5.7 \pm 0.8$	0.5500
Augmentation Index	$0.1 \pm 10.6$	$1.0 \pm 11.1$	0.6817	$-2.4 \pm 12.1$	$-4.1 \pm 9.9$	0.4507
SDNN (m/sec) [median (Q1, Q3)] <sup>†</sup>	56.4 (36.3, 80.5)	52.4 (36.7, 71.9)	0.7998	66.0 (47.3, 83.9)	55.1 (45.1, 79.9)	0.3118
RMSSD [median (Q1, Q3)] <sup>†</sup>	48.6 (27.8, 79.1)	43.2 (28.0, 66.4)	0.9539	49.5 (32.2, 79.6)	49.9 (32.7, 74.8)	0.6773

\*p-value from t-test

<sup>†</sup> t-test uses log-transformed values

P1-1806

## REVISITING THE ROLE OF AUTOANTIBODIES IN THE IMMUNOPATHOGENIC MECHANISMS OF TYPE 1 DIABETES USING STEM CELL DERIVED BETA CELLS

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**Objectives:** Mothers of children diagnosed with Type 1 Diabetes Mellitus (T1DM) under the age of 5 years have to face numerous challenges, both physical and psychological, which leads to maternal anxiety. This affects competency in coping with their child's condition, ultimately affecting their child's metabolic control. While there are numerous studies focussing on psychological well-being of children and adults with T1DM, very few studies have investigated the psychological status of the primary care giver for a T1DM child diagnosed under the age of 5 years. Thus, the objectives of this study were to explore anxiety and competency levels of mothers who had one child with type 1 Diabetes mellitus diagnosed under 5 years of age and to determine the effect of anxiety among mothers on the metabolic control of their children.

**Methods:** We conducted a cross-sectional, exploratory study on 87 mothers who had 1 child with T1DM diagnosed under 5 years of age attending a tertiary care hospital in Pune, India. Records of the children were used to obtain date of diagnosis, disease duration, anthropometric data and HbA1C levels. Mothers' anxiety and competency levels were assessed by trained psychologists using the Hamilton Anxiety Rating Scale (HARS) (Hamilton M. 1959) and the Parental Sense of Competency (PSOC) (Gibaud-Wallston & Wandersman, 1978) respectively.

**Results:** The mothers were aged  $30.1 \pm 4.9$  years and the mean age of their children was  $5.8 \pm 3.1$  years. The mean maternal anxiety score was  $32.2 \pm 13.4$  and mean competency score was  $62.9 \pm 7.7$ . A significant negative correlation was observed between maternal anxiety and competency scores. A trend was observed of increasing HbA1C as maternal anxiety increased and decreasing HbA1C as maternal competency increased as judged by the respective rating scales. This trend was observed even after adjusting for child's duration of disease and maternal age.

**Conclusions:** Preliminary analysis indicates that maternal anxiety negatively influences and maternal competency positively influences glycaemia control of children with T1DM.

P1-1808

#### FEASIBILITY AND ACCEPTABILITY OF PROFESSIONAL CONTINUOUS GLUCOSE MONITORING SYSTEM IN YOUNG CHILDREN WITH TYPE 1 DIABETES MELLITUS

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**Objectives:** Frequent self-monitoring of blood glucose (SMBG) is the only accurate method available for insulin dose titration in patients with T1DM. Professional continuous glucose monitoring (p-CGM) has been approved for use in adults and children with T1DM. However, there is dearth of literature on its use in children with T1DM in India. This study was planned to assess feasibility and acceptability of p-CGM with iPro™2 in young children (below 10 years) with T1DM.

**Methods:** A single center prospective observational study was conducted among children (2-10 years) with T1DM. A total of 42 children used the p-CGM (iPro™2 Professional CGM, Medtronic, USA) for 3-5 days after informed consent. Patients continued SMBG for 3-4 times/day and kept records of diet, exercise, adverse effects and hypoglycemic symptoms. CGM data was downloaded using CareLink® Pro Software and analyzed by a physician who further guided diabetes management in these children in OPD visits. Pre-defined criteria for feasibility and acceptability were assessed in all children.

**Results:** A total of 47 sensors (disposable component of the CGMS) were used for 42 patients. Three patients underwent repeat CGM as recording was less than 48 hours on first attempt. Two sensors were damaged while insertion as they could not be inserted properly. Average duration of CGM recording was 84.6 hours. Premature and accidental removal occurred in 2 (4.8 %) patients among 7 (16.7 %) children who had problems of fixing and stability of p-CGM. Minimum of 3 calibrated paired gluco-meter readings per day were taken as acceptable for data quality and was acceptable in 40 (95.2%). Other parameters for acceptable data quality like, mean absolute difference (MAD) of  $< 28\%$  was seen in 35 (83.3 %) and correlation coefficient of  $> 70\%$  was seen in 31 (73.8 %) patients. Most common adverse events were local redness noticed in 11 (26.2%) patients, local irritation in 16 (38.1%) patients and parental anxiety was reported in 12(28.5%) cases.

**Conclusions:** There were no significant adverse effects noticed with the procedure and Professional CGM (using iPro™2) appears feasible and acceptable to children (2-10 years) with T1DM as well as their caregivers.

P1-1809

#### WHETHER RULE 500 CAN BE USED TO CARBOHYDRATE COUNTING IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES?

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**Objectives:** Objective: Carbohydrate counting was not widely used in the treatment with diabetic patients in china. This study explores the feasibility and safety of using carbohydrate counting in pediatric diabetic patients. Because the patients are growing with age in childhood, the 500 Rule of adult patients might not fit for pediatric patients. We try to find a parameter can be used in children and young person.

**Methods:** Methods: 41 patients with type 1 diabetes were treated with rapid acting insulin and long-acting insulin analogs, multiple insulin injection. The dosage of insulin was calculated by the ratio of insulin to carbohydrate (ICR). The blood glucose (BG) were checked 8 times a day, and used as parameter to adjust the ICR. We compared the values of BG, total insulin dosage, ICR and the correction factor of the 3<sup>rd</sup> day after admission (to eliminate the influence of blood glucose fluctuation after diabetic ketosis) and 1 day before

discharge. The difference of highest and lowest BG value was calculated as daily BG fluctuations.

The result of carbohydrate by total insulin was used as an index parameter to assess whether 500 Rule was fit for pediatric patient. We can use this parameter as a constant to calculate the initial ICR in pediatric type 1 diabetic patients.

**Results:** Result: This study included 41 patients with type 1 diabetes; male to female ratio was 19: 22; age of  $5.65 \pm 3.48$  yrs. At the time of admission, the HbA1c level was  $9.1 \pm 2.6\%$ . There were significant differences in the highest value of BG per day and blood glucose fluctuation between initial treatment and before discharge. The incidence of hypoglycemia was 0-2 times per day. There was no significant difference of the incident of hypoglycemia between the initial treatment and before discharge, and no severe hypoglycemia occurred. The incidence of euglycemia was 68.3% and 65.9%, respectively, no statistical difference. The initial insulin dose was  $0.77 \pm 0.24$  iu/kg.d, and the dose before discharge was about  $0.76 \pm 0.24$  iu/kg.d.

The initial ICR was  $18.49 \pm 8.93$ , and before discharge was  $17.45 \pm 11.48$ . The 500 Rule was used in adults with diabetes to calculate the initial ICR, which was calculated from insulin by ICR. The similar values were  $306.76 + 121.36$  and  $275.55 + 76.77$  respectively. The correction factor was  $5.46 \pm 2.17$  and  $5.48 \pm 3.23$  respectively.

**Conclusions:** Conclusion: The study showed that carbohydrate counting could be used in the treatment of type 1 diabetes in children and adolescents. It is suggested that the 500 Rule should be modified to be the "300 Rule" in the calculation of the initial coefficient of ICR. We also recommend 18, an empirical value, as an initial ICR; and 5.5 could be used as the initial correction factor. The method of calculating counting can be used in children and adolescents with diabetes.

P1-1810

#### EVALUATION OF A DIABETES COACH PROGRAM AIMED TO IMPROVE THE CARE OF CHILDREN AND YOUTH WITH TYPE 1 DIABETES

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**Objectives:** Management of Type 1 Diabetes (T1D) in children and adolescents can be challenging, and only a minority of patients achieve hemoglobin A1C (A1C) targets. Health coaching can be effective to improve the self-management of diabetes. The objective of this project was to evaluate the impact of the Diabetes Coach Program (DCP) on A1C levels in youth with T1D.

**Methods:** Subjects included youth who were referred to and participated in the DCP from October 2011 to May 2016. The Diabetes Coach visited families in their homes every 1-2 weeks and updated patients' diabetes teams regularly. A1C prior to the DCP were compared to A1C during and after

discharge from the DCP. Six participating families completed a telephone satisfaction survey.

**Results:** Twenty-three patients participated in the DCP (43% male; average age 11 years, range 8.8-14.5 yrs); average duration of T1D 2.3 yrs (range 0.1-6.3 yrs); average time in the DCP 1.4 yrs (range 0.2-2.5 yrs). During involvement in the program, A1C decreased from baseline (11.4% [range 8.9-15.3] vs 10.2% [range 7.6-12.4] ( $p=0.004$ )). For 11/13 patients discharged from the DCP, the most recent mean A1C, 11.2% (range 9.1-13.6), was not different from the initial A1C ( $p=0.46$ ). Family feedback about the program was overwhelmingly positive.

**Conclusions:** Participation in an in-home support program decreased A1C values in pediatric patients, however this was not sustained after the visits stopped. Pediatric health coaches may play an important role in the management of T1D, however, further research is needed to explore their benefits and how positive effects can be sustained after the intervention.

P1-1811

#### EFFECT OF POINT OF CARE GLYCOSYLATED HAEMOGLOBIN ON CONTROL OF TYPE 1 DIABETES IN CHILDREN AT A SOUTH AFRICAN TERTIARY HOSPITAL

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**Background:** Hemoglobin A1c (HbA1c) levels correlate with complications of diabetes, and this can be done at a laboratory or at the point of care (POC). POC tests are available in minutes, thus management decisions can be made immediately. In January 2014, a POC testing device was donated to the hospital and reagents provided for a year. Previously, all HbA1c tests at the hospital were conducted at the local laboratory.

**Objectives:** To assess whether the use of POC HbA1c and the associated immediate management decisions, will improve HbA1C levels and reduce the number of episodes of diabetic ketoacidosis (DKA).

**Methods:** Hospital records of diabetic children, whose POC HbA1c levels had been tested regularly in 2014, were reviewed. Information on the following was obtained; age at the start of POC HbA1c testing, gender, weight, height, insulin regimen at start of HbA1c testing, and insulin regimen 12 months later. Information on the number of episodes of DKA in the 12 months prior to POC HbA1c testing, and of episodes 12 months after start of POC HbA1c was also noted.

**Results:** In all, 27 children's records were reviewed. Over the 12 months, there was no significant improvement in HbA1c levels. There were significantly fewer episodes of DKA over the period.

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**Table 1:** General characteristics of enrolled children

	At start of POC HbA1c testing
Age (months)	139.93 (51.31)
Female n (%)	15 (56)
WAZ	-0.61 (1.13)
HAZ	-1.11 (1.10)

Values noted as mean (SD), except gender; WAZ=Weight-for-age Z-score, HAZ=Height-for-age Z-score

**Table 2:** Insulin regimens and diabetes control

	At start of HbA1c testing
Insulin regimen n (%)	
Biphasic insulin bd	17 (63)
Three insulin injections daily	10 (37)
HbA1c (%)	12.83 (3.11)
Number of DKA episodes in preceding 12 months	0.48 (0.73)

Values noted as mean (SD), except insulin regimen; \*Insulin regimens slightly different after 12 months, p=0.06;

#Significantly fewer episodes of DKA after 12 months

**Conclusions:** The introduction of POC HbA1c resulted in a marginal change in insulin regimens. There were significantly fewer episodes of DKA, but there was no change in HbA1c.

P1-1812

**CGM INCREASES PARENTAL COMFORT WITH LOWER GLUCOSE LEVELS IN YOUNG CHILDREN WITH TYPE 1 DIABETES (T1D)**

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**Objectives:** T1D Exchange Clinic Registry Data suggest that most (75%) young children do not achieve HbA1c targets; this study used interviews of parents with children <8 years old with T1D to better understand parental perceptions of target glucose ranges.

**Methods:** Semi-structured interviews were carried out with 79 parents of children <8y with T1D for ≥1y (child age 5.2±1.5y, T1D duration 2.4±1.3 years, A1c 7.9±0.9%) to explore parental experiences in diabetes management.

Interviews were transcribed and reviewed, data is presented only for interviews in which numeric responses were given to questions regarding the glycemic targets advised by the

child's medical team and/or ranges in which parents felt comfortable. Comments specifying daytime vs. overnight targets were not available. Data are presented as mean±SD. **Results:** Parents generally felt comfortable with their child in target glucose ranges that were slightly higher (93±25 to -177±42 mg/dl, 5.2±1.4 to 9.8±2.3 mmol/l) than the targets they reported as recommended by their clinicians (87±19 to 166±33 mg/dl, 4.8±1.1 to ± 9.2±1.8 mmol/l). Almost 40% of parents were uncomfortable with blood glucose values below 100 mg/dl (<5.6 mmol/l). Parents whose children used continuous glucose monitoring (CGM) reported comfort with significantly lower glucose levels than parents not using CGM (Table) (p = 0.0017); whereas no difference was seen in pump versus injection users.

**Conclusions:** Further exploration into how use of diabetes technologies and other factors relate to parents' target glucose ranges is important to develop strategies to improve glucose time-in-range for very young children with T1D. In the future, use of automated insulin delivery systems may be impacted by parental comfort with preset glucose targets.

		User	Non-User	p-value
Lower Limit of Parental Comfort Range for Glucose	CGM	82±13 mg/dl 4.6±0.7 mmol/l (n=33)	104±31 mg/dl 5.8±1.7 mmol/l (n=24)	0.0017
	Pump	91±28 mg/dl 5.1±1.6 mmol/l (n=39)	92±15 mg/dl 5.1±0.8 mmol/l (n=18)	0.231

P1-1813

**STREAMLINING THE USE OF DIABETES-ASSOCIATED ANTIBODIES IN THE CLASSIFICATION OF NEW ONSET DIABETES IN CHILDREN AND ADOLESCENTS**

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**Objectives:** The goal was to determine if a pediatric new onset diabetes diagnostic algorithm created in the Northeastern United States would be applicable in the Southwestern US.

**Methods:** Data from patients with new onset diabetes seen in an academic hospital in Tucson, AZ between 01/01/2014 and 12/31/2015 were retrospectively reviewed. Values of their diabetes-associated antibodies (DAA) on admission were recorded, including glutamic acid decarboxylase (GAD) Ab, insulinoma-associated antigen 2 (IA-2) Ab, and insulin Ab. If at least one DAA was positive, patients were classified as "Type 1 Diabetes Mellitus" (T1DM). They were classified as "Antibody-Negative DM" if none of them were positive. An algorithm developed by von Oettingen et al. utilizing weight z-score, age, and race was also used to assess diabetes type. If the algorithm score was <3, the patient was labeled "T1DM via algorithm" whereas a score of ≥3 was labeled "Equivocal, obtain DAA." Sensitivity, specificity, and positive predictive values were calculated.

**Results:** The sample included 111 pediatric patients with new onset DM. Of those, 72 patients had results for the full

complement of antibodies used in the original paper and were included in the analysis. The median age was 11.13 years (range: 0.92-18.82 years, SD: 4.25). The racial composition was 66.66% White or Caucasian, 2.77% Black or African American, 2.77% American Indian or Alaska Native, 18.05% Other, 1.38% Multiracial, and 8.33% of Unknown race. 38.88% of patients were Hispanic or Latino while 58.33% were not, and 2.77% were of unknown ethnicity. Based on DAA results, 84.72% of participants were classified as "T1DM" and 15.27% were classified as "Antibody-Negative DM." The algorithm categorized 70.83% of patients as "T1DM via algorithm" while 29.16% were "Equivocal, obtain DAA." The algorithm had an 83.60% sensitivity, 100.00% specificity, and a positive predictive value of 100.00%.

**Conclusions:** A clinical algorithm to assess likelihood of T1DM created in the NE US appears to be applicable to a pediatric population seen in the SW US. In those with all three antibodies recorded, all patients identified as T1DM by the algorithm were confirmed by DAA results. Thus, not all patients with new onset T1DM may require DAA. Judicious ordering of DAA may decrease overall healthcare cost.

P1-1814

#### EARLY SIGNS OF MICROVASCULAR COMPLICATIONS IN PAEDIATRIC PATIENTS WITH SHORT DURATION OF TYPE 1 DIABETES MELLITUS SEEN IN SOUTHEASTERN NIGERIA.

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**Objectives:** To determine the prevalence of microvascular complications in adolescents aged 9-19 years with short duration of T1DM by screening for retinopathy and nephropathy.

**Methods:** A cross sectional study of 24 patients who were consecutively enrolled from the endocrinology clinic at Federal Teaching Hospital Abakaliki. Patients completed a questionnaire type survey recording their demographic data. General physical examination and mydriatic ophthalmoscopy were conducted. Three early morning spot urine specimen for albumin/creatinine ratio were estimated three months apart and glycosylated haemoglobin (HbA1c) determined.

**Results:** Twenty four of 36 adolescents with type 1 diabetes mellitus aged 9-19 years followed up at the clinic were enrolled for the study. Fifteen (62.5%) were males and mean age at diagnosis was 12.4+/-2.3 years. Mean duration of diabetes was 23.8+/-20.6 months. Their mean HbA1c was 11.4%. Retinopathy was seen in 16.7% (6/18) while 33.3% (6/18) had microalbuminuria. Blood pressure range (both systolic and diastolic) of all the participants was within the 50th to 90th centile.

**Conclusions:** A high prevalence of early signs of microvascular complications was seen among adolescents with short duration of onset of T1DM in Abakaliki.

**Keywords-** Diabetes, microalbuminuria, retinopathy, short duration, microvascular complication.

P1-1815

#### MICRONUTRIENT PROFILE AND STATUS OF BLOOD ANTIOXIDANT SYSTEM IN CHILDREN WITH TYPE 1 DIABETES MELLITUS

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**Objectives:** It is known that progress of diabetes mellitus may alter the blood antioxidant system. There is an interest in the relationship between micronutrient profile, status of antioxidant system and diabetes control in prepubertal children. So the aim of this study is to examine the amount of some micronutrients and antioxidant status in prepubertal children with type 1 diabetes mellitus (T1DM).

**Methods:** The 21 prepubertal children with T1DM (9 girls, 12 boys; aged 4-7 yr, median 6.0 years; duration of disease 0.5-3 yr, median 1 yr; HbA1c 7.2-9.6, median 8.5) were observed. The levels of trace elements (boron, calcium, chromium, cobalt, copper, iron, magnesium, manganese, molybdenum, nickel, lead, potassium, selenium, sodium, zinc,) and vitamins (A, B<sub>1</sub>, B<sub>3</sub>, B<sub>5</sub>, B<sub>6</sub>, B<sub>9</sub>, B<sub>12</sub>, C, D<sub>3</sub>, E and K) were measured. Activity of the antioxidant system was assayed via thiobarbituric acid reactive substances (TBARS), ceruloplasmin (CP) levels and total antioxidant capacity (TAC) of plasma.

This work was supported by Alfa-Endo Program of Charities Aid Foundation Russia, funded by Alfa-Group.

**Results:** The most of measured values of micronutrients were within the reference ranges but the values of lead and vitamin B<sub>12</sub> exceed the upper limit of reference range (48% and 19%, respectively) and values of copper, zinc and vitamin D<sub>3</sub> below lower limit of reference range (38%, 29% and 19%, respectively). Also the elevated level of TBARS (median 6.85 vs 3.15 nMol/mL) in patients with T1DM in compare with health children was observed. In addition, the value of HbA1c were weak correlated with CP level and vitamin D<sub>3</sub> level (the Spearman r 0.608 and 0.494, respectively, p<0.05).

**Conclusions:** We observed a mild oxidative stress and altered micronutrient profile in prepubertal children with T1DM.



# AUSTRALIAN CHILDREN WITH TYPE 1 DIABETES CONSUME HIGH SODIUM AND HIGH SATURATED FAT DIETS: LONGITUDINAL COMPARISON WITH NATIONAL AND INTERNATIONAL GUIDELINES

Lucinda Adams, MBBS Student; Rebecca Thomson, PhD; Jenny Couper, Professor; Jemma Anderson, MBBS; Oana Maftai, PhD; Lynne Giles, Associate Professor; Alexia S Peña, PhD, The University of Adelaide, Adelaide, Australia

**Objectives:** Healthy diet is essential during the rapid growth phase of puberty. We aimed to evaluate the diets of Type 1 Diabetes (T1D) children against recommended Australian dietary intakes and international T1D guidelines, and to compare with healthy children.

**Methods:** Diet was assessed using a validated food frequency questionnaire (Australian Child and Adolescent Eating Survey). Diet was cross-sectionally analyzed in 91 children (age  $13.6 \pm 2.4$  years, 42 males, BMI z score  $0.89 \pm 0.57$ ) with T1D duration of  $5.5 \pm 3.8$  years and 28 age and gender matched controls, and longitudinally at 0, 3, 6, 12 months in 90 T1D children enrolled in a randomized control trial evaluating the effects of metformin on vascular health [ACTRN12611000148976](Anderson J. BMC Pediatr 2013). Diet quality was assessed in reference to recommended servings and nutrient intake of the 2013 Australian National Health and Medical Research Council Dietary Guidelines and the 2014 ISPAD Nutritional Guidelines.

**Results:** Diet quality was not different between the T1D and control groups. Both groups did not meet the majority of the Australian Dietary Guidelines: 53% of children achieved the recommended number of fruit serves per day, 31% achieved vegetables, 30% achieved dairy, 20% achieved grains, and 11% achieved meats/alternatives. 87% of children were over consuming non-core foods and this was contributing to  $37.2 \pm 10.6\%$  (mean  $\pm$ SD) of their energy intake. 90% of children achieved recommended intake of fiber ( $35.1 \pm 10.3$  g/day) and all were consuming at least double the sodium recommended intake ( $2811 \pm 760$  mg/day). T1D children met the majority of the ISPAD guidelines, except 78% over consumed saturated fat and trans fatty acids.

In 90 T1D children, linear mixed effects models showed that daily energy intake, macronutrient intake including saturated fats and fiber; and sodium intake did not change with metformin or placebo over 12 months (all  $p > 0.1$ ).

**Conclusions:** The majority of children with and without T1D are not meeting the recommended dietary intakes. Significant over-consumption of saturated fat and trans fatty acids, and non-core foods attracts the most concern. Systematic dietary advice should particularly target reducing the intake of non-core foods.

# A SHORT EDUCATIONAL WORKSHOP IMPROVED KNOWLEDGE AND CONFIDENCE REGARDING CARE OF PEDIATRIC IN-PATIENTS WITH DIABETES MELLITUS.

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**Objectives:** Hospital inpatient care for children with diabetes is frequently mentioned by parents as unsatisfactory, mostly due to lack of knowledge amongst the healthcare staff. The aim of the study was to evaluate the effect of a short educational workshop for hospital inpatients care personal (junior pediatric physicians and nurses) on their knowledge and confidence in treating diabetes patients in the pediatric departments.

**Methods:** The pediatric diabetes team designed a short 4-hour educational workshop regarding management of diabetes mellitus among in-patients. Diabetes specialists delivered the education program to 73 healthcare professionals (qualified nurses and junior doctors) in 2 blocks. Participants completed a multiple choice questionnaire before, immediately after and 3 months after the education intervention to evaluate acquisition of knowledge and confidence. Knowledge was assessed by 22 multiple question exam, maximum score of 100. Confidence was evaluated using 10 categorical questions, ranged 1-5. Quantitative assessments were performed prior to workshop, immediately after, and 3 months later.

**Results:** Healthcare professional population included 21 physicians and 52 nurses, 66 females. There was a significant improvement in the median knowledge score from pre-workshop to immediate post-workshop score (60 (IQR=47-67) vs. 81 (IQR=69-81),  $p < 0.001$ ), and 3 month post workshop, 69 (IQR=63-81),  $P < 0.001$ . The 3 months achievement was lower than the immediate post-workshop grade ( $P = 0.026$ ). The median confidence score also improved significantly from 1.8 (IQR=1.6-2) to 2.4 (IQR=2.1-2.6),  $P < 0.001$ , but the 3-month post workshop assessment was 2.2 (IQR=2-2.6), significantly higher than the pre-workshop state ( $P < 0.001$ ), but lower than the immediate post workshop assessment ( $P = 0.013$ ).

**Conclusions:** A short, one-session based educational tool regarding diabetes mellitus management improved pediatric hospital inpatient care personal knowledge and confidence.

# DEPRESSION AND SUICIDAL IDEATION IN ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS

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**Objectives:** Through retrospective analysis of adolescents aged 13-17 seen in an academic outpatient diabetes clinic, we

aimed to identify differences between Type 1 diabetics who endorsed suicidal ideation (SI) with those who denied SI.

**Methods:** At scheduled appointments patients were given the Clinical Depression Inventory – Short (CDI-S), Barriers to Adherence (BDA), and Pediatric Quality of life 3.2 Diabetes Module (PedsQL) questionnaires. Permission was granted to modify the CDI-S by adding an item to ask about SI. A total of 746 CDI-S screens were completed by a total of 710 unique patients. Two cohorts were identified: those reporting SI and those denying SI. Thirty-eight patients reported SI. Of these, 11 scored low risk for depression, 6 were moderate, and 21 were high. A control group (n=82) was selected among patients with negative SI. Due to limited numbers, all patients with moderate or high scores on CDI-S who denied SI were included in the control group. The controls for the low CDI-S group were matched by age, sex, race, ethnicity, age at diagnosis of diabetes, and CDI-S score.

**Results:** Variables included age, sex, race, ethnicity, insurance type, insulin delivery, known psychiatric diagnosis, hemoglobin A1c (HgbA1c), frequency of blood glucose monitoring, number of emergency room or hospital visits in the last year, and scores on PedsQL and BDA questionnaires. Overall, HgbA1c levels were similar among all groups. However, while not statistically significant, patients with low CDI-S scores who reported SI trended towards higher HgbA1c compared to those with low CDI-S scores who denied SI (10.0 vs 8.9,  $p=0.199$ ). Patients endorsing SI had higher rates of psychiatric diagnosis ( $p=0.013$ ). Among all subjects, higher CDI-S scores were correlated with known psychiatric history ( $p<0.001$ ), increased hospitalizations ( $p<0.001$ ), and higher scores on BDA ( $p<0.001$ ).

**Conclusions:** Depression screening in adolescents with Type 1 diabetes is useful in identifying those with depression. Higher depression scores were seen in patients with known psychiatric diagnoses, more barriers to adherence, and more hospitalizations. Notably, SI can be present without depressive symptoms and should be specifically addressed in depression screens.

P1-1819

#### COMPARISON OF NATURAL KILLER (NK) CELLS AND NATURAL KILLER T-LIKE CELLS IN SIBLINGS OF PATIENTS WITH TYPE 1 DIABETES MELLITUS TO HEALTHY CHILDREN.

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**Objectives:** Natural killer cells are a type of cytotoxic lymphocytes critical to the innate immune system. CD3(+) CD56(+) natural killer T (NKT)-like cells are a subset of T cells characterized by co-expression of the T-cell receptor and NK receptors, including CD56+, and potent antitumour activity. It has been suggested that they have a role in autoimmune disease, including diabetes mellitus type 1 (DM1). The aim of the study is to compare the number of NK cells and NKT-like cells in healthy siblings of children with DM1 to healthy children from non-diabetic families and to children with DM1.

**Methods:** Peripheral blood mononuclear blood cells were obtained from 78 children with DM1, their siblings - 102, and 30 healthy children. NK cells were characterized by flow cytometry FACSCalibur (Becton Dickinson, USA). The results were shown as a NK percentage and NKT-like percentage of lymphocytes and were analyzed with STATISTICA 10 PL.

**Results:** The number of NK from the siblings was lower (average percentage  $11.93\pm5.62$ ) than that in the control group of healthy children (average percentage  $14.89\pm7.78$ ) ( $p=0.02$ ). There was no significant difference in the number of NK cells between children with DM1 and their siblings ( $p=0.11$ ).

The levels of NKT-like cells were similar in both groups - children with DM1 and their siblings ( $p=0.20$ ). There was no significant difference in the number of NKT-like cells between the siblings (average percentage  $2.19\pm2.24$ ) and the control group of healthy children ( $1.95\pm1.51$ ) ( $p=0.74$ ).

There was a positive correlation between the age of the sibling group ( $p=0.0009$ ) and NKT-like ( $p=0.0000001$ ). There was no difference between girls and boys in the number of NK cells ( $p=0.49$ ) and NKT-like cells ( $p=0.28$ ).

**Conclusions:** The reduced number of NK cells in siblings and DM1 patients in comparison to healthy children has suggested that they could be involved in one or multiple steps at the beginning of the immune-mediated attack that leads to DM1. The results suggest that the dysfunction of NK cells contributes to the autoimmune pathogenesis of type 1 diabetes and is connected with genetic predisposition to DM1. NKT-like cells were probably not involved in the pathogenic process of DM.

P1-1820

#### A RARE COMPLICATION OF SEVERE DIABETIC KETOACIDOSIS: ACUTE RENAL FAILURE

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**Objectives:** Acute renal failure (ARF) is a rare but potentially fatal complication of diabetic ketoacidosis (DKA). Early recognition and aggressive treatment of ARF during DKA may improve the prognosis of these patients. We present a case report of a patient admitted to the hospital with severe DKA.

**Methods:** -

**Results:** A 4 year old female patient admitted to emergency room for polyuria and rapid breathing. She had an acidotic breathing and her Glasgow coma scale was 13. Laboratory tests revealed venous glucose 383 mg/dl, urinary ketones (++++), venous pH:6.7,  $\text{HCO}_3^-$ :4 mmol/L, BE -30 and patient diagnosed with severe DKA. Serum urea was slightly elevated and creatinine was normal at admission (68 mg/dl and 0.8 mg/dl, respectively). Serum creatinine kinase and phosphorus were in normal range. The patient treated with intravenous rehydration and short acting insulin infusion and gradual improvement in both clinic condition and serum glucose levels, as well as blood gas were seen. Serum creatinine levels gradually increased and it was 1.97 mg/dL at 48th hour of the

treatment. Firstly it was thought to be prerenal acute renal failure secondary to dehydration. So, intravenous hydration continued. But serum creatinine levels continued to increase and on day 4 after admission it increased to 2.05 mg/dL. Urine output was in normal range (0.5-1 ml/kg/hour). Fluid restriction was started and furosemide therapy initiated. The patient didn't need renal replacement therapy and renal function start to improve on day 5 and it was completely normal on day 9.

**Conclusions:** In conclusion, ARF is a rare complication of severe DKA. Therefore, careful monitoring of renal function is essential in patients with severe DKA.

P1-1821

#### REDUCTION OF INSULIN REQUIREMENTS ON A GLUTEN-FREE DIET FOR TYPE 1 DIABETES MELLITUS: A CASE REPORT

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**Objectives:** Type 1 diabetes mellitus is the most common metabolic illness of childhood. Despite its increasing rate of incidence, little has proven effective in preventing or limiting the progression of disease once detected. Recently, there has been increasing evidence linking the role of the gut microbiome and pancreatic islet cell function. Moreover, it has been shown that a gluten-free diet maintains a diverse and healthy intestinal microbiome.

**Methods:** We present a case of two siblings, both diagnosed with antibody positive type 1 diabetes at the age of 5. At the age of 6 and 8, they were started on a gluten-free diet and demonstrated improved glycemic control with a reduction of total daily insulin.

**Results:** For one, this required the discontinuation of an insulin pump and reduction of insulin to a 'honey-moon' like state from 0.6 units/kg/day to 0.3 units/kg/day. For the other, insulin was completely discontinued from an insulin dose of 0.1 units/kg/day. At the age of 9 and 11, their insulin requirement continues to be in a 'honey-moon' like range with hemoglobin A1Cs between 5.9-7.7%.

**Conclusions:** This case illustrates the importance of further exploring how the gut microbiome can affect endogenous insulin production and its potential impact on the long-term health of patients with type 1 diabetes.

P1-1822

#### ASSESSMENT OF ENDOTHELIAL FUNCTION IN CHILDREN AND ADOLESCENTS WITH AND WITHOUT DIABETES: IMPACT OF WEIGHT AND GLYCEMIC CONTROL

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*Vivian L Chin, MD; Sheila Perez-Colon, MD, SUNY Downstate Medical Center and Kings County Hospital Center, Brooklyn, NY, United States*

**Objectives:** Endothelial dysfunction (ED) is an early sign of vascular damage. A1C predicts vascular complications in diabetes mellitus (DM). Peripheral arterial tonometry (PAT) is a non-invasive device that measures endothelial function calculated as reactive hyperemic index (RHI). The greater the vasodilation, higher the RHI. We hypothesized that children with poorly controlled DM and obese non-DM (obese) have abnormal RHI.

**Methods:** A cross-sectional study using PAT device was performed on T1DM and T2DM with A1C  $\geq 7.5$  without vascular disease, and in obese children with normal blood pressure (BP) and lipid profile (LP). Fifty eight children were enrolled, age  $13.1 \pm 3.42$  yr. Age, sex, race, BMI, BMI Z-score, pubertal status (PS), systolic (SBP) and diastolic (DBP) BP, latest (past 3 months) and mean A1C (within last year), LP and RHI were obtained. ANOVA, t-test, Mann-Whitney U, multiple linear regression and Spearman correlation were used.

**Results:** Among the 33 T1DM, 8 T2DM and 17 obese children, 85% were African American, 60% female (F) and 79% pubertal. Age, SBP, DBP, LP, PS and RHI were not significantly different among the 3 groups. RHI of DM ( $n=41$ ,  $1.42 \pm 0.48$ ) versus obese ( $n=17$ ,  $1.40 \pm 0.34$ ) was similar ( $p=0.86$ ) regardless of DM type or BMI. Negative correlation was seen between RHI and latest A1C ( $p=0.01$ ), while none with mean A1C. Among DM, for every 1% increase in latest A1C, RHI decreased by 0.1 ( $p: 0.01$ ) adjusted for age, sex, and DM type. RHI of DM children with latest A1C  $\leq 9$  ( $n=18$ ,  $1.70 \pm 0.58$ ) was higher than those with A1C  $\geq 10$  ( $n=23$ ,  $1.21 \pm 0.19$ );  $p=0.002$ . Among all, males (M) had lower RHI ( $1.28 \pm 0.36$ ) compared to F ( $1.51 \pm 0.46$ ),  $p=0.04$ ; however after adjusting for PS, the difference was not seen. Among obese, subgroup analysis showed the difference between genders persisted ( $p<0.01$ ) after controlling for PS, while no difference was found in the DM group.

**Conclusions:** Poorly controlled DM compromises endothelial function. A1C  $\geq 10$  was associated with lower RHI. Negative correlation was seen between A1C and RHI in DM and obesity. Early detection of ED may help detect vascular compromise. Addition of PAT tool as routine care may be useful to identify vascular changes in at risk DM and obese children.

P1-1823

#### FLASH GLUCOSE MONITORING SYSTEM (FREESTYLE): NEW METHOD OF CONTROL IN DIABETIC CHILDREN

*Concepcion Freijo, MD; Laura Bertholt, MD; Cristina Naranjo, MD, Hospital University of Marques de Valdecilla, Santander, Spain*

**Objectives:** The Flash glucose monitoring system (Freestyle) is a new method of control of glucose, that represents a comfortable, simple and very little aggressive way for a

**Objectives:** Osteocalcin (OCN) released from the turnover of bones have been shown to affect the glucose metabolism.

OCN knock-out mice have fewer beta-cells and produce less insulin. Type-1-diabetic patients have lower levels of OCN compared to non-diabetics and an inverse relationship between OCN and HbA1c have been found. This is the first study of the relationship between OCN and the residual insulin production (estimated by stimulated C-peptide) in newly diagnosed type-1-diabetic children and adolescents.

**Methods:** OCN ( $\mu\text{g/L}$ ) were analyzed on samples from 32 (16 boys and 16 girls) newly diagnosed patients (mean age 13.12 (SD=1.92) years). Stimulated C-peptide was evaluated by mixed meal stimulation tests 1, 3, 6 and 12 months after diagnosis. Since OCN Z-scores are currently not available analyses were done in boys and girls separately. T-tests was used to compare means between groups with OCN above the mean (HIGH) and below the mean (LOW).

**Results:** Despite similar ages in boys and girls, girls had significantly lower OCN after 1 (86.96 vs 119.56;  $P=0.044$ ) and 6 months (82.79 vs 130.27;  $P=0.008$ ). Boys in the HIGH OCN group had higher stimulated C-peptide compared to the LOW OCN group, but only significantly after 1 month (1023.29 vs 537.03;  $P=0.008$ ). There were no age-differences between the HIGH and LOW OCN groups among boys. Girls had opposite results with significantly lower stimulated C-peptide in the HIGH OCN group after 3 months (758.58 vs 1174.9;  $P=0.031$ ), but the HIGH OCN group were also significantly younger (11.74 vs 13.70;  $P=0.030$ ).

**Conclusions:** There is a positive association between C-peptide and OCN in boys whereas the association is opposite in girls. Because there are significant age-differences between the HIGH and LOW OCN groups amongst girls, but not boys, the opposite results may partly be explained by differences in age. OCN Z-scores are needed to further elucidate the role of OCN in newly diagnosed type-1-diabetic children and adolescents.

P1-1825

## METABOLIC CONTROL OF PEDIATRIC PATIENTS WITH TYPE 1 DIABETES MELLITUS

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**Objectives:** type 1 Diabetes Mellitus (DM1) is one of the disease that mianly affects the child and adolescent population. proper management prevents and / or delay acute and chronic complications. The objeotive of study is to describe the metabolic control in children and adolescents with DM1 and to analyze the coexisting factors.

**Methods:** this is a quasi-experimental educational intervention study and subjects as its own control. we included 9 patients diagnosed with Type 1 Diabetes Mellitus with a middle age of 14,6 years, treated al the outpatient clinic of Pediatric Endocrinology of the Materno Infantil Hospital of La Paz - Bolivia. The Variables investigated were:

diabetic child. This sensor inserted in the arm allows to measure the interstitial glucose at any time of the day what entails an improvement in the quality of life of the child and his family. Objective: to assess the efficiency of the new method of control of glucose through the measurement of HbA1c at the beginning and successive controls every 3 months until the year and its impact on the weight through the control of the BMI (index mass body).

**Methods:** Method: retrospective study of 29 patients diagnosed with type 1 diabetes who controlled their blood glucose by the Freestyle system, we analysed age, sex, time duration diabetes, insulin administration mode, the BMI at the beginning and the end and HbA1c at the beginning every 3, 6 and 12 months. The analysis statistical was carried out by the SPSS v20 system.

**Results:** Results:29 children, 15 women (52%), mean age 10.45 (3.3-17.5), mean duration diabetes 48.7 months (12-110), 12 patients (41%) were receiving multiple doses of insulin (MDI), 11 (38%) used the insuflon\*catheter for rapid-acting insulin and 6 (21%) were SCII. Mean HbA1c at the beginning  $7.29\pm0.64\%$ , at 3 months  $7\pm0.64\%$ , at 6 months  $6.88\pm0.60\%$ , at 12 months  $7.03\pm0.6\%$ . Using the Wilcoxon test HbA1c at the beginning with each of the following shows a significant difference at 6 months, almost significant at 3 but not 12 months nevertheless the range of values is maintained within normal parameters. (table 1). In relation to BMI mean  $17.9\pm3\text{kg/m}^2$  and 12months later  $18.6\pm3.3\text{kg/m}^2$ , it raised significant ( $p<0$ ) but in normal parameters. In 3 patients (10%) was withdrawn by allergic reaction (1) and to come off continually before the 14 days(2). Nobody had serious hypoglycaemia.

**Conclusions:** Conclusions: The control of blood glucose by the flash glucose monitoring system (Freestyle) seems to be a safe, effective and easy method for the control in pediatric population without impact on weight gain.

	BEGINNING	3 MONTHS	6 MONTHS	12 MONTHS
HbA1c	7.29±0.65	7±0.64	6.88±0.60	7.03±0.61
BEGINNING				
P<0.05		p : 0.057	P:0.022	P:0.28
BMI	17.9±3			18.6±3.3
P<0.05				P:0

Table. 1

P1-1824

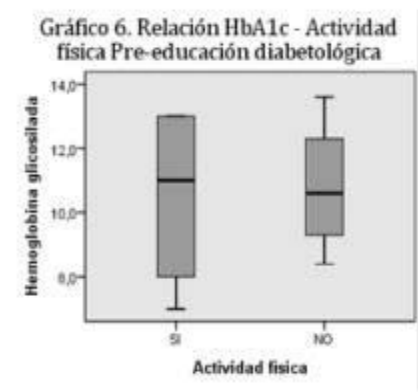
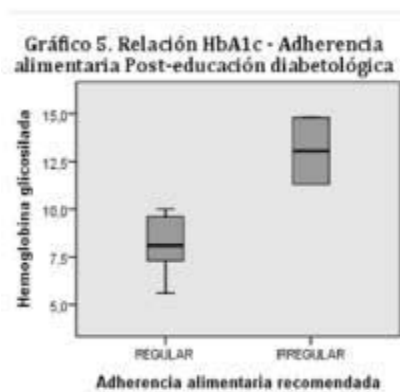
## ASSOCIATION BETWEEN OSTEOCALCIN AND STIMULATED C-PEPTIDE IN 32 NEWLY DIAGNOSED TYPE-1-DIABETIC CHILDREN AND ADOLESCENTS WITHIN THE FIRST YEAR POST DIAGNOSIS.

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gender, age somatometry, metabolic profile and glycosylated hemoglobin before and after the educational program applied from October to December of 2016 and material for intensive glycemic self monitoring was provided. Descriptive and inferential parametric statistics were used.

**Results:** There was a significant decrease in glycosylated hemoglobin values from 10,6% to 9,3% ( $p < 0,017$ ). There were no changes in nutritional status.

**Conclusions:** The application of the diabetes education and intensive glycemic self monitoring program in pediatric patients with DM1 improved metabolic control, a fact reflected in the decrease in glycosylated hemoglobin.



P1-1826

## THE ATTITUDE OF CAREGIVERS OF CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES TOWARD USING CONTINUOUS GLUCOSE MONITORING SYSTEMS

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**Objectives:** Glycemic control in children with type 1 diabetes (T1D) is important to avoid long-term complications of diabetes. Continuous glucose monitoring systems (CGMS) are useful tools to improve glycemic control and prevent hypoglycemia and hyperglycemia. However, its use is limited because of lack of insurance reimbursement. This study aimed to assess caregivers' perception of advantages and disadvantages of real time- CGMS in children and adolescents with T1D.

**Methods:** Forty- five patients with T1D have been used real time –CGMS for at least 6 months were included in the study. Caregivers of these patients completed an online questionnaire.

**Results:** The mean age of study group was 9.8 yr (range 2.8- 18.9 yr), 26 (58%) of them were female. The mean duration of CGMS use was 15 months (range 6- 15 months), type 1 diagnosis was 3.6 yr (range 0.8- 11.9 yr). 10 (22 %) patients were on insulin pump therapy. All of the patients were wearing their CGMS every day. On the basis of the questionnaire responses, the most common reasons for continuing to use CGMS were elimination of hypoglycemia-fear (40%) and improvement of glucose regulation (40%). The percentage of caregivers who reported at least one application to emergency room with hypoglycemia/hyperglycemia before using CGMS was 27%, meanwhile this ratio decreased to 4.4% after CGMS usage ( $p: 0.006$ ). 4 caregivers (9%) decided against using CGMS because of its high cost. 42 (93%) of caregivers reported an improvement of quality of life, meanwhile 34 (76%) and 20 (44%) reported annoyance from the sensor alarm and irritation at insertion site, respectively.

**Conclusions:** The most of the caregivers think that using CGMS reduces their anxiety related to hypoglycemia and improve their children's glucose regulation and quality of life. Lack of insurance coverage is an important obstacle to continue use of CGMS.

P1-1827

## IMMUNOGENETIC CHARACTERISTICS OF TYPE 1 DIABETES IN YOUNG CHILDREN

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**Objectives:** The aim of our study was to determine human leucocyte antigen (HLA) genetic markers and possible immunogenetic heterogeneity in preschool children with type 1 diabetes mellitus (T1DM) in Russian population.

**Methods:** HLA antigens were investigated in 100 children with type 1 diabetes (50 girls and 50 boys, 0.9 to 6.5 years old) and in 150 healthy subjects. The age of T1DM manifestation was 0.25 – 6.4 years (mean  $2.7 \pm 1.1$  yrs); before 1 year – 12 patients, 1-3 years – 64 patients, older than 3 years – 24 children. Standard lymphocytotoxic test with a broad spectrum of typing antisera to 59 HLA class I and class II antigens (A, B, DR, DQ loci) was used.

**Results:** HLA-markers of predisposition to T1DM in early childhood were revealed: DQw3 (82% vs 41.0%,  $RR=6.5$ ,  $p=8.8 \cdot 10^{-11}$ ,  $P_{cor}=3.4 \cdot 10^{-5}$ ), DR4 (64.0% vs 18.0%,  $RR=8.1$ ,  $p=1.3 \cdot 10^{-13}$ ,  $P_{cor}=7.8 \cdot 10^{-12}$ ), DR3 (58.0% vs 23.0%,  $RR=49$ ,  $p=1.1 \cdot 10^{-8}$ ,  $P_{cor}=6.3 \cdot 10^{-7}$ ), B8 (36.0% vs 13.0% in control,  $RR=3.7$ ,  $p=4.4 \cdot 10^{-5}$ ,  $P_{cor}=2.6 \cdot 10^{-8}$ ). The most significant positive correlation with T1DM was shown in heterozygotes DR3/4 (33.0% vs 2.7%,  $RR=18.0$ ,  $p=2.7 \cdot 10^{-11}$ ,  $P_{cor}=1.6 \cdot 10^{-9}$ ). HLA-DR4 antigens occurred more frequently in girls (74%,  $RR=13.0$ ,  $p=9.7 \cdot 10^{-13}$ ), than in boys (54%,  $RR=5.3$ ,  $p=2.2 \cdot 10^{-6}$ ). The occurrence of HLA-DR3 antigens was increased in patients with early diabetic complications and hereditary susceptibility to T1DM. There was a correlation between HLA-antigens and the age of manifestation of T1DM: B12 antigen was the key marker of T1DM in infants before 1 year, if diabetes onsets in age 1-3 years, the most frequent antigens were HLA-DR3/4 and DR3. HLA-DR3/4 correlated with severe course of diabetes and predisposition to allergic diseases. B13 indicated an etiologic relationship of T1DM with rubella, DQ1, DR1, and B35 – with varicella.

**Conclusions:** Our study shown that genetic markers of high risk type 1 diabetes mellitus in preschool children in Russian population are HLA antigens DR3/4, DR3, DR4, DQw3, B8. We found the immunogenetic heterogeneity with age of manifestation of T1DM, course of diabetes and predisposition to allergic diseases.

P1-1828

#### ANALYSIS OF THE EFFECTIVENESS OF DIFFERENT MODELS OF MONITORING OF CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES

Marina Koshmeleva, MD; Yulia Samoilova, Professor, Siberian State Medical University, Tomsk, Russian Federation; Olga Kobyakova, Professor, SSMU, Tomsk, Russian Federation

**Objectives:** Chronic hyperglycemia in diabetes accompanied by dysfunction and failure of various organs. Frequent lack of control over the patient results in chronic diabetes in these patients that leads not only to complication of the disease, but also to a deterioration in the quality of life of patients and reduce the lifespan. Inadequate compensation diabetes may be related, including the availability of qualified medical assistance in remote areas. Evaluation of pharmacoeconomic effectiveness of remote monitoring blood glucose in patients

with diabetes will allow more extensive use of this method in the in the compulsory health insurance when calculating the cost of treatment of patients with diabetes under outpatient and inpatient care.

**Methods:** Patients were followed up for 24 weeks, 6 person visits were held and 12 remote consultations. Patients was equipped with a device CareLinkPersonal opportunities for self-monitoring carried out by insulin and diet doctor through the server and specialized software. Also patients was installed system iPro-2 for a certain time. Patients in the comparison group went to the doctor for a personal to each of the visits. During the study the patients were also given questionnaires. The patients blood sample was produced on HbA1c. Pharmacoeconomic methods included analysis of direct medical costs. Also was Cost-effectiveness and cost-utility analysis. The critical level of significance for verification of statistical hypotheses in the study will be made 0.05.

**Results:** Reducing the level of HbA1c in the subjects by 1-2% in comparison with the original, increase in the percentage of surveyed that have reached. Identification of significant economic efficiency, reducing the financial costs of the state. Achieving compensation diabetes patients, low variability of the glycemic curve. Reducing the daily insulin dose, dose reduction of basal and bolus insulin, reducing podkolok for food. Reduced hypoglycemia and ketoacidosis episodes. Identification of significant economic efficiency of remote monitoring method that will introduce this method of monitoring patients with diabetes in the compulsory health insurance and ensure quality control of glycemia.

**Conclusions:** Remote monitoring of type 1 diabetes is recommended for compulsory medical insurance in Russia

#### POSTER SESSION 1

Thursday, September 14, 2017, 5:45-6:45pm

#### P1 - Type 2 diabetes and other carbohydrate metabolism

#### P1-1900 – P1-1907

P1-1900

#### USE OF FLOWCHARTS AND TEMPLATED CLINIC NOTES TO IMPROVE TYPE 2 DIABETES COMORBIDITY SCREENING

Sam Engle, DO, Medical College of Wisconsin, Milwaukee, WI, United States; David Wyatt, MD, Medical College of Wisconsin, Milwaukee, WI, United States; Wolfgram Peter, MD, Medical College of Wisconsin, Milwaukee, WI, United States

**Objectives:** To assess our Diabetes clinic's baseline adherence to ADA and ISPAD guidelines for obtaining urine creatinine/albumin ratio (UACR) and lipids at diagnosis with type 2 diabetes (T2D), and improve screening adherence with flowcharts and a revised note template.

**Methods:** Data from all patients seen at the Children's Hospital of Wisconsin Diabetes clinic from 7/2014-2/2017 with a new diagnosis of T2D was extracted from the electronic medical record (Epic). Order entry date and



**Objectives:** Our objective was to determine if caregiver-reported consumption of sugar-sweetened beverages (SSBs) may be associated with higher hemoglobin A1c (HbA1c).

**Methods:** We examined 236 children and adolescents with obesity, age 2-20 years, in an outpatient multidisciplinary weight management clinic at an urban children's hospital. At the baseline visit, anthropometrics, HbA1c, and caregiver-reported intake of SSBs during the previous 7 days by their child were assessed. BMI-Z and HbA1c were log-transformed for parametric analyses. Spearman and partial Pearson (adjusting for age, sex, race, and BMI-Z) correlations examined the association between HbA1c and SSB intake.

**Results:** Subjects characteristics: age (mean  $\pm$  SD) 12.1  $\pm$  3.6 years; 58% female; 74% African-American, 17% Caucasian, 6% Hispanic; BMI 36.1  $\pm$  8.6 kg/m<sup>2</sup>; BMI-Z 2.55  $\pm$  0.40. Trends toward positive correlations with A1c were observed for flavored juice ( $p=0.06$ ), non-diet soda ( $p=0.08$ ), and other SSB ( $p=0.06$ ), while the combined score for all SSBs was nominally positively correlated with HbA1c ( $p=0.03$ ,  $\rho=0.14$ ). After adjusting for age, sex, race, and BMI-Z, only the category "other SSB" ( $p=0.03$ ,  $r=0.14$ ) was nominally associated with HbA1c, but this was not significant after correcting for multiple comparisons.

**Conclusions:** In our predominantly African-American, demographically representative cohort of pediatric patients with obesity, we observed only weak trends for association between HbA1c and caregiver-reported SSB intake by their children. Analyses are underway examining child's self-reported SSB intake as well as longitudinal changes in body composition and glucose homeostasis.

P1-1902

## URINE METABOLOMIC PROFILING REVEALS A UNIQUE SIGNATURE FOR TYPE 2 DIABETES IN YOUTH

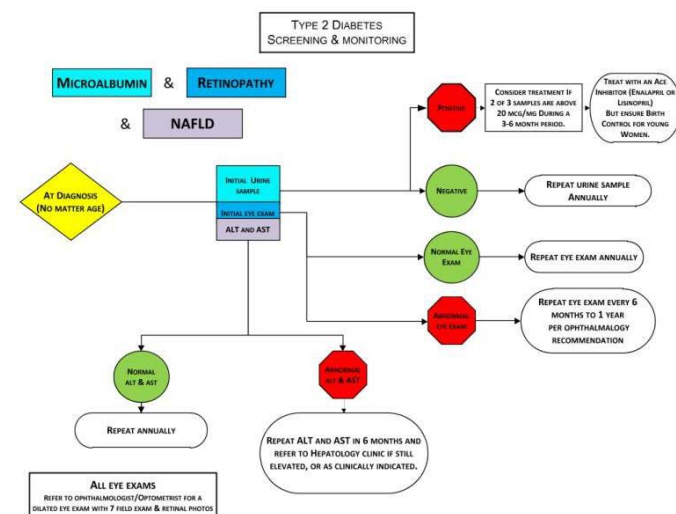
Jennifer Concepcion, MD; Katherine Chen, BS/BA; Rintaro Saito, PhD; Satoshi Miyamoto, PhD; Jon Gangoiti, MS/MA; Loki Natarajan, PhD; Bruce Barshop, MD; Kumar Sharma, MD; Jane Kim, MD, University of California, San Diego, La Jolla, CA, United States

**Objectives:** Type 2 diabetes (T2D) is increasing more rapidly in adolescents than in any other age group. Moreover, pancreatic beta cell failure and complications such as hypertension, nephropathy and retinopathy may appear faster in youth than in adults. Increased circulating branched chain amino acids (BCAAs) are associated with T2D and insulin resistance. However, it is not clear whether increased plasma BCAA concentrations result from increased synthesis, or impaired degradation or excretion. Here, we employed a targeted metabolomics approach to identify urine metabolites associated with T2D in youth, presenting potential urine biomarkers for clinical prediction and further insight into disease pathogenesis.

specimen collection date for urine ACR and lipids were obtained. A provider was considered adherent to the ADA/ISPAD guidelines if labs were resulted in the previous 6 months or ordered within 120 days of diagnosis. Vizio flowcharts and a new clinic note template including ADA/ISPAD guidelines were created and presented to the 15 providers on 7/8/2016 (date of intervention). Each provider was given the flowcharts and the choice of using the new note template. Pre- and post-screening rates were compared using the chi-square test.

**Results:** There were 61 patients included in the analysis, 45 pre-intervention and 16 post. Only 4 of the 16 post-intervention visits used the new note template. From pre-to post-intervention the UACR order entry rates increased from 44% to 81% ( $p = 0.01$ ), while UACR specimen collection rates were unchanged from 88% to 67% ( $p = 0.10$ ). Lipid order entry rates (62% to 75%,  $p=0.36$ ) and lipid panel collection rates (97 to 100%,  $p=0.58$ ) were unchanged. In the 4 post-intervention visits in which the new note template was used 100% met UACR and 75% met lipid guidelines. The one chart with a new templated note missing a lipid order indicated that the lipid panel had been obtained within the past year. Post-intervention visits without use of the templated note had 66% adherence for both UACR and lipid guidelines.

**Conclusions:** The ordering rate of UACR significantly increased following introduction of the flowcharts and new templated clinic note. The new templated note may be more effective in aiding adherence to guidelines compared to the flowcharts, although small sample size limit interpretation. Further monitoring and encouragement of RNs and providers to use the new clinical notes will continue for the next 2 years.



P1-1901

## ASSOCIATION OF SUGAR SWEETENED-BEVERAGE CONSUMPTION AND HEMOGLOBIN A1C IN CHILDREN AND ADOLESCENTS WITH OBESITY

Grace Bazan-Nelson, MD; Shelby A Cole, MS/MA; Raquel T Mack, RN, University of Tennessee Health Science Center, Memphis, TN, United States; Giuliana H Taralli, MD, Faculty of

**Methods:** We measured 145 urine metabolites by LC-MS/MS in 3 cohorts consisting of obese youth with T2D (n=30), obese youth without T2D (n=30), and age- and gender-matched healthy normal-weight control subjects (n=28). We also examined kidney cortex of *db/db* and control *db/m* mice to measure gene expression by Illumina microarray and protein expression by western blot.

**Results:** Following FDR correction, 36 of the 145 measured metabolites were found to differ between the 3 cohorts. These metabolites represented intermediates in three major pathways: BCAA metabolism, fatty acid metabolism and the TCA cycle. In T2D youth, BCAAs were increased in plasma but decreased in urine, suggesting impaired BCAA catabolism. To further investigate BCAA metabolism, we examined kidney tissue from *db/db* mice and found that gene expression of key enzymes related to BCAA catabolism was decreased. Western blot studies confirmed that renal expression of branched-chain ketoacid dehydrogenase was reduced in *db/db* mice compared with controls.

**Conclusions:** Prior studies have reported increased plasma BCAA metabolites in youth and adults with T2D. In our study, the pattern of urine BCAA metabolites may reflect impaired mitochondrial BCAA metabolism in classical insulin target tissues such as adipose, muscle and liver. Moreover, reduced renal expression of BCAA enzymes supports a role for dysregulated BCAA metabolism by the kidney. This dysregulated BCAA metabolism may affect insulin resistance and the development of kidney disease with T2D.

P1-1903

#### THE EFFECT OF MATERNAL DIABETES MELLITUS (DM) ON PLACENTAL VEGF165B, A NOVEL ISOFORM OF VASCULAR ENDOTHELIAL GROWTH FACTOR

Jonathan D. Meyer, MD; Jeanie B. Tryggstad, MD; Shaoning Jiang, PhD; April M. Teague, MS/MA, University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States; Timothy J. Lyons, MD, Queens University, Belfast, Northern Ireland, N/A, United Kingdom; Steven D. Chernausk, MD, University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States

**Objectives:** Diabetes mellitus (DM) affects vascular health, and fetal exposure to maternal DM yields both immediate and long-term effects on offspring. We have shown in preliminary data that vascular endothelial growth factor (VEGF), which is essential in fetoplacental vascular formation, is increased in the cord serum of diabetic pregnancies. Newly discovered anti-angiogenic isoforms of VEGF, such as VEGF<sub>165b</sub>, have not been studied extensively in diabetic pregnancies. We hypothesized that the diabetic milieu leads to a decrease in VEGF<sub>165b</sub> in both cord blood and placenta, thereby altering regulation of normal vasculogenesis in the fetoplacental unit.

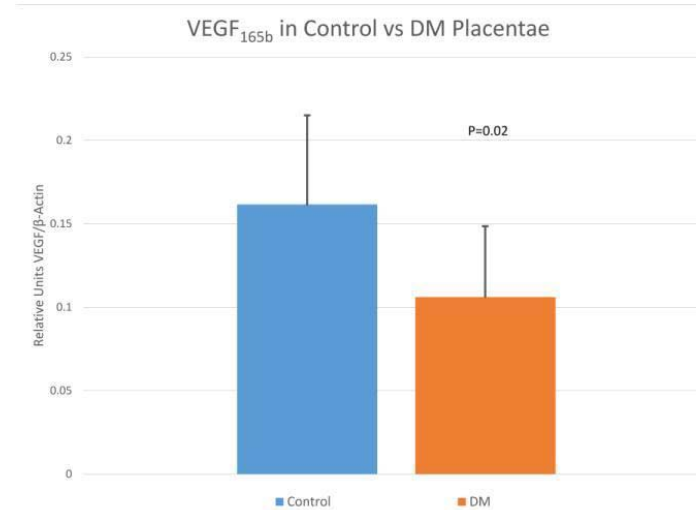
**Methods:** Cord blood and placenta were collected at delivery from healthy term offspring of women with type 2 or gestational DM and normoglycemic controls. Pregnancies were otherwise uncomplicated. VEGF<sub>165b</sub> was measured in

cord blood by ELISA and in placenta by Western blot. Results were analyzed using student T-test, and p<0.05 was considered significant.

VEGF<sub>165b</sub> was not detectable in cord blood with the use of two different assays. VEGF<sub>165b</sub> (normalized to  $\beta$ -Actin), was found to be higher in control placenta compared to DM (p=0.02). VEGF<sub>165b</sub> was not detectable in cord blood with the use of two different assays. VEGF<sub>165b</sub> (normalized to  $\beta$ -Actin), was found to be higher in control placenta compared to DM (p=0.02).

**Results:** VEGF<sub>165b</sub> was not detectable in cord blood with the use of two different assays. VEGF<sub>165b</sub> (normalized to  $\beta$ -Actin), was found to be higher in control placenta compared to DM (p=0.02).

**Conclusions:** *In utero* exposure to DM increases VEGF in cord blood of infants born to mothers with diabetes; however, the ratio of angiogenic to anti-angiogenic factors may be an even more important marker of vascular health. A relative decrease in VEGF<sub>165b</sub> in the fetoplacental unit may be associated with increased pathological vascular formation *in utero*. We suspect that hypoxia and oxidative stress associated with DM, along with excess glucose, work to upregulate IGF-1 and downregulate TGF- $\beta$ , thereby altering the pro to anti-angiogenic ratio of VEGF. Further studies include the need to determine the relative abundance of total VEGF in both DM and normal pregnancies, and to further investigate the underlying cause of these changes.



P1-1904

#### GLP1 AND GLP2 BASAL AND CARBOHYDRATE STIMULATED PROFILES IN SERUM AND ON TISSUE, IN PEDIATRIC CELIAC DISEASE.

Marianna Rachmiel, MD, Assaf Haroffeh Medical Center, Tel Aviv University, Zerifin, Israel; Gilad Ben-Yehuda, MS/MA, Assaf Haroffeh Medical Center, Zerifin, Israel; Haim Shirin, MD, Assaf Haroffeh Medical Center, Zerifin, Israel; Efrat Broide, MD, Assaf Haroffeh Medical Center, Zerifin, Israel

**Objectives:** Abnormalities of glucagon-like peptide-1 (GLP-1) and glucagon-like peptide-2 (GLP-2), were suggested with Celiac Disease (CD), by involvement of L-cells. The aim of study was to explore the difference in ; duodenal expression of GLP1 Receptors and plasma concentrations of GLP-1 and

GLP-2 during a carbohydrate stimuli between patients with naïve celiac disease (CD), 6 months post gluten free diet (GFD), and controls.

**Methods:** Twenty eight pediatric patients undergoing endoscopic gastroscopy agreed to add duodenal samples for GLP1-R and GLP2-R. Patient was included if was diagnosed as normal gastroscopy with negative antibodies or as CD, with positive antibodies. All underwent oral glucose tolerance test (OGTT) for assessment of glucose, C-peptide, GLP1 and GLP2 secretion pattern . CD patients underwent a second OGTT after 6 months GFD.

**Results:** Twelve patients were diagnosed with CD , Marsh 3, 7 males, mean age 9.2±2.5 years. Ten were in control group, 5 males, mean age 12±4 years, (p=0.14). Similar clinical, body composition and glycemic parameters were observed in both groups. Secretion pattern of glucose demonstrated a peak after 15-30 minutes , and C-peptide level after 30-60 minutes, similar in all groups . Similar secretion pattern of GLP1 and GLP2 were detected in all groups, with a peak level after 15 minutes. The expression of GLP1 - R and GLP2 –R in duodenal tissue , as expressed by the mRNA ratio of those receptors to GAPDH , was similar between groups.

**Conclusions:** our study revealed no significant difference in pre as well as post-prandial secretion pattern and gut receptor expression of gut hormones, GLP-1 and GLP-2.

P1-1905

INSULIN RESISTANCE IN PREPUBERTAL CHILDREN

Vera M Zdravkovic, MD, University Children's Hospital, University of Belgrade, Belgrade, Serbia; Jovana Vukovic, MD, University of Belgrade, Belgrade, Serbia; Maja Jesic, MD, University Children's Hospital, University of Belgrade, Belgrade, Serbia; Vladislav Bojic, MD, University Children's Hospital, Belgrade, Serbia; Silvija Sajic, MD, University Children's Hospital, University of Belgrade, Belgrade, Serbia

**Objectives:** Since it is well known that insulin resistance increases at puberty, the objective of our study were:  
- to estimate the insulin resistance in obese children before puberty onset  
- to compare the indices of insulin resistance in prepubertal and pubertal children

**Methods:** The case-control study included 73 obese patients with BMI above the 97 th percentile for age and gender. Children were classified into prepubertal and pubertal group according to Tanner staging criteria. We collected following data: BW and BL, breastfeeding duration, eating patterns and family history of Type 2 diabetes. We performed physical exam (height, weight, BP) and fasting glucose and lipid profile. For assessment of insulin sensitivity and secretion we completed oGTT and calculated following indices: HOMA-IR, QUICKI, WBISI, McAuley i Insulinogenic index (IGI).

**Results:** Our study showed a statistically significant difference in relation to age, gender, weight, height and BMI between groups.

Characteristics PDF

No significant difference was found in relation to birth weight and length, or the length of breastfeeding. Unhealthy eating

was reported in 21.05% prepubertal children and 34.62% of children in puberty. Blood pressure was not different between two study groups. Study revealed significant increase in total cholesterol, LDL and HDL cholesterol, CRP, AST and phosphorus levels in prepubertal children, while triglycerides, ALT, calcium levels and HbA1c remained non significantly different between two groups. Indices of insulin sensitivity and secretion between groups didn't show a statistically significant difference. Insulin resistance was present in almost 80% of the patients according to the HOMA index. However, lower values of HOMA (3.5 vs 4.7), WBISI (2.1 vs 2.2) and higher IGI (2.9 vs 2.2) were found in prepubertal subjects.

**Conclusions:** In our study we have found a high prevalence of insulin resistance and lipid disorders in a group of obese children before puberty onset. This demand's for early intervention to prevent the obesity at earlier stage.

Characteristics	Prepubertal	Pubertal	p
Age (y)	10.1±2.1	13.6±1.3	0.000
Gender (M/F)	26 / 12	10 /25	0.001
Height	153.1±13.6	166.4±7	0.000
Height SDS	2.1±1.5	1.2±1.4	0.006
Weight	73.9±20.2	96.7±18.6	0.000
Weight SDS	3.3±0.9	3.5±0.9	0.353
BMI	31.0±5.5	35.0±7	0.007
BMI SDS	3.2±0.7	3.1±0.6	0.558

P1-1906

IDENTIFICATION OF A NOVEL INSULIN RECEPTOR GENE MUTATION IN PATIENT WITH TYPE A INSULIN RESISTANCE SYNDROME

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**Objectives:** INTRODUCTION: Hyperandrogenism, acanthosis nigricans (AN) and severe insulin resistance in the absence of obesity clinically define Type A IR syndrome. Most cases of this syndrome are due to mutations in the insulin receptor gene (*INSR*) or its signaling pathway.

**Methods:** CASE REPORT: A 14 year-old girl presented with hirsutism, AN and absence of menarche. The physical exam revealed normal height (50th centile), BMI 14.3 kg/m<sup>2</sup> (-1.3 SD), F&G score 32 and clitoral hypertrophy, biochemical hyperandrogenism (Testosterone 128 ng/dL, RV:10-50; Androstenedione: 995 ng/dL, RV: 80-280). OGTT showed fasting glucose level of 73 mg/dL and 136 mg/dL at 120 min, with severe hyperinsulinemia (47.7 and 600 µU/mL, respectively). Pelvic ultrasound showed enlarged, polycystic ovaries

**Results:** Exome analysis was performed using the Illumina TrueSight One assay in a NextSeq500 system. NGS results were analyzed taking into account mutation impact (high or moderate), population frequency (*INSR*: NM\_000208.3 (*INSR*): c.3449T>C (p.Leu1150Pro). Sanger sequencing confirmed the finding in the patient and revealed that her mother was heterozygous for the same variant. According to ACMG guidelines, this variant, which is located in the tyrosine kinase domain, is classified as likely pathogenic. Variant p.Leu1150Pro was not reported in publicly available 1000G, ExAC, EVS and NCBI dbSNP databases and was predicted to be pathogenic by 5 in silico bioinformatics tools. Based upon these findings, the variant p.Leu1150Pro could be responsible for the patient’s phenotype. Therefore, treatment with metformin at 1700 mg/day was initiated.

**Conclusions:** By using a NGS approach, we identified a novel heterozygous mutation in the Insulin Receptor gene in an adolescent with Type A insulin resistant syndrome. It was an objective way of confirming the genetic diagnosis, thus orientating a targeted treatment and taking proactive actions related to the disease clinical course. Moreover, extending genetic diagnosis to other family members might explain the phenotypic variability.

P1-1907

# EVALUATION OF $\beta$ -CELL FUNCTION BY MIXED MEAL TOLERANCE TEST AND ORAL GLUCOSE TOLERANCE TEST IN OBESE CHILDREN AND ADOLESCENTS WITH METABOLIC SYNDROME COMPARED TO ISOLATED OBESITY

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**Objectives:** To evaluate islet  $\beta$ -cell function during the MMTT(liquid mixed-meal tolerance test) and OGTT(oral glucose tolerance test) in obese children and adolescents with clinical diagnosis of MS, cMD(component metabolic disorders), or iOB(isolated obesity) to provide a reference for [clinical interventions](#) and early prevention.

**Methods:** We prospectively designed three groups of participants for study: MS, cMD and iOB, clinically data from obese [children and adolescents](#) (50 iOB, 72 cMD, and 59 MS) between May, 2013, and May, 2015 were obtained. All of the participants underwent MMTT and OGTT, and indices of insulin secretory function and insulin sensitivity were calculated for study.

**Results:** Islet  $\beta$ -cell function relative to AUC CP120 ( $P=.007$ ) and peak CP ( $P=.007$ ) derived from MMTT were significantly higher in the MS group compared with the iOB group both before and after adjusting for BMI. The MS group had higher HOMA- $\beta$ % compared with the cMD and iOB groups after adjusting for BMI ( $P=.036$ ,  $P=.008$ ). However, there was no difference in  $\Delta I_{30}/\Delta G_{30}$  and oDI derived from OGTT among the three groups.

**Conclusions:** Compared with iOB children, there were no signs of defects of early phase insulin secretion in MS and cMD children, indicating that youth with MS and cMD still had a commendable pancreatic  $\beta$ -cell function in response to their severe insulin resistance, offering a window in time for intervention before development of diabetes.

## POSTER SESSION 2

Friday, September 15, 2017, 11:30am-12:30pm

### P2 - Adrenals

#### P2-100 – P2-130

P2-100

#### ADRENARCHE IN SILVER-RUSSELL SYNDROME: PREDICTORS AND CONSEQUENCES

*Gerhard Binder, MD; Roland Schweizer, MD, University Children's Hospital Tübingen, Tübingen, Germany; Gunnar Blumenstock, MD, University of Tübingen, Tübingen, Germany; Nawfel Ferrand, Student, University Children's Hospital Tübingen, Tübingen, Germany*

**Objectives:** Premature adrenarche has been reported to be frequent in Silver-Russell syndrome (SRS), but systematic studies are lacking. Here, we studied the prevalence, predictors and consequences of early adrenarche in SRS based on documented cases with long-term follow-up.

**Methods:** This is a retrospective longitudinal single-center study including 104 SRS patients (56 boys) with a positive Netchine-Harison score who were seen at our center over the past 20 years. Clinical and biochemical characteristics were collected from patient records. Adrenarche was defined by reaching a serum DHEAS level > 500 ng/ml.

**Results:** Boys reached adrenarche at a median age of 9.2 y (range 2.3-13.8) and pubarche (PH2) at a median age of 11.0 y (range 5.4-14.8). Girls reached adrenarche at a median age of 8.1 y (range 5.3-13.2) and PH2 at a median age of 10.5 y (range 6.6-13.2). Premature adrenarche occurred in 16% of the patients. Predictors of age at adrenarche were young age at rhGH start ( $P < 0.05$ ) in both sexes and low birth weight only in boys ( $P = 0.027$ ). Consequences included bone age acceleration in both genders, but early puberty only in boys. Response to rhGH treatment (median dose 50  $\mu$ /kg\*d) and adult height were not compromised by early adrenarche.

**Conclusions:** Early or premature adrenarche is frequent in SRS and seems to be triggered by rhGH treatment. Response to rhGH and adult height were not compromised by early adrenarche.

P2-101

#### ON THE IDENTITY OF THE MAMMALIAN ENDOGENOUS CARDIOTONIC STEROID

*Fred Chasalow, PhD, IOMA LLC, Belmont, CA, United States*

**Objectives:** Identification of the endogenous cardiotonic steroid (ECS)

**Methods:** On the basis of cross reaction with the corresponding specific antibodies, there have been two candidates for the mammalian cardiotonic steroid: digoxin and ouabain. For each candidate, antibodies specific for the corresponding cardiotonic glycoside were used. Investigators have isolated 10  $\mu$ g of their candidate from about 100 liters of plasma, determined serum levels of their candidate (~0.1 ng/mL) and claimed that their candidate is the authentic

endogenous mammalian cardiotonic steroid (ECS). However, both digoxin and ouabain contain glycoside moieties that are not of mammalian origin. Second, no precursors or metabolites have ever been detected in mammals. Third, although the amount of glycoside isolated is consistent with the amount detected by RIA, that amount is less than 20% of the amount known to be functional. Thus, the belief that either ouabain or digoxin is the ECS is a major scientific misunderstanding.

**Results:** Independently, we also used the assay for digoxin to isolate an ECS from mammalian plasma and adrenals. We propose IONOTROPIN is the mammalian ECS. LC-MS fragmentation analysis indicates that Ionotropin is a phosphocholine ester of a steroid with 23 carbons. It is readily detected by LC-MS in serum of humans, cattle, pigs, rats, horses, mice, rabbits, chickens, and turkeys. NMR analysis is consistent with a steroid. In addition, to Ionotropin, there are three other steroid phosphoesters present in serum. Bovine adrenal extracts contain all 4 steroids as both the phosphocholine and phosphoethanolamine esters. The eight compounds outline the biosynthesis pathway from sterols to Ionotropin with known enzymes. The structure of Ionotropin is consistent with a lactone ring fused to the steroid backbone. Spironolactone has a similar lactone ring fused to its steroid backbone and functions as a potassium sparing diuretic.

**Conclusions:** Based on the structural similarities between Ionotropin and spironolactone, we propose that Ionotropin is the long-sought endogenous digoxin-like material (or ECS) and that it functions as a potassium sparing diuretic.

P2-102

#### CLINICAL AND MOLECULAR CHARACTERISTICS OF X-LINKED ADRENAL HYPOPLASIA CONGENITA

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**Objectives:** X-linked adrenal hypoplasia congenita (AHC) is a condition clinically featuring adrenal insufficiency and hypogonadotropic hypogonadism caused by mutations of *NROB1* (*DAX-1*). This study investigated clinical characteristics and molecular defects of *NROB1* in 11 patients with X-linked AHC.

**Methods:** This study included 11 patients with X-linked AHC from 10 independent families. Clinical features and endocrine functions were evaluated by retrospective chart review. All coding exons and exon-intron boundaries of the *NROB1* were



amplified by polymerase chain reaction and directly sequenced.

**Results:** Nine patients from 8 families presented with skin hyperpigmentation, hyponatremia, and hyperkalemia during the neonatal period. Two patients presented with skin hyperpigmentation and adrenal insufficiency at age 4.4 and 6 years, respectively and were classified as late-onset type. Three patients have been treated with testosterone enanthate due to hypogonadotropic hypogonadism. Interestingly, a male with contiguous gene deletion syndrome manifested central precocious puberty at the age of 45 months. Direct sequencing of *NROB1* identified 5 truncating mutations in 5 unrelated patients: c.1156\_1157delCT, c.306\_316del, p.W105\*, p.Q252\*, and p.Q401\*. Complete deletion of *NROB1* was found in 6 patients from 5 pedigrees. Deletions of the *IL1RAPL*, *GK*, *DMD*, and *OTC* genes were identified in one patient, and the others revealed deletions of *IL1RAPL* and *GK*.

**Conclusions:** Clinical phenotypes of X-linked AHC is diverse from neonatal onset adrenal crisis to late onset mild adrenal failure. As the patients can manifest precocious puberty or hypogonadotropic hypogonadism, pubertal status should be monitored. In addition, continuous gene deletion syndrome should be considered in X-linked AHC patients with complete deletion of *NROB1*.

P2-103

#### TOPICAL CORTICOSTEROIDS: SHOULD ONE BE CONCERNED ABOUT ADRENAL SUPPRESSION IN PEDIATRIC PATIENTS?

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**Objectives:** To determine the likelihood of hypothalamic-pituitary-adrenal (HPA) axis suppression following short term cutaneous treatment of dermatologic conditions such as atopic dermatitis and psoriasis with topical corticosteroids in pediatric patients.

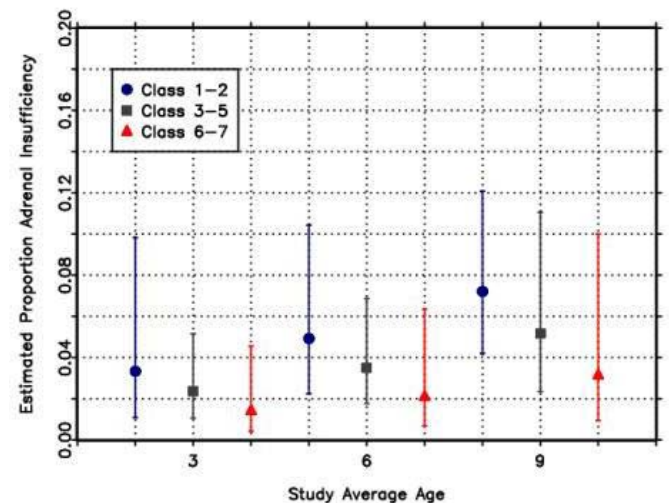
**Methods:** Our systematic review and meta-analysis included published English literature in four electronic databases (EMBASE, MEDLINE, Web of Science and The Cochrane Library) along with the references of captured articles. Eligible studies were clinical trials including HPA axis assessment using ACTH stimulation testing, with serum cortisol levels at baseline and following at least 2 weeks of topical corticosteroid use in children younger than 18 years. The definition of HPA suppression was a post-stimulated level less than or equal to 18 mcg/dL. Topical corticosteroids were ranked in descending level of potency, from Class 7 low potency to Class 1 ultra-high potency using the World Health Organization classification of corticosteroids. Duration and location of use with treated body surface area (BSA) were included in the analysis, if described in the selected studies.

**Results:** Of 88 eligible trials, 13 were selected for meta-analysis with a total of 581 participants. There were 26 observed cases of HPA axis suppression [4.5%, 95% CI (3.5-6.5)]. The incidence of HPA axis suppression with low (class 6-

7), mid (class 3-5) and high (class 1-2) potency topical corticosteroid use was 1.9% [3 of 155 patients, (CI 0.6-5.8%)], 3.3% [8 of 240 patients, (CI 1.7-6.5%)], and 8.1% [15 of 186 patients, (CI 4.9-13%)] respectively.

**Conclusions:** There is a low incidence of HPA axis suppression with use of mid-to-low potency corticosteroids compared to more potent formulations. In pediatric clinical practice, the limited use of mid-to-low potency topical corticosteroids is rarely associated with clinically significant adrenal insufficiency or adrenal crisis. In the absence of signs and symptoms of adrenal insufficiency, there is little need to test the HPA axis of these patients. Testing may be necessary in those requiring higher potency and/or prolonged use of corticosteroids.

**Figure 1:** Estimated proportion of adrenal insufficiency as a function of study average age (years) and corticosteroid potency class (1-7).



P2-104

#### ANDROGEN PRODUCTION IN PEDIATRIC ADRENOCORTICAL TUMORS OCCURS APPARENTLY AT RANDOM VIA THE CLASSIC AND/OR THE ALTERNATIVE BACKDOOR PATHWAY

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**Objectives:** Children with adrenocortical tumors (ACT) often present with virilization due to high tumoral androgen production, with dihydrotestosterone (DHT) as most potent androgen. Recent work revealed two pathways for DHT biosynthesis, the classic and the backdoor pathway. In the backdoor pathway, DHT is produced by largely specific enzymes. Usage of alternate routes for DHT production has been reported in castrate-resistant prostate cancer (CRPC), CAH and PCOS. In this study, we assessed the role of the backdoor pathway in virilizing pediatric ACTs.

**Methods:** Seven children, aged 8 months to 17 years, suffering from androgen producing tumors were investigated. Clinical and biochemical characteristics were assessed and



tumors were characterized by specific immunohistochemical (IHC) studies for steroid enzymes involved in the classic and backdoor pathways.

**Results:** All cases (4 adrenocortical carcinoma (ACCs), 3 adenoma) produced large amounts of androgens. IHC studies showed variable expression of steroid enzymes without being discriminative between ACCs and adenomas.

**Conclusions:** Virilization due to excess DHT production via the backdoor pathway may occur in pediatric ACTs, but ACTs may also produce excess androgens through the classic pathway. We found no pattern for ACTs in our case series. This suggests that enhanced androgen production in pediatric ACTs is the result of deregulated steroidogenesis in benign and malign tumors and may occur through multiple steroid pathways. Thus future treatments of ACTs targeting androgen overproduction should consider these novel steroid production pathways as currently considered in CRPC.

P2-105

#### **BONE MINERAL DENSITY AND BODY COMPOSITION IN CHILDREN WITH CONGENITAL ADRENAL HYPERPLASIA**

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**Objectives:** To compare bone mineral density (BMD) and visceral adipose tissue in children with congenital adrenal hyperplasia (CAH) to healthy controls.

**Methods:** 42 CAH cases (mean age 12.3 years; 40% males) were matched to 101 healthy controls (43% males) on age, sex, and BMI Z-scores. All participants underwent anthropometric measurements and a dual energy absorptiometry (DXA) scan. Total body BMD (TBMD) was adjusted for height-for-age Z-score (TBMD<sub>HAZ</sub>). Hydrocortisone doses (mg/m<sup>2</sup>/day) were averaged over the past year, and bone age Z-scores were used as a surrogate marker of androgen exposure.

**Results:** CAH cases had lower TBMD and TBMD<sub>HAZ</sub> Z-scores than controls (0.81 vs. 1.27, p=0.003 for TBMD; -0.51 vs. -0.01, p=0.001 for TBMD<sub>HAZ</sub>). TBMD and TBMD<sub>HAZ</sub> Z-scores in CAH cases were not associated with hydrocortisone dose; however, they were positively correlated with bone age Z-scores (r=0.63, p<0.0001 for TBMD; r=0.51, p=0.001 for TBMD<sub>HAZ</sub>). Although the percentage of total tissue fat was similar in CAH cases and controls (30.6% vs. 32.4%, p=0.052), visceral adipose tissue was lower in CAH cases vs. controls (171 vs. 273 cm<sup>2</sup>, p=0.009). This difference remained after adjusting for sex, BMI Z-scores, hydrocortisone dose, and bone age Z-scores.

**Conclusions:** CAH cases had lower TBMD and TBMD<sub>HAZ</sub> Z-scores compared to controls. The lack of correlation with hydrocortisone dose may be due to inter-individual variability in glucocorticoid sensitivity and cortisol pharmacokinetics.

Lower visceral adipose tissue in CAH children may reflect the positive effect of androgen exposure on visceral adipose tissue and a more complex interplay of androgens and cortisol fluctuations on bone and fat metabolism in CAH.

P2-106

#### **PEAK CORTISOL LEVELS DURING LOW-DOSE ACTH STIMULATION TESTING: IS A SINGLE SAMPLE SUFFICIENT?**

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**Objectives:** Debate exists about the optimal protocol to use for a low-dose ACTH stimulation test. While it has been suggested that a single 20 or 30 minute stimulated cortisol value is sufficient, this has the potential to result in a misdiagnosis of adrenal insufficiency (AI) and unnecessary glucocorticoid replacement. Our objective was to determine when cortisol levels reach the threshold for a normal response during low-dose ACTH stimulation testing in children with an intact hypothalamic-pituitary-adrenal (HPA) axis.

**Methods:** A retrospective review of children who underwent ACTH stimulation testing from 2013-2016 was conducted. Variables analyzed included anthropometric data, reason for the study, dose of Cosyntropin, timing and results of cortisol measurements.

**Results:** Sixty-two patients (48% female) who had a low-dose (1 mcg or 10 mcg Cosyntropin) ACTH stimulation test performed were identified. Mean age at testing was 3.1 ± 5.2 years (age range newborn – 16.3 years old). In addition to Endocrinology, primary services of patients referred for testing included Neonatology (42%), Critical Care (11%), Gastroenterology (8%) and others. Collection intervals at baseline, 20, 40 and 60 minutes were used in 33 tests. Of these, a passing cortisol value of ≥ 18 mcg/dL was obtained in 18 (55%) patients. The earliest time at which this threshold was reached was 20 minutes in 11 (61%) patients and 40 minutes in 7 (39%) patients. Collection intervals at baseline, 30 and 60 minutes were used in 29 tests of which 21 (72%) revealed a normal response. Among these, a cortisol value of ≥ 18 mcg/dL was obtained at 30 minutes in 19 (90%) patients and at 60 minutes in 2 (10%) patients.

**Conclusions:** Among our patients undergoing low-dose ACTH stimulation testing, nine patients (23%) with an intact HPA axis failed to reach a normal peak cortisol by 30 minutes. If a single sample testing algorithm had been used, these children would have been started on glucocorticoids, needlessly incurring the risks of iatrogenic adrenal suppression. Our data suggest that inclusion of serial cortisol measurements during low-dose ACTH stimulation testing is necessary in order to avoid misclassifying normal children as being adrenally insufficient.

# ANDROGEN EXCESS IN YOUNG CHILDREN WITH CLASSIC CONGENITAL ADRENAL HYPERPLASIA TREATED WITH HYDROCORTISONE IS DUE TO ELEVATED ADRENAL-DERIVED 11-OXYGENATED ANDROGENS

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**Objectives:** Adrenal androgen excess is the hallmark of classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. Recently, 11-oxygenated C19 steroids, a new class of highly active androgens, have been described in patients with CAH.

**Methods:** We retrospectively analysed 190 daily urinary steroid profiles of glucocorticoid-, 17 $\alpha$ -hydroxyprogesterone (17OHP)-, and androgen metabolites determined by gas chromatography-mass spectrometry of 99 children aged 3.0 to 10.9 years with classic CAH on hydrocortisone and fludrocortisone treatment. Daily urinary steroid metabolite excretion rates were transformed into z-scores using references of age- and sex-matched healthy children. Androgen metabolite z-scores were separately calculated for: androsterone (AN), the urinary metabolite of androstenedione, testosterone and 5 $\alpha$ -dihydrotestosterone; urinary metabolites of dehydroepiandrosterone (DHEA); and 11 $\beta$ -hydroxyandrosterone (11OHAN), the urinary metabolite of adrenal-derived 11-oxygenated androgens.

**Results:** Z-scores of 11OHAN (median 1.79 z), cortisol metabolites (median 4.46 z) and 17OHP metabolites (median 5.05 z) were elevated in treated children with CAH, whereas z-scores of AN (median -0.85 z) and DHEA metabolites (-0.61 z) were suppressed. 11OHAN z-scores were significantly higher than AN z-scores in boys aged 3-10 years and in girls aged 5-10 years.

**Conclusions:** Androgen excess in treated children with classic CAH is solely due to elevated adrenal-derived 11-oxygenated androgens. 11-Oxygenated androgens represent better biomarkers of adrenal androgen status and treatment response than conventional androgens.

P2-108

# STUDY OF GROWTH PARAMETERS AND FINAL HEIGHT IN INDIAN CHILDREN WITH CONGENITAL ADRENAL HYPERPLASIA

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**Objectives:** To study growth parameters and final height in children with congenital adrenal hyperplasia (CAH).

**Methods:** Retrospective analysis of 30 children (mean age 3.4 $\pm$ 2.6 years, 16 girls) with classic CAH (11 Salt wasters, 19 simple virilisers) followed for a mean duration of 9.9 $\pm$ 2.4 years (from December 2002 to December 2016) was performed. Height Z scores, target height Z scores, height velocities and laboratory parameters were analysed. Of all patients, 18 (10 girls, 8 boys) reached final height (at mean age of 14.2 $\pm$ 1.6 years).

**Results:** Patients were treated with hydrocortisone at a mean dose of 15.7 $\pm$ 3.3 mg/m<sup>2</sup>/day; fludrocortisone was also prescribed to 18 patients (mean dose in children <5 years of age was 111.1 $\pm$ 18.1 mcg/m<sup>2</sup>/day and >5 years was 52.1 $\pm$ 9.6 mcg/m<sup>2</sup>/day). Mean serum concentrations of 17-hydroxy progesterone in boys and girls were 10.8 $\pm$ 6.7 ng/ml and 11.3 $\pm$ 9.3 ng/ml respectively. Mean testosterone concentration in boys was 29.3 $\pm$ 36.6 ng/dl and in girls was 15.7 $\pm$ 18.6 ng/dl. 15 children (7 boys) entered central precocious puberty at mean age of 7.6 $\pm$ 1.8 years and were treated with gonadotropin-releasing hormone analogue for 3.5 years. Average height velocity before pubertal onset was 6.8 cm/year and 6.6 cm/year in boys and girls respectively, while, after pubertal onset (breast stage 2 in girls and testicular volume 4 ml in boys), height velocity was 4.7 cm/year (boys) and 4.6 cm/year in girls who entered precocious puberty and for the rest it was 3.8 cm/year in boys and 4.8 cm/year in girls. Mean final height achieved was 158.0 $\pm$ 8.5 cm in boys (mean target height was 165.5 $\pm$ 3.8 cm) and 149.9 $\pm$ 6.7 cm (target height 154.7 $\pm$ 6.4 cm) in girls. 83.3% children (87.5% boys and 80% girls) remained shorter than their target height. Of the remaining 12 children (6 girls) who were yet to attain their final height, height SDS scores were 0.42 $\pm$ 1.03 (boys) and -0.24 $\pm$ 0.90 (girls) with target height SDS scores of -0.95 $\pm$ 0.29 (boys) and -0.49 $\pm$ 0.75 (girls).

**Conclusions:** Hyperandrogenemia, precocious puberty resulted in reduced pubertal spurt and final height in children with CAH. Our study highlights the importance of close follow up of growth in children with CAH.

P2-109

# CLINICAL OUTCOME AFTER GENITOPLASTY OF GIRLS WITH CONGENITAL ADRENAL HYPERPLASIA IN A DEVELOPING COUNTRY

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**Objectives:** To report the clinical, laboratory, radiologic and endoscopic findings and evaluate early surgical outcomes of congenital adrenal hyperplasia (CAH) in a developing country.

**Methods:** All cases of CAH (32) who attended Ped. Endocrine Clinic in Alexandria University Children's Hospital during 2014 were subjected to virilization Prader staging. Serum 17-Hydroxyprogesterone (17-OHP), cortisol and testosterone were done. They all had ultrasonography to assess internal genitalia, adrenals and the urinary tract and cysto, vagino and urethroscopies as indicated. Feminizing genitoplasty was performed for 20 patients. Timing of the operation (early

before the age of 2 years or late  $\geq 2$  years) was recorded. Overall cosmetic results were assessed 6 months later.

**Results:** All patients had 46 XX Karyotype. 20 patients had consanguineous parents. All patients had clitoromegaly; 10 patients were classified as Prader 1, 6 as Prader 2, 6 as Prader 3, 5 as Prader 4 while 5 patients were severely virilized (Prader 5). Their mean serum 17-OHP, cortisol and testosterone levels were  $47.53 \pm 48.57$  ng/ml,  $9.64 \pm 5.82$   $\mu$ g/dl and  $6.99 \pm 24.11$  ng/ml respectively. Sex re-assignment was indicated in 6 patients who were wrongly named as males, 4 of them officially changed their name and sex, however, parents of 2 patients refused to do feminizing genitoplasty or to change the name of their babies due to cultural and social issues. 16 patients had early surgical intervention while 4 patients had late intervention because their parents were concerned of revealing their sexual ambiguity. Cosmetic results were reported as good in 17 (85%), satisfactory in 2, and poor in 1 patient. There was a positive correlation between Prader staging and the overall cosmetic results ( $r=0.428$ ). 4 patients required further surgery. Two patients died, one of adrenal crisis before surgery and the other due to aspiration pneumonia.

**Conclusions:** Better overall cosmetic results are observed in patients who had early feminizing genitoplasty (before the age of 2 years). More virilized females with higher Prader staging, had poorer cosmetic results after genitoplasty. Cultural and social issues in our region still influence proper sex assignment and might delay appropriate management plans.

P2-110

#### CUSHING SYNDROME IN SUDANESE CHILDREN

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**Background:** Endogenous Cushing syndrome is a rare disease especially in children. Pediatric cases from Africa are scanty & no pediatric cases were reported from Sudan.

**Objectives:** Our objectives are to review cases of Cushing syndrome in our unit since it was started in January 2006, and to highlight on our difficulties in diagnosis and management.

**Methods:** Case series from two tertiary centers in Khartoum, Sudan where medical records of all cases diagnosed as Cushing syndrome between 2006 to 2016, were reviewed. Data including age, sex, clinical presentation, diagnostic tests and treatment as well as outcome were extracted. All investigation including endocrine tests, imaging and surgery were done locally. Barriers faced were identified and addressed.

**Results:** During this period, 13 cases were diagnosed as having Cushing Syndrome. Five (38.5%) had Cushing disease, one of whom had cyclical Cushing syndrome, two were micro-adenoma and in two, MRI was negative. Three of them had operation locally, one abroad and one passed away before surgery.

Eight (61.5%) had primary adrenal pathology. Five had carcinoma, one macro-nodular disease, one adrenal adenoma and one had McCune Albright syndrome. All were operated locally or had chemotherapy. The prognosis was poor for carcinoma cases as three passed away and two lost their follow up.

Investigation, though available (except for petrosal sinus sampling IPSS), were expensive and had to be raised to cover.

#### Conclusions:

- Facilities to manage Cushing syndrome are available but expensive particularly brain surgery.
- Adrenal carcinoma is relatively common in Sudan but cases present late with poor prognosis.
- In developing countries, algorithm to diagnose Cushing syndrome has been tailored according to local facilities.

P2-111

#### CYP17A1 INHIBITOR ABIRATERONE, AN ANTI PROSTATE CANCER DRUG, ALSO INHIBITS THE 21 HYDROXYLASE ACTIVITY OF CYP21A2

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**Objectives:** Abiraterone was developed to inhibit CYP17A1 activities. Currently it is being used for the treatment of castration resistant prostate cancer. Serum concentrations of abiraterone in recommended doses range from 0.1 to 1.3  $\mu$ M in patients. Some recent studies from different groups have indicated the negative effect of abiraterone on 21-hydroxylase activity of CYP21A2 at the higher end of serum concentration (1 $\mu$ M).

It is not known at what concentration the abiraterone starts to inhibit 21-hydroxylase activity and what is its mechanism of inhibition. This study tried to complete this missing data and provided detailed information about inhibition of CYP21A2 activity by abiraterone.

**Methods:** Effect of abiraterone on 21-hydroxylase was tested in an adrenal carcinoma cell line (NCI-H295R) as well as recombinant purified CYP21A2. Cells were treated with abiraterone at different physiologic concentration from 0.001 to 1.0  $\mu$ M for 24 hours. The 21-hydroxylase activity was assessed by conversion of labelled [ $^3$ H] 17-hydroxyprogesterone to 11-deoxycortisol by thin layer chromatography (TLC). Whole steroid profile changes were determined by Gas Chromatography Mass Spectrometry. Binding of abiraterone to purified CYP21A2 protein was measured spectroscopically. A computational analysis of abiraterone binding to CYP21A2 protein structure was used to understand the structural basis of abiraterone mediated inhibition.

**Results:** We observed significantly decreased 21-hydroxylase activity in cells treated with abiraterone at concentrations

from 0.1  $\mu\text{M}$  to 1  $\mu\text{M}$ . Similar inhibition of CYP21A2 activity was observed in experiments using recombinant purified proteins. Abiraterone binds to CYP21A2 with an estimated  $K_d$  of 6.3  $\mu\text{M}$ . Treatment with abiraterone seems to affect CYP21A2 mediated steroidogenic pathways at concentrations in clinical use. Computational docking and molecular dynamics simulations showed binding of abiraterone to CYP21A2 structure and detailed kinetic analysis provided mechanisms of inhibition.

**Conclusions:** The inhibition of CYP17A1 with combination of significantly decreased 21-hydroxylase activity could be a source of very severe complications such as adrenal insufficiency and may require caution for possible adrenal crisis in emergency situation.

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#### HEIGHT, OBESITY AND PUBERTAL OUTCOME IN CHILDREN WITH CONGENITAL ADRENAL HYPERPLASIA 21-HYDROXYLASE DEFICIENCY

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**Objectives:** Growth and pubertal disorders are seen in children with Congenital Adrenal Hyperplasia 21-Hydroxylase Deficiency (CAH21OHD). Age at onset, genetic study and glucocorticoid (GC) dose have been implicated in various studies.

We aimed to study height, obesity and pubertal outcome of children with CAH21OHD with regular follow-up for  $\geq 5$  years and correlate factors affecting the same.

**Methods:** Clinical, anthropometry, genotype, hormonal and biochemical profile were evaluated at presentation. On follow-up, growth, metabolic control (8am 17OH-Progesterone), bone age and replacement doses of GC and mineralocorticoid were studied. Growth parameters expressed as SDS. Obesity, BMISDS  $\geq 2$  and short stature, HtSDS  $\leq -2$  were correlated with variables using appropriate statistical tools.

**Results:** Of 119 children (50M,69F;79 Salt Wasters(SW),40 Simple Virilizers(SV)) diagnosed over 24 years, growth parameters were studied in 43 children (16M,27F;32SW,11SV;36 mutation proven) with regular follow-up  $\geq 5$  years. Mean duration of follow-up was  $11 \pm 4.14$  years. Of 36 cases, 6(16.7%;6F) had mild, 12(33.3%;5F) had moderate and 18(50%;11F) had severe genotype of CYP21A2 gene. At last follow-up, HtSDS was  $\leq -2$  in 27.9%(N=12/43;8F;9SW). Normal age at onset of puberty noted in 64%(N=16/25;5M,11F).

Age at onset of puberty ( $p=0.035$ ), higher GC dose at presentation ( $>40\text{mg}/\text{m}^2/\text{day}$ ) ( $p=0.034$ ) and at 3 years of age ( $p=0.047$ ) and use of Hydrocortisone and/or Prednisolone ( $p=0.002$ ) had a negative correlation with HtSDS. 6(13.95%;5F;6SW) had achieved adult height (AH) SDS of  $-2.36 \pm 1.25$  and AH SDS-TH SDS (Target height) was  $-0.11 \pm 1.23$ .

BMISDS  $\geq 2$  found in 32.6%(N=14/43;12F;8SW), correlated positively with 17OHP values ( $p=0.013$ ). Girls were heavier than boys ( $p=0.006$ ). Adiposity rebound occurred at 4 years for both genders.

At the time of analysis, HtSDS and BMISDS showed a distinct shift to the left and the right of mean of the reference population respectively.

**Conclusions:** In the present series, there was a higher incidence of obesity (32.6%) and short stature was noted in 27.9%. These parameters were not affected by genotype. Aggressive lifestyle management, dietary control, optimizing dose of therapy and regular monitoring should be an integral part of long term management of patients with CAH21OHD.

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#### ADULT HEIGHT IN PATIENTS WITH NON-CLASSICAL CONGENITAL ADRENAL HYPERPLASIA DUE TO 21-HYDROXYLASE DEFICIENCY DIAGNOSED IN THE PEDIATRIC AGE

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**Objectives:** Data on final height (FH) and pubertal growth, including the effect of corticosteroid treatment and genotype, in non-classical congenital adrenal hyperplasia (NCCAH) due to 21-hydroxylase deficiency are sparse. To evaluate FH and the growth spurt in patients with NCCAH diagnosed during childhood and the relationship between FH and treatment or CYP21A2 mutations.

**Methods:** Clinical records were reviewed and data logged in a REDCap platform. Height at diagnosis, puberty and FH, expressed as SDS, and corrected height (final height SDS-midparental height SDS) were analyzed, as well as mean corticosteroid dose in treated patients and genotype.

**Results:** Patients (95) who had reached FH (71 females, 24 males) were included; age at diagnosis  $8.3 \pm 3.3$  years (y) in girls,  $9.2 \pm 4.4$  y in boys; 77.2% patients were diagnosed before puberty onset (77.8% girls, 22.2% boys); 79 (60 girls, 19 boys) were treated with hydrocortisone (HC), mean dose  $9.8 \text{ mg}/\text{m}^2$ , mean age at treatment onset: 8.3 y. Bone age SDS at diagnosis was higher than chronological age in treated girls and boys than in non-treated (2.4 DE vs 1.2;  $P 0.0004$ ). Bone

age at diagnosis in patients with mild/mild mutations was +1.9 DE and +2.5 DE in mild/severe ( $P$  0.056). Mean age at pubertal onset was 9.7 y in girls and 11.0 y in boys. There was no significant change in dose of HC at puberty (9.8 vs 10.5). Height SDS at last visit was lower than at diagnosis: -0.3 vs 1.0 in girls ( $P$ <0.001), -1.0 vs 1.0 in boys ( $P$ <0.001). Mean pubertal growth spurt was 18.0 cm and 21.9 cm, respectively. Corrected FH SDS did not differ between patients diagnosed before (-0.1) or during puberty (-0.4). (Table). Age at menarche was 12.0 y and 12.7 y in mothers ( $P$ <0.01). Treatment did not affect corrected FH (treated -0.1 vs untreated -0.5), with no association between FH SDS and age at treatment onset or between FH SDS and HC dose. No significant difference was observed between corrected FH SDS and genotype in treated children (mild/mild -0.2 or mild/severe +0.2;  $P$ =0.09)

**Conclusions:** FH in NCCAH patients diagnosed in childhood is inferior to the general population but within their genetic potential. No relationship between HC treatment or *CYP21A2* mutations and corrected FH was found in treated patients.

	Treated			Untreated		
	Girls	Boys	Total	Girls	Boys	Total
Age at diagnosis (years)	7.4 (6.1-8.7)	9.1 (7.3-11.0)	7.7 (6.4-9.2)	13.7 (10.1-15.8)	9.8 (6.2-14.0)	12.6 (9.8-15.1)
Bone Age at diagnosis (SDS)	2.4 (1.3-3.5)	2.5 (1.7-3.3)	2.4 (1.5-3.3)	1 (0.7-1.4)	1.8 (0.9-2.7)	1.2 (0.9-1.7)
Height at diagnosis (SDS)	1.2 (0.3-2)	1.5 (0.7-1.9)	1.2 (0.4-2)	0 (0.3-0.6)	-1 (1.2-0.3)	-0.3 (0.8-0.4)
Predicted final height at diagnosis (SDS)	1 (1.8-0.3)	0.1 (1.4-0.7)	-0.5 (1.7-0.1)	-1.9 (2-0.5)	1 (2.2-2.8)	-1.5 (1.2-0.5)
Mid parental height (SDS)	-0.5 (1.1-0.5)	-0.4 (1.8-0.7)	-0.4 (1.1-0.5)	0 (0.4-0.4)	-1 (1.6-0.7)	-0.4 (1.4-0.2)
Age at pubertal onset (years)	9.5 (8.9-10.4)	10.9 (10.3-11.7)	10 (9-11)	10.3 (9.6-11)	11.3 (10.6-12)	10.8 (10-11.5)
Predicted final height at puberty onset (SDS)	-0.9 (1.7-0.5)	0.4 (0.7-0.6)	-0.6 (1.5-0.5)	-1.6 (2-0.7)	0.7 (0.8-2.6)	-0.8 (1.4-0.7)
Final Height (cm)	158 (153.6-163.3)	169 (166.3-171.9)	163.2 (155.5-167.5)	157.6 (156.5-160.5)	163 (161.9-166.3)	160 (157.2-162.6)
Final Height (SDS)	-0.4 (1.1-0.2)	-1.1 (1.5-0.1)	-0.4 (1.1-0.2)	-0.5 (0.6-0.1)	-2 (1.2-2-1.2)	-0.5 (1.3-0.2)
Corrected Final Height (SDS)	0.3 (0.4-0.5)	-0.3 (1.1-0.2)	0 (0.5-0.5)	-0.4 (0.1-0.2)	-1 (1.5-0.1)	-0.5 (1.3-0.2)
Final Height (SDS)- Predicted final height at diagnosis (SDS)	0.9 (0.1-1.6)	-0.8 (1.5-0.2)	0.4 (0.5-1.4)	0.6 (0.5-1.4)	-3.3 (1.6-0.1)	0.5 (0.1-0.8)
Growth spurt (cm)	18.6 (14-21.3)	21.2 (17.9-25.9)	20 (14.3-22.9)	18.8 (16-23.9)	16.2 (15.9-26.3)	16.2 (15.9-26.3)
Genotype (n) (Mild-Mild/Mild-Severe)	13 / 22	9 / 7	40 / 29	9 / 2	2 / 3	11 / 5

All quantitative data are expressed as median and [IQR]

P2-114

## RECIPROCAL REGULATION OF 11 $\beta$ -HSDS MAY PREDICT STEROID SENSITIVITY IN CHILDHOOD NEPHROTIC SYNDROME

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**Objectives:** Synthetic glucocorticoids (GCs) are used as the first-line treatment for childhood idiopathic nephrotic syndrome (NS). However around 60% of steroid-responsive patients experience frequent relapses with some becoming steroid resistance. The mechanisms of steroid resistance remain unclear and there are currently no reliable biomarkers to identify steroid resistance. We have previously shown that both the type 1 and type 2 isozymes of the pre-receptor GC metabolizing enzyme, 11 $\beta$ -hydroxysteroid dehydrogenase (11 $\beta$ -HSD1 and 11 $\beta$ -HSD2, respectively) are associated with steroid sensitivity in childhood acute lymphoblastic leukemia. Therefore, we hypothesized that 11 $\beta$ -HSDs in PBMCs could be associated with steroid responsiveness in childhood NS.

**Methods:** We studied eight nephrotic syndrome children. Clinical GC-sensitivity/resistance was determined by the initial response to prednisolone treatment at 2 weeks (4 sensitive and 4 resistant patients). Blood sampling was carried out before and after prednisolone treatment (2 and 4

weeks) with informed consent. Peripheral blood mononuclear cells (PBMC) were isolated by density gradient centrifugation. Cells were cultured for 24h in the presence or absence of 10<sup>-6</sup> M dexamethasone. RNA (1  $\mu$ g) was extracted and reverse transcribed. 11 $\beta$ -HSD1, 11 $\beta$ -HSD2 and GR mRNA levels were quantified by real-time PCR. mRNA levels were calculated, relative to levels in vehicle-treated cells.

**Results:** 11 $\beta$ -HSD1 mRNA levels following dexamethasone tended to be higher in GC-sensitive than in GC-resistant NS. In contrast, 11 $\beta$ -HSD2 mRNA levels were significantly increased by dexamethasone treatment of PBMC collected from GC-resistant NS patients both prior to, and following prednisolone therapy, whereas 11 $\beta$ -HSD2 mRNA levels were unchanged in GC-sensitive NS patients. GR mRNA were unaffected by *in vitro* treatment of PBMC with dexamethasone.

**Conclusions:** The different responses of 11 $\beta$ -HSD1 and 11 $\beta$ -HSD2 mRNAs following *in vitro* dexamethasone revealed a qualitative difference between GC-sensitive and resistant NS. Reciprocal regulation of 11 $\beta$ -HSD types 1 and 2 could potentially provide a marker to identify patients in which aggressive therapy is required.

P2-115

## X-LINKED ADRENOLEUKODYSTROPHY – A GENERAL PICTURE OF THE PATIENTS OF INSTITUTO DA CRIANÇA DO HCFMUSP

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**Objectives:** To describe the experience with x-linked ADL patients in the Pediatric Endocrinology unit of Hospital das Clínicas da Faculdade de Medicina da USP.

**Methods:** Retrospective review of medical records of 19 patients with x-linked ADL followed in our Pediatric Endocrinology unit.

**Results:** Mean age at diagnosis was 8,15  $\pm$  3,4 (2-17) years. All 19 patients had high levels of VLCFA. At diagnosis, 7 patients (36%) had Loes Score higher than 8 in CNS MRI and significant neurologic impairment, which did not fulfill criteria for bone marrow transplantation, and 2 patients underwent this procedure. Adrenal insufficiency started at 8,3  $\pm$  3,6 (3-18) years. 14 patients (73%) have mineralocorticoid deficiency. Most patients were sent to us by the Pediatric Neurology unit

with alterations of serum cortisol (low) and ACTH (high), some of them symptomatic.

**Conclusions:** X-Linked Adrenoleukodystrophy happens exclusively in male population and is suspected when the child shows neurologic or hypocortisolism symptoms. VLCFA dosage, CNS MRI and genetic testing are used to diagnose them. Adrenal insufficiency is associated with high morbidity in patients with ADL if not early diagnosed and treated, which brings out the importance of orienting parents and health care professionals of signs and symptoms of adrenal insufficiency or adrenal crisis.

P2-116

#### **METABOLIC AND ANTHROPOMETRIC PARAMETERS IN CONGENITAL ADRENAL HYPERPLASIA**

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**Objectives:** Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder which is seen commonly in countries that consanguineous marriage is widespread. Instability in metabolic parameters can be observed commonly due to both androgen excess and supraphysiological treatment doses of glucocorticoids.

The metabolic and anthropometric evaluation of patients with 21 hydroxylase deficiency are retrospectively evaluated in this report and the risk factors are expected to be determined.

**Methods:** Anthropometric measurements and metabolic parameters of 29 children (average age 10.9) with CAH are evaluated. Neck, waist, hip and middle arm circumference, weight, height measurements of patients are recorded. Skin fold thickness of biceps, triceps, subscapular and supra iliac regions are measured by a caliper. Body lipid composition of 22 patients whom are above the age of 10 are measured by bioimpedance analyzer. The treatment dose of hydrocortison are recorded and fasting lipid profile are measured along with surrenal gland hormones.

**Results:** Patients are classified according to their diagnosis as classical type (%24.1), simple virilizing type (%27.8) and nonclassical type (%48.1). The average height of 11 male and 18 female patient was  $141 \pm 21$ . 3cm. Mean blood pressure was 100/70mm Hg. Average hydrocortisone dosage was 16.5 mg/m<sup>2</sup>/day. The anthropometric measurements were recorded as below: circumferences of waist  $70.1 \pm 13.2$ cm, neck  $30.6 \pm 3.4$ cm, arm  $23.8 \pm 6.5$ cm, hip  $85.4 \pm 17.2$ cm and thickness of triceps  $14.9 \pm 7.8$ mm, biceps  $10.6 \pm 7.7$ mm, subscapula  $13.8 \pm 9$ mm, supra iliac  $9.6 \pm 6.8$ mm. Fasting blood glucose was  $72 \pm 15.1$ mg/dl, and insulin was  $25.03 \pm 5.9$ . Lipid profile was as below: cholesterol  $159, 3 \pm 35$ , triglyceride  $76.9 \pm 26.9$ , HDL  $66.4 \pm 54.3$  ng/ml. In comparison between groups, biceps and subscapular skin measurements were different while other parameters were similar.

**Conclusions:** Metabolic imbalance can be observed in CAH due to both androgen excess and high doses of

glucocorticoid treatment. Changes in body fat composition and tendency to obesity are expected problems. In this study the body fat composition in patients with nonclassical CAH was different than in patients with other types. Based on this findings we suggest a close monitoring of metabolic and anthropometric parameters in patients with CAH.

P2-117

#### **MANAGEMENT OF FLUDROCORTISONE AND SALT THERAPY IN 0-3 YEAR OLD CHILDREN WITH CONGENITAL ADRENAL HYPERPLASIA (CAH) – PRELIMINARY ANALYSIS**

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**Objectives:** Congenital adrenal hyperplasia (CAH) is one of the most common inherited autosomal recessive disorders. Most European countries have a newborn screening program for CAH. Salt wasting crisis can be mostly prevented due to early treatment. However, there are no evidence based guidelines how to treat young infants especially with respect to salt and mineralcorticoid treatment. Aim of our study is to evaluate the current medical treatment in CAH-children

**Methods:** Retrospective study using the new developed longitudinal module of the I-CAH registry. Dose of GC, FC and salt supplementation was collected. Height, weight, blood pressure and use of medication were collected anonymously after written informed consent at the age of 3, 6, 9, 12, 18, 24, 30 and 36 months in genetically confirmed CAH patients. Here we present preliminary data from two participating centres from Berlin and Nijmegen.

**Results:** 58 patients with CAH (21 hydroxylase deficiency) from Berlin (n=25) and Nijmegen (n=33) born between 2001 and 2015 were included. All patients started with hydrocortisone (HC) within the first week of life. All patients from Nijmegen (30/58) were treated with salt supplementation within the first year of life, on 3 patients there was no information, while patients from Berlin (25/58) were not treated. In 52/58 patients therapy with FC was started at the first visit; no information was given in 6 patients. Initial FC dosage is lower in the salt treated patients from Nijmegen. After the first year FC dosage was not significantly different, whereas hydrocortisone dosage/m<sup>2</sup> is significantly lower in patients from Nijmegen until the age of 2 years. To compare growth, weight gain and blood pressure during the first 3 years of life further analysis is done.

**Conclusions:** The I-CAH registry offers the opportunity to compare treatment regimens and outcome from different centres. Salt supplementation is primarily dependent on



treatment centre. To evaluate influence of FC dose and salt supplementation on growth and blood pressure in the first 3 years inclusion of other international centres is planned.

P2-118

#### ESTABLISHMENT OF HORMONE CONTROL WITH DEXAMETHASONE IN PATIENTS WITH CLASSICAL CONGENITAL ADRENAL HYPERPLASIA AFTER FINAL HEIGHT

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**Objectives:** Hormone control may deteriorate in some patients with classical congenital adrenal hyperplasia (CAH) on glucocorticoid (GC) replacement during peripubertal period. Long acting GCs (i.e. dexamethasone) may help improve hormone control. Herein we report clinical characteristics of patients with classical CAH whose GC replacement was switched to dexamethasone (DXM).

**Methods:** Medical records of the patients followed with the diagnosis of classical CAH in the last ten years were screened and those of patients whose control deteriorated peripubertally under GC replacement with HC were analyzed retrospectively to identify those who were switched to DXM after final height. Clinical characteristics, daily doses of GCs, and hormone levels both before, during, and after switch to DXM were analyzed. Non-parametric tests were used in the analyses.

**Results:** Nine patients (7 females) met the inclusion criteria. Three had simple virilizing, and six had salt-wasting type of 21-hydroxylase deficiency. The median age of deterioration in hormone control was 10.4 (range: 8.2 to 12.2) years, while the median age when treatment was switched to DXM was 14.8 (range: 10.2 to 18.2) years. An increase in body mass index (BMI)–SDS preceded deterioration of hormone control, however the difference was not statistically significant. Latest median dose of HC and median 17-OH-progesterone level prior to switch to DXM were 18.3 (15.1 - 24.5) mg/m<sup>2</sup> and 109.8 (37.7 - 249.0) ng/mL, respectively. The median dose of DXM that established hormone control (0.3 mg/m<sup>2</sup> - HC equivalent 16.7 mg/m<sup>2</sup>) was similar to prior HC dose. Median dose of DXM that maintained control (0.2 mg/m<sup>2</sup> - HC equivalent 9.7 mg/m<sup>2</sup>) was significantly less than the HC dose prior to hormonal deterioration.

**Conclusions:** Deterioration of hormone control in patients with classical CAH may be associated with excess weight gain in the peripubertal period. Switching HC to long acting DXM may establish hormone control. Improvement of hormone control with a dose of DXM equivalent to the latest dose of HC prior to deterioration may be explained by increased compliance as well as variations in the half-life, duration of action, and potency of DXM vs HC.

P2-119

#### PERIOPERATIVE STRESS DOSE STEROID MANAGEMENT FOR CLASSICAL CONGENITAL ADRENAL HYPERPLASIA: TOO MUCH OR TOO LITTLE?

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**Objectives:** In order to avoid adrenal crisis perioperatively, patients with classical CAH are given increased doses of glucocorticoids. However, there is no consensus on dosages given during the perioperative and postoperative stages. We hypothesized that current clinical protocols may be overestimating the endogenous response to perioperative stress. Our aim was to evaluate CAH patients using our current protocol for perioperative stress dosing of corticosteroids and determine if their urinary steroid level was higher than in untreated controls undergoing surgery of a similar duration.

**Methods:** We recruited pediatric patients with classical CAH (n=14) that were scheduled to have genital surgery and a control group of unaffected pediatric patients (n=10) scheduled to have surgery of a similar duration. Our current protocol is to give 25 mg/m<sup>2</sup> of hydrocortisone (HC) on call to OR and 50 mg/m<sup>2</sup> of HC continuously during the operation. Afterwards, patients receive 50 mg/m<sup>2</sup> divided every 6 hours during the first 24 hours postoperatively. All patients had a Foley catheter placed and urine was collected on POD 1. Urinary 17-hydroxycorticosteroids and urinary free cortisol were measured in all samples. Data were analyzed to determine if urinary steroid metabolites were higher in subjects treated with stress dose HC.

**Results:** We studied 14 patients with CAH; this group was compared to 10 controls. Mean age at time of surgery was 16.3±14.6 months in CAH patients compared to 9.6 ± 9.5 months in controls. We examined urinary cortisol in both treated CAH patients and untreated controls. We found that urinary cortisol was significantly higher in CAH patients (115.8±24.6 nmol/m<sup>2</sup>; p < 0.05) than in controls (26.5 ± 12.2 nmol/m<sup>2</sup>). Urinary 17-OH corticosteroids were also higher in CAH patients than in controls (6.5 ± 0.5 nmol/m<sup>2</sup> vs. 3.4 ± 0.5 nmol/m<sup>2</sup>; p < 0.05).

**Conclusions:** We demonstrated that both urinary cortisol and 17-OH corticosteroid levels were higher in treated patients with CAH at 1 day post-operatively as compared to controls. These results suggest that our current stress dosing protocol overestimates the need for glucocorticoids in CAH patients

postoperatively. Results of this study need to be confirmed in a larger group of patients, before proposing new lower dosing regimens.

P2-120

#### **AUTOIMMUNE DISEASES AFTER RESOLUTION OF ENDOGENOUS CUSHING SYNDROME IN CHILDREN**

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**Objectives:** Glucocorticoids are widely used for their immunosuppressive properties in autoimmune diseases. Similarly in patients with endogenous Cushing syndrome it has been hypothesized that the hypercortisolemic state can suppress the presentation of autoimmune diseases. After the resolution of hypercortisolemia, the regulation of the immune system recovers allowing for autoimmune diseases to manifest. Here we investigate the presence of autoimmune diseases that developed after cure of endogenous Cushing syndrome in children.

**Methods:** Out of the 195 children who were diagnosed and successfully treated for endogenous Cushing syndrome at the National Institutes of Health from 1997 until 2017, 127 children were followed for at least 6 months after treatment (mean age at diagnosis: 12.4 years). We performed a retrospective chart review analysis to identify the presence of autoimmune diseases after cure.

**Results:** Nine children were diagnosed with a new autoimmune disorder after resolution of hypercortisolemia. The various autoimmune diseases identified were: celiac disease (n=1), psoriasis (n=1), Hashimoto thyroiditis (n=1), Graves disease (n=1), optic neuritis (n=2), skin hypopigmented lesions (n=2) and allergic rhinitis/asthma (n=1). This results in a frequency of 7% of our pediatric Cushing syndrome population. The reported time between the treatment of Cushing syndrome and diagnosis ranged from 6 months to 3.4 years. All patients were successfully treated medically and did not experience any serious complication of their autoimmune disease.

**Conclusions:** The presence of autoimmune diseases might be masked by the hypercortisolemic state in endogenous Cushing syndrome. After resolution of hypercortisolemia, the presentation of new autoimmune diseases or recurrence of previously known autoimmune conditions should be considered when concerning symptoms arise; this possibly applies also to children with iatrogenic Cushing syndrome.

P2-121

#### **REPORT OF A PATIENT WITH SEVERE GLUCOCORTICOID RESISTANCE SUCCESSFULLY MANAGED WITH HIGH DOSE DEXAMETHASONE**

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**Objectives:** Glucocorticoid resistance syndrome (GRS) is caused by mutations of the *NR3C1* gene and presents with signs of mineralocorticoid and androgen excess of variable degree. A patient with severe glucocorticoid resistance who was reported as carrying a heterozygote *NR3C1* defect (R714Q) (Nader *et al. JCE&M* 95:2281, 2010) was found to have a nonsense mutation on the other allele that was previously missed by sequencing of the cDNA; the defect was revealed by deep sequencing of the genomic DNA (Dseq).

**Methods:** The patient is a 17 yr-old girl who was referred to the National Institutes of Health at the age of 11 yrs. She originally presented at the age of 2 yrs-10 mos with nausea, vomiting and seizure activity, secondary to hypokalemia (K=2.6mEq/L), hypoglycemia (Glu=18mg/dL) and hypertension (BP=138/90mmHg). Further evaluation revealed elevated 24hour urine free cortisol (646mcg/24h), morning serum cortisol (81mcg/dl) and ACTH levels (431pg/mL). She was initially treated with low doses of dexamethasone resulting in persistent hyperandrogenemia (acne and hirsutism), premature adrenarche (4 yrs), precocious puberty (7 yrs), and advanced bone (12 yrs-6 mos at chronologic age of 6 yrs-6 mos). She also had significant hypertension requiring 4 antihypertensive medications with MRI findings of punctuate microinfarcts at the basal ganglia, left thalamus and pons; she was also found to have mild brain structural abnormalities that are not known to be part of GRS. Increase of the dexamethasone dose to 14mg/day resulted in sufficient control of the blood pressure (currently controlled only with amlodipine), resolution of acne and hirsutism, and regular menses; she however achieved a short final height (height SDS, -3.2).

**Results:** With deep sequencing (confirmed by Sanger sequencing), we identified two heterozygote mutations of the *NR3C1* gene, c.592G>T:p.E198X (novel) and c.2141G>A:p.R714Q, which were proven to be on different alleles. Dseq identified also a heterozygote mutation of the *SIX3* gene (c.109G>T:G37C) which is associated with the development of brain defects.

**Conclusions:** Glucocorticoid resistance syndrome may present with life threatening complications that may require high doses of dexamethasone. DSeq may reveal defects that explain the phenotype, if previous analyses did not make sense.

**HYPERTENSION AND CONGENITAL ADRENAL HYPERPLASIA (CHA) CAUSED BY A MUTATION OF GEN CYP  $\beta$  11 OF ENZYME 11  $\beta$  HIDROXYLASE**

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**Objectives:** To describe a patient with Congenital adrenal hyperplasia (CHA) caused by a genetic alteration of the gen CYP  $\beta$  11

**Methods:** Molecular analysis of the gene CYP  $\beta$  11 and its clinical correlation

**Results:** Twelve and half girls presenting with hypertension and genitalia abnormaties such as clitoromegaly (5cm) pseudovagina and monorlip scrotalis. Pelvic ultrasound showed an infantile uterus and poly cistic right ovary

**LABORATORY**  
: DHEASO4 10,39ng/dl 17OHProgesterona 550 ng /dl (high) andostenediona 6,64 ng /dl , creatubube 0.68 , Na 142 K 3 ,53 Karyotype 46XX

Molecular studies revealed a double mutation of the 11 beta hydroxylase gene pQ356X witch generates a trunkated protein

and IVS +5G>C intronic protein .

Patient was treated with calcioantagonists ,prednisona , control of blood pressure and reconstruction of the external genitalia

**Conclusions:** Genetic studies should be performed in all patients with hypertension and CAH to discard 11  $\beta$  hydroxylase deficiency .

In Colombia there is only one reported such study but the genetic abnormality is different

**MOLECULAR ANALYSIS AND GENOTYPE PHENOTYPE CORRELATION IN GROUP OF PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA IN SOUTH WEST COLOMBIA.**

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**Objectives:** To determine the presence of point mutations of the genes CYP21A2 ,11BETA OH and STAR and their clinical correlation in patients with congenital adrenal hyperplasia in south west Colombia.

**Methods:** Analisis of the genotype phenotype correlation clinical and molecular analysis of point mutations of the genes CYP21A2 ,11BETA OH and STAR in 13 patients with hyperplasia adrenal

**Results:**

Paci e	Ag	Karyo	HP	Mutación	External Ge	Diagn	Enzy
ent	(da	type	Ng		nitalia	osis	me
	ys)		/ dl				
1	60	46XX	1090	Q318X	AN	HASL	210H
2	60	46XX	3000	Q318X	AN	HASL	210H
3	26	46XX	>2000	Q318X	AN	HASL	210H
4	60	46XX	4640	V281LHomocygous	AN	HASL	210H
5	10	46XX	2500	V281Lhomozygous	AN	HASL	210H
6	30	46XY	2500	V281Lhomo	AN	HASL	210H
7	1080	46XY	1216	V281L heterozygous	AN	HANC	210H
8	300	46XY	54400	In2 homo zygyous,V281L Heterozygous	N	HASL	210H
9	45	46 XY	>2000	In2 Homozygous	AN	HASL	210H
10	3650	46xx	3900	IN2,V281Lheterozygous	N	HANC	210H
11	24	46xx	5200	Q356x,hetero zygyous. Exon 6 R384X Exon 7 heterozygous	Clitoromegaly HTA	HAC	11 $\beta$
12	5110	46xx	550	p.Q356X ,IVS+5G>C , (intron)	Clitoromegaly, HTA	HAC	11 $\beta$
13	112	46Xy	250	INTRON 1 c.64+1G>T Gene STAR	N	HAC	STAR

Table 1:HA Adrenal Hyperplasia , NC: no clasic ,SL : salt losen , C classic N normal .AN abnormal,STAR ,21OH: 21 hydroxylase ,11  $\beta$  hydroxylase 11  $\beta$

**Conclusions:** We found a deficit of 21oh in 76% of the patients and 11% I 15% of them .And one patients with deficiency STAR

Genetic studies allowed to know the frequency of the mutations in a given community ,so early treatment is initiated

# CLINICAL MANIFESTATIONS & MOLECULAR ANALYSIS OF SIX PALESTINIAN PATIENTS WITH PSEUDOHYPOALDOSTERONISM TYPE 1 (PHA 1) REVEALING FOUR NOVEL MUTATIONS IN THE ENAC SUBUNIT GENES

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**Objectives:** Pseudohypoaldosteronism type 1 (PHA 1) is a rare hereditary disorder characterized by resistance to the actions of aldosterone. Two different modes of inheritance with different mechanisms and clinical manifestations have been described , Autosomal recessive that affects the epithelial sodium channel (ENaC),the defect is permanent and affects all aldosterone target organs. Autosomal dominant or sporadic PHA 1, affects the mineralocorticoid receptor in most patients.

**Methods:** Six unrelated Palestinian infants to a consanguineous Palestinian families presented in the first week of life with severe dehydration, hyponatremia, hyperkalemia and severe metabolic acidosis, assessed to have pseudohypoaldosteronism and were managed with hypertonic saline and kayexalate, and did not improve on mineralocorticoids. Plasma renin activity & Aldosterone levels were extremely elevated.

**Results:** Whole exom sequencing and subunit genes of the ENaC were sequenced and revealed four novel mutations, R73C (Arg73Cys)mutation in the SCNN1A gene in one patient, c.142-143insC mutation that leads to frameshift and premature stop codon(p.S47fsX69) of SCNN1G gene in another patient, c.69delG causing frameshift and stop codon (p.G23GfsX26) of SCNN1A in another patient and G315R (Gly315Arg) in exon 6 of codon 315 of SCNN1B gene.

**Conclusions:** To our knowledge, this is the first description of this disease in a Palestinian family with molecular confirmation, allowing accurate genetic counseling, early diagnosis of affected kindreds, early therapeutic interventions and avoiding complications and checking if the clinical presentation does correlate well with the specific genotype.

P2-125

# SHORT STATURE AND HYPERGONADISM WITH RESOLUTION OF HYPERCORTISONISM AND HYPERTHYROIDISM IN SEVERE MCCUNE ALBRIGHT SYNDROME

Ying T Chang, MD, Penn State University, Hershey, PA, United States

**Objectives:** To demonstrate a case of severe McCune Albright syndrome with remission of hypercortisonism and hyperthyroidism while growth failure, hypergonadism, polyostosis fibrous dysplasia and pauciductal cholestasis remain at 9 y of age.

**Methods:** Case report

**Results:** An African American male was diagnosed with McCune Albright syndrome at age 2 mo due to R201H

mutation of GnAs1. He had multiple large cafe-au-laid spots, growth failure, hyperthyroidism, hypercortisonism, hypergonadism, polyostotic fibrous dysplasia, severe pauciductal cholestasis, nephrocalcinosis, hypertension, developmental delay, and bilateral hip rotations. His initial serum cortisol was 38 mcg/dl and post-dexamethason cortisol was 28.4 mcg/dl. He was treated with metyraponsince at age 3 mo, peak dose 450 mg/m2/day during the first 4 y, but not increase thereafter. The dose was 57 mg, t.i.d at age 9 y. A 24-h urine free cortisol was 30.8 mcg/24h (1-30 for age 5-9 y) after withholding metyrapone for 5 days, and was 11.2 mcg/24 h after withholding for 10 days.

At age 1.7 mo, TSH <0.01 uIU/ml, free T4 was 3.27 ng/dl. He was treated with methimazole at 3.8 mo of age, and stopped at age 8 y 4 m. TSH was <0.02, free was 1.34 two weeks after methimazole was withheld. TSH and free T4 remained normal 9 mo after methimazole was stopped.

At age 5 y, testicles were 2.7x1.3 cm and penile length was 4.3 cm. At age 9 y 2 mo, testis were 3.7 x 1.7 cm. The bone age (BA) was 6 y 6 mo while chronological age (CA) was 3 y 8 mo. BA was 11 y 6 mo when CA was 7 y 8 m. Testosterone was 52 ng/dl (was 41 ng/dl at 2 y of age). GnRH stimulation test was prepubertal. Alpha-FP and hCG were normal. Because of his severe liver disease, ketoconazole was not used.

He has been very short since infancy. Ht Z = -4.2 at 2 y 8 mo. At 8 y 9 mo, ht z =-3.7. Wt 19.1 kg, z =-3.2. His peak GH was 10 ng/ml after stimulation at age 2 y 2mo, and was 30 ng/ml at age 7 y 8 mo.

**Conclusions:** Hypercortisonism and hyperthyroidism in severe McCune Albright syndrome may resolve years later. Treatment with GnRH analog or aromatase inhibitor or tamoxifen for hypergonadism in this case is debatable due to severe fibrous dysplasia and uncertain effectiveness.

P2-126

# 17-HYDROXYLASE DEFICIENCY: RARE CAUSE OF DELAYED PUBERTY

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**Objectives:** 17-Hydroxylase deficiency (17OHD) is a very rare disorders characterized by glucocorticoid deficiency, hypergonadotropic hypogonadism, hypertension, and hypopotasemia. Mutations in the CYP17A1 gene cause 17OHD. Three adolescents, one single and two cousin with delayed puberty were presented hereç

**Methods:** The patients were raised as girls. All of the patients were pre-pubertal. Initial clinical findings are given in the Table1. Hydrocortisone, 17-beta estradiol and antihypertensive treatments were initiated. First case achieved Tanner 5 breast development at 15.64 and had menarche at 15.72 years old. Alendronate was started due to osteoporosis (L1-L4 BMD was -3.1). Second girl achieved

Tanner 5 breast development at 15.08 and had menarche at 16.64 years old. The third patient could only be followed for six months because of advance age. A known mutation in first patient and a novel mutation in the second patient was found in the *CYP 17A1* gene (Table 2).

#### Results:

Cases	Genomic	cDNA	Protein
1	g.6452 G>A	c.1319 G>A	p.R440H
2	g.276_280delCCCTGc.104_108delCCCTGp.P35fs*15		
	Case 1	Case 2	Case 3
Karyotype	XX	XX	XY
Age, years	12.80	14.24	18.16
Height SD	-1.29	-2.10	-0.52
Weight SD	-0.96	-0.77	1.61
BP mmHg	145/120	171/119	165/125
FSH, mIU/mL	31.82	84.15	45.17
LH, mIU/mL	11.86	26.46	35.54
ACTH <sub>u</sub> pg/mL	140	107	99
Stimulated cortisol, mcg/dL	3.46	0.76	<1
Na, mEq/L	141	141	140
K, mEq/L	3	3.5	3.9
DOC, pmol/mL (0.12-0.6)	11.9	2.76	2.58

**Conclusions:** Adrenal functions as well as gonadotropins should be examined in the adolescent girls with no thelarche and pubarche associated with hypertension, and 17-hydroxylase deficiency should not be forgotten.

Table 1

	Case1	Case2	Case 3
Karyotype	XX	XX	XY
Age, years	12.80	14.24	18.16
Height SD	-1.29	-2.10	-0.52
Weight SD	-0.96	-0.77	1.61
BP mmHg	145/120	171/119	165/125
FSH, mIU/mL	31.82	84.15	45.17
LH, mIU/mL	11.86	26.46	35.54
ACTH, pg/mL	140	107	99
Stimulated Cortisol, ug/dL	3.46	0.76	<1
Na, mEq/L	141	141	140
K, mEq/L	3	3.5	3.9
DOC, pmol/mL, (0.12-0.6)	11.9	2.76	2.58

Table 2

Cases	Genomic	cDNA	Protein
1	g.6452G>A	c.1319G>A	p.R440H
2	g.276_280delCCCTG	c.104_108delCCCTG	p.P35Rfs*15

Infants under 6 months of age are more prone to developing systemic reaction due to topically applied medications because of their higher ratio of total surface area to body weight.

#### Methods:

It is reported a case of an infant with iatrogenic Cushing Syndrome due to overuse of topical steroids for diaper dermatitis.

#### Results:

CVQC, 6 month old boy was admitted to the pediatric endocrinology clinic with the complaint of failure to thrive. He had a history of diaper dermatitis at 7 days of age. In that occasion it was prescribed topical Betamethasone dipropionate, a high potency corticosteroid. The skin lesions healed in a few days, but since then the child received uninterrupted treatment with the Betamethasone cream in the perineum 4-6 times per day.

At 6 months his weight was 4,45 kg (-4,94 Z-Score), his length was 53 cm (-7,11 Z-Score).

He had a Cushingoid appearance with moon face and mild hypertrichosis on his forehead. Vital signs were normal. Blood pressure was 120/60 mmHg. Basal serum cortisol was < 1mcg/dl and ACTH was 1,38 pg/ml (normal range: 10-60). The peak cortisol response to low dose ACTH stimulation test was insufficient.

Topical corticosteroid was suspended and oral hydrocortisone was prescribed on physiological doses, and discontinued after 6 months.

#### Conclusions:

Misuse or overuse of total steroids in infants may lead to Cushing's syndrome. Patients who are given topical steroids treatment should be offered information about the dosage, duration and possible systemic side effects of the therapy. Such medications should be prescribed in small amounts and, if possible, their use should be limited to a short period.

P2-128

#### ATYPICAL PRESENTATION, LOCATION AND HORMONAL PROFILE OF ADRENAL CORTICAL TUMOR IN 5-YEAR-OLD BOY WITH PUBARCHE

Allison J Pollock, MD; Yashoda G Naik, MD; Margo Hoover-Regan, MD; David B Allen, MD, University of Wisconsin School of Medicine and Public Health, Madison, WI, United States

**Objectives:** We report a 5-year-old boy with premature pubarche found to have an adrenal cortical tumor of ectopic adrenal rest origin. The case highlights diagnostic and therapeutic dilemmas created by the atypical location and hormonal profile of this tumor.

**Methods:** A 5-year-old boy presented with 4-5 pubic hairs at base of the penis, 2ml testes, normal size phallus, no acne, axillary hair or voice change, and apparent normal linear growth velocity. Exogenous androgen exposure was ruled out. Bone age was 8 years. Initial labs revealed an elevated androstenedione 2.550 (<0.949 ng/mL), 17-hydroxyprogesterone 108.00 (≤208 ng/dl), LH < 0.1 (0.0-0.3 mIU/ml), FSH < 0.1 (0.0-2.8).

P2-127

#### FAILURE TO THRIVE IN AN INFANT DUE TO SUPPRESSION OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS, A CASE REPORT.

Renata M Pinto, MS/MA, Federal University of Goiás, Goiânia, N/A, Brazil

#### Objectives:

Topic corticosteroids are often used to treat diaper dermatitis. The application of ointments containing corticosteroids on large surface areas of skin, use of more potent derivatives and higher concentrations, or their prolonged use increases the risk of Cushing's syndrome and Hypothalamic-Pituitary-Adrenal axis suppression.

**Results:** Prepubertal testes, normal 17OHP, and elevated androgens suggested possible adrenal neoplasm. Ultrasound: heterogeneous echogenic 6.4cm mass with scattered internal calcifications. Abdominal CT: 5.6x6.3x6.7cm soft tissue mass distinct from R adrenal gland, R kidney and liver; both adrenal glands appeared normal. Surgical resection confirmed ectopic location and lack of continuity with adrenals, and pathology revealed an 8x7x6.5cm adrenal cortical neoplasm of uncertain malignant potential, with negative margins and lymph nodes. Post-resection adrenal ablation treatment was not recommended. Post-resection androgen levels have fluctuated in and out of the pre-pubertal ranges but MRI has not revealed residual, recurrent, or metastatic disease.

**Conclusions:** Adrenocortical tumors in children are rare (0.2% of all pediatric malignancies) and ectopic adrenal rest tissue tumors rarer still. Typical presentation includes noticeable virilization, growth rate acceleration, and marked increases in DHEA and DHEA-S, none of which were present in this child.

Functional adrenal rest adenomas are often benign and usually secrete only androgens (predominantly DHEA, DHEAS, androstenedione, but only rarely testosterone). In this case, androstenedione and free testosterone were markedly elevated. The rarity of tumor, atypical location and hormone-secreting features in this case make confident determination of malignant potential challenging.

P2-129

#### AN UNUSUAL ADRENAL HYDATID CYST MIMICKING PHEOCHROMOCYTOMA

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**Objectives:** Pheochromocytomas can present with a mass effect or incidentally from symptoms and findings related to an increase in catecholamine secretion.

**Methods:** We report here an adolescent case found to have hypertension and an adrenal mass during hospitalization due to drug intoxication and diagnosed with adrenal hydatid cyst after operation.

**Results:** A sixteen year old patient referred to our department because of hypertensive values of 190/140 mmHg was found to have taken sertraline and nine captopril pills for attempted suicide. She did not have any history of hypertension. Her height was 156 cm (-1.06SD), body weight was 44 kg (-2 sd) and Tanner puberty stage was Stage V according to the physical examination. Biochemical tests and thyroid function tests were normal. Cortisol: 12.50 µg/dL, ACTH: 95.8 pg/mL, renin: 62 pg/ml (3–32), aldosterone: 244 pg/ml (12–340), serum adrenaline: 118.7 pg/ml (0–241), serum metanephrine: 35 ng/mL (<90), neuron specific

enolase: 17.8 ng/ml (<16.3), 24 hour urine metanephrine: 225 mcg/24hours (33–185), normetanephrine: 171 ng/mL (57 – 286), norepinephrine: 16.53 ng/mL (15 – 80), epinephrine: 4.72 ng/mL (0.5 – 20), VMA: 1.16 mg/24 hours (0 – 6). A soft tissue filling the left surrenal location with calcific foci inside and in the surrounding tissue with dimensions of 70x52x40 mm was observed on abdominal MRI. MIBG scintigraphy was normal. MEN scanings were negative. 1 mg/day doxazosin treatment was started with possible pheochromocytoma pre-diagnosis for the patient who had 76% cystolic and 88% diastolic loading during the day and 74% cystolic and 96% diastolic loading at night in 24 hour-arterial blood pressure monitoring. The patient was operated on the 10th day of treatment. Hypertension was not observed during the operation. A 5x6x8 cm encapsulated cystic structure containing lamellose membrane in the left surrenal location was excised. Hydatid cyst pericyst and membrane bonded to adrenal and kidney parenchyma were reported from the pathology. Albendazole treatment was started.

**Conclusions:** Hydatid cysts are located very rarely in the adrenal gland and these cases may present with mass effect-related hypertension. Adrenal hydatid cysts should be considered in the differential diagnosis of adrenal masses, especially when presenting with hypertension.

P2-130

#### A PATIENT WITH X-LINKED ADRENAL HYPOPLASIA CONGENITA CAUSED BY A NOVEL NROB1 MUTATION ONSET IN CENTRAL PRECOCIOUS PUBERTY

*Jun Zhang, MD; Song Guo, MD; Qiuli Chen, MD, the first affiliated hospital of Sun-Yet sen University, Guangzhou, China; Minlian Du, MD, Sun-Yat sen University, Guangzhou, China*

**Objectives:** The puberty disorder in X-linked adrenal hypoplasia congenita (AHC) by a *NROB1* gene mutation is classically characterized with hypogonadotropic hypogonadism. Currently, rare cases of AHC with central precocious puberty (CPP) have been reported. To explore the possible regulatory role of *NROB1* on hypothalamic–pituitary–gonad axis (HPGA), we analyzed the clinical and molecular character in a rare case with *NROB1* mutation developed CPP.

**Methods:** To review the clinical characteristics and direct sequencing of *NROB1* gene in a case with a novel *NROB1* mutation developed CPP, and evaluated the relationship between clinical and molecular characteristics.

**Results:** A 11-month-old male patient was with premature pubarche, enlargement of penis/ testes and penile erections for 7 months, without the manifestations of adrenal insufficiency. Clinical diagnosis was AHC with CPP.

The *NROB1* gene by direct sequencing, which revealed a novel mutation in exon 1 [a c.913C>T, p. (Gln305\*)]. This mutation may induce premature truncation of the transcription protein DAX-1. Hydrocortisone replacement therapy had made remission in manifestations of CPP and the gonadotropins and testosterone levels returned to the prepubertal



range. During the last three years of follow-up, there was no recurrence.

**Conclusions:** Developed CPP with novel mutation c.913C>T in the *NROB1* gene, which had not been reported previously in China. *NROB1* gene involves the restraining regulation for the prepubertal HPGA and the gene mutation may result in loss of the repressor function of *NROB1*. To speculate, it may relate to development CPP in patient with AHC. Further research for exploring the exact mechanism of *NROB1* gene on puberty regulation is needed.

## POSTER SESSION 2

**Friday, September 15, 2017, 11:30am-12:30pm**

### P2 - Bone and mineral metabolism

#### P2-200 – P2-219

P2-200

#### THE PREVALENCE AND RISK FACTORS OF VERTEBRAL FRACTURE IN CHILDREN WITH ACUTE LEUKEMIA

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**Objectives:** To investigate the overall prevalence and associated risk factors of vertebral fractures (VF) in acute leukemia survivors and ascertain the use of glucocorticoid as a strong VF trigger

**Methods:** Retrospective review of children with hematologic diseases at a single institution was performed. After termination of treatment, VF were assessed from the lateral thoracolumbar spine radiographs between November 2014 and April 2016. Statistical analyses were executed focusing on the clinical and biochemical factors associated with VF.

**Results:** A total of 85 children completed the baseline evaluation (62.3 % of male; 69.4 % of lymphoblastic leukemia; mean age at diagnosis of  $7.9 \pm 4.5$  years; mean duration of treatment of  $2.4 \pm 0.9$  years). 29.4 % had either prevalent VF or a first incident VF. Later age at diagnosis ( $9.6 \pm 3.9$  years,  $p=0.024$ ) and extended period of treatment ( $2.9 \pm 1.0$  years,  $p<0.001$ ) were associated risk factors of VF. VF was prone to a lower lumbar spine bone mineral density z-score ( $-0.8 \pm 0.7$ ,  $p=0.005$ ). VF prevalence ( $R^2=0.846$ ,  $OR=1.002$ ,  $p=0.0016$ ) and severity ( $R^2=27.9\%$ ,  $p=0.007$ ) positively correlated with higher amount of glucocorticoid administered. Using a receiver operating characteristic (ROC) curve, a potential cutoff of glucocorticoid dose for VF incidence was 7585 mg (area under curve=0.953,  $p<0.001$ ).

**Conclusions:** In young survivors after completion of leukemia treatment, lateral thoracolumbar spine radiograph detects

substantial numbers of VF, and a total therapeutic dose of glucocorticoid is critical factor for bone health assessment.

P2-201

#### ASSOCIATION BETWEEN OBESITY AND SERUM 25(OH) VITAMIN D LEVELS AND DENTAL HEALTH IN TURKISH CHILDREN.

*Gülçin Dogusal, MD; Tolga Ünüvar, MD, Adnan Menderes University, Aydin, Turkey; Ahmet Anik, MD, Adnan Menderes University, Medical School, Aydin, Turkey; Isil Sönmez, MD, Adnan Menderes University, Aydin, Turkey*

**Objectives:** The aim of this study is to investigate an association between obesity and serum 25(OH) vitamin D levels and dental caries in Turkish children.

**Methods:** The study conducted in Adnan Menderes University between December 2015 and January 2016 and included 324 obese children with a body mass index (BMI) above the 95th percentile, who applied to our department with complaint of weight gain and 138 healthy subjects with a BMI below the 85th percentile who had similar age and gender distribution. Before the outset of the study, all the patients and control subjects underwent physical examination and laboratory evaluation. Fasting plasma glucose, serum insulin, HOMA-IR, serum free T4, TSH, 25(OH)D, Ca, P and ALP were evaluated in all of the participants. Also, oral examination performed by the same pediatric dentist and DMFT/dft (decayed, missing, filled teeth), DMFS/dfs (decayed, missed, filled surface) indices were recorded.

**Results:** Serum 25(OH)-vitamin D levels were significantly lower in obese children than those of normal subjects ( $9.87 \pm 7.41$  ng/mL vs.  $17.2 \pm 7.26$  ng/mL, respectively,  $p<0.05$ ). There was a statistical significant difference between obese and normal subjects in DMFT and DMFS indices for permanent teeth. There was a similar and more distinct difference in dft and dfs indices for primary teeth between obese and normal subjects ( $p<0.05$ ). 80.5% of obese children have at least one tooth decay. A positive correlation between body mass index, HOMA-IR and dental caries was found. A lower levels of serum 25-OH vitamin D was associated with higher risk of caries.

**Conclusions:** Childhood obesity and low serum 25-OH vitamin D levels seem to increase the risk of dental caries in children.

P2-202

#### MUSCLE DENSITY MEASUREMENT IN DUCHENNE MUSCULAR DYSTROPHY

*Susanne Bechtold, MD; Astrid Blaschek, MD; Wolfgang Müller-Felber, MD; Claudia Weissenbacher, MD; Julia Roeb, MD; Carmen Sydlík, MD; Heinrich Schmidt, MD, University Children's Hospital, LMU, Munich, Germany*

**Objectives:** Muscular dystrophy is characterized by lower skeletal muscle quality, lower muscle strength and physical performance. The aim of the study was to assess regional

muscle density and its correlation with regional muscle area in Duchenne muscular dystrophy (DMD) subjects and able bodied controls.

**Methods:** Skeletal muscle pQCT (peripheral quantitative computed tomography) scans at the non-dominant forearm were performed in patients with muscle dystrophy at different ages and compared with muscular healthy patients with familiar short stature or diabetes type 1.

**Results:** We included 45 children and adolescence with clinical and molecular diagnosis of MD (2 Becker-Kiener, 2f) and 105 controls (68 f). Mean age for MD was  $9.73 \pm 3.7$  years and  $14.77 \pm 4.6$  years for controls. Younger MD patients were ambulatory, the majority of them were treated with intermittent glucocorticoids. Muscle density was constant between 70 and 80 mg/m<sup>3</sup> in the control population (mean  $77.90 \pm 2.16$ ) irrespective of age and sex, whereas muscle density for MD was significantly reduced with  $48.38 \pm 12.8$  mg/m<sup>3</sup> and decreased with age ( $r = -0.39$ ,  $p = 0.009$ ). There was no correlation between muscle density and muscle cross sectional area (MCSA) for each of the groups. With age MCSA increased in controls ( $r = 0.73$ ,  $p < 0.001$ ) but not in MD.

**Conclusions:** In healthy or able bodied controls muscle density is a constant parameter. Measurements of this parameter in MD seem to reflect the progressive loss of muscle fibers and might be an early marker at a stage where muscle CSA is still within normal range.

P2-203

#### MILK, CHEESE OR PHOSPHATE TABLETS IN THE TREATMENT OF HYPOPHOSPHATEMIC RICKETS: A PILOT STUDY

*Cecilie Siggaard, MD; Vibe Poulsen, MD; Mads Sandahl, MD; Line Underbjerg, PhD, Aarhus University Hospital, Aarhus, Denmark; Isabella Piec, MD, University of East Anglia, Norwich, Norwich, United Kingdom; Sine Beck-Nielsen, PhD, Kolding Hospital, Kolding, Denmark; Lars Rejnmark, Professor; Niels H Birkebæk, PhD, Aarhus University Hospital, Aarhus, Denmark*

**Objectives:** Hypophosphatemic rickets (HPR) is a rare disease with an estimated incidence of 3.9 per 100,000. HPR is most commonly caused by an increase in fibroblast growth factor 23 (FGF23) levels due to X-linked inherited mutations in the PHEX gene. Standard treatment is oral phosphate tablets and vitamin D analogs. Due to their rapid absorption, phosphate tablets are difficult to administer and secondary hyperparathyroidism may be a consequence. We hypothesized that dietary phosphate from milk or cheese is absorbed at a slower rate, thereby, reducing the fluctuations in serum phosphate. Therefore, we designed a randomized, multiple crossover study, investigating the feasibility and efficacy of phosphate supplement administered as either phosphate tablets, milk or cheese.

**Methods:** Seven females, 14-39 years old, were included. All patients underwent three four-day treatment periods consisting of two phosphate tablets given four times a day (800 mg phosphorus) or the same phosphate dose given four times a day as either milk or cheese. Each period was

terminated by an inpatient day. Blood samples for calcium, phosphate, parathyroid hormone (PTH), bone specific alkaline phosphatase (BSAP) and FGF23 (c-terminal) were taken at 8 am (fasting), 10 am, 12 am, 2 pm, and 4 pm. Urine samples for calcium and phosphate were taken at 8 am (fasting), 12 am and 4 pm. Patients were supplemented with their usual doses of D vitamin analogs, but no other phosphate or calcium modifying treatments. Statistical tests were performed using One-Way-ANOVA.

**Results:** All patients had genetic verified X-linked HPR. Treatment feasibility was independent of the phosphate source. Serum values of calcium, phosphate, PTH, BSAP and FGF23 did not differ between the treatment periods. Phosphate excretion was highest between 8-12 am during phosphate tablet treatment ( $P < 0.01$ ).

**Conclusions:** Our pilot study showed that phosphate supplement in HPR can be administrated as phosphate tablets, milk or cheese. In dosing phosphate supplement to HPR, the phosphate content in dairy products should be included. However, our study is limited by a low patient number, and further studies are needed.

P2-204

#### OVERWEIGHT AND OBESITY IN CHILDREN AND ADOLESCENTS WITH MODERATE AND SEVERE FORMS OF OSTEOGENESIS IMPERFECTA

*Luiz Claudio Castro, PhD; Beatriz Ribeiro, MD; Paula Carrijo, MD; Maria Carolina Medeiros, MD; Delia Braz, MD; Lais Oliveira, MD; Naiara Martins, MD; Fernanda Lopes, MD; Renata Oliveira, MS/MA, University of Brasilia, Brasilia, Brazil*

**Objectives:** To evaluate the prevalence of overweight and obesity among pediatric patients with moderate and severe forms of osteogenesis imperfecta (OI); compare those figures with the ones from a local pediatric population; and to investigate the existence of correlation between overweight/obesity and age, type of OI and recurrence of fractures.

**Methods:** This is a cross-sectional study with review of the patients' medical records. It was analyzed clinical, anthropometric and body mass index (BMI) data from patients with OI, younger than 20 years of age and who were on disodium pamidronate therapy. Anthropometric data from the OI group was compared with data from the control group (n: 154; female: 86; age:  $10.1 \pm 4.6$  years; overweight: 24.6%; obesity: 11.7%), being the last composed of subsequential patients followed at the hospital pediatric outpatient clinic.

**Results:** Data from 84 patients with OI were evaluated (female: 45; type 1: 15, type 3: 38, type 4: 31), current mean age  $10.3 \pm 4.8$  years. OI group BMI Z-score:  $0.9 \pm 1.6$  kg/m<sup>2</sup>; control group:  $0.6 \pm 0.9$  kg/m<sup>2</sup> ( $p = 0.02$ ). In the OI group, overweight (39.3%,  $p = 0.002$ ) and obesity (22.6%,  $p = 0.03$ ) were significantly more prevalent than among controls. Prevalence of obesity was significantly higher in the group with the more severe forms of OI -type 3 (35.7%,  $p = 0.04$ ). In the OI group, overweight and obesity were observed, respectively, in 14.3% and 14.3% in the younger than 5 years

of age children and in 18.6% and 24.2% among the ones older than 5 years of age. There was no significant correlation between BMI and age ( $r = -0.003$ ) nor with recurrence of fractures ( $r = 0.13$ ).

**Conclusions:** The prevalence of overweight and obesity among patients with OI was statically higher than that found in the local pediatric population, regardless of age, especially in those with the more severe forms of the disease. In this phase of the study there was no negative impact of BMI on the pattern of recurrence of the patients' fractures.

P2-205

**CHILDREN, ADOLESCENTS AND YOUNG ADULTS WITH PWS PRESENT WITH LOW-NORMAL BONE MINERAL CONTENT DESPITE TREATMENT WITH GROWTH HORMONE DURING CHILDHOOD**

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**Objectives:** Bone mineral density (BMD) in Prader-Willi syndrome (PWS) is reported to be low in adults (1) but normal in prepubertal children (2). It has been suggested that BMD declines in adolescent patients despite GH therapy (3), possibly due to pubertal delay and insufficient exposure to sex steroids.

**Aim:** Cross-sectional assessment of radiographic bone strength in children, adolescents and adults with PWS, and subanalysis of data from a pediatric PWS cohort before and during growth hormone treatment.

**Methods:** For assessment throughout GH treatment, radiographic bone strength was evaluated by calculating the Bone Health Index (BHI)-SDS from 254 X-rays of the left hand of 29 patients with PWS (17 female) using the BonExpert® software. Mean bone age (Greulich and Pyle) at initial visit was  $4.03 \pm 2.39$  (range 1.24 – 12.23 years) and mostly adequate for chronological age. Patients were followed from age  $4.38 (\pm 1.78)$  to  $11.87 (\pm 3.72)$  years. After initial evaluation, all patients were treated with daily sc growth hormone ( $0.027 + 0.01$  mg/kg BW). Body height, Bodyweight, pubertal status and medical history were assessed at all visits. For cross-sectional analysis, both 25 BHI-SDS of adolescent patients (17 female) and 38 DXA Z-scores of adult patients (18 female, mean age 25.84 , range 17.72 – 50.05 years) were obtained.

**Results:** For BHI-SDS or DXA Z-scores, no significant differences were found (Table 1). However, changes in BHI-SDS over time differed substantially between girls and boys (Fig. 1). BHI-SDS showed a weak positive correlation with GH-dose (mg/kg BW/d) ( $r = 0.25$ ,  $P = 0.0015$ ;) and age ( $r = 0.25$ ,  $P = 0.0011$ ) in girls, but not in boys (NS).

**Conclusions:** Bone strength, determined by BHI SDS, is lower than expected in patients with PWS. In this cohort the BHI SDS or DXA Z-scores respectively, remained remarkably stable

in different age groups, even in adults without growth hormone treatment. However, in female patients, treatment with growth hormone might play an important role to reach peak bone mass.

**References:**

- 1) Longhi S, Calcif Tissue Int (2015) 96:160 – 166
- 2) van Wijngaarden; JCEM 2009; 94 (10):3763 - 3771

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**RESISTANT RICKETS WITH ALOPECIA: IS IT ALWAYS VITAMIN D- DEPENDENT RICKETS TYPE II (VDDR II) ?**

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**Objectives:** The association of resistant rickets with alopecia is typically described in vitamin D-dependent rickets type II (VDDR-II) due to mutations in the vitamin D receptor gene. VDDR-II usually presents with rachitic changes not responsive to vitamin D treatment and the circulating levels of  $1,25(\text{OH})_2$  vitamin D are elevated, differentiating it from other types of rickets.

We describe five cases of rickets with alopecia in which serum levels of  $1,25 (\text{OH})_2$  vitamin D and clinical response to calcitriol were not typical of VDDR-II.

**Methods:** We retrospectively analyzed five patients who had rickets with alopecia. Their clinical presentation, laboratory findings, radiological features and response to therapy were assessed.

**Results:** We studied five patients from four families, with onset of rickets at 3 months to 24 months of life. They presented with signs and symptoms of severe rickets, with poor response to high dosage of oral cholecalciferol. All of them had alopecia totalis. None reported seizures. Hypocalcemia was seen in 3/5 patients and hypophosphatemia in 2/5 patients as described in table 1. All of them had elevated serum alkaline phosphatase,  $25(\text{OH})$ vitamin D and serum parathyroid hormone. Serum  $1,25 (\text{OH})_2$  vitamin D was low or inappropriately normal in all the patients (10.3 to 26.3pg/ml).

The patients showed good clinical and biochemical response to calcitriol. however, their alopecia persisted.

**Conclusions:** Our patients behaved biochemically and clinically like VDDR-I rather than VDDR -II, with the exception of the presence of alopecia. Mutational analysis of the CYP27B1 gene may be helpful in definitive diagnosis.

**PLEASE SEE TABLE ON THE FOLLOWING PAGE**

Table 1: Biochemical and treatment profile of the cases

Cases	Age at onset (months)	Investigations results at presentation						Treatment		Time for normalization of ALP (months)	Current ALP (U/L)
		Serum Calcium (mg/dl)	Serum Phosphate (mg/dl)	Serum ALP (U/L)	25(OH)D (ng/ml)	1,25(OH)2D (pg/ml)	Serum PTH (pg/ml)	Calcitriol (ng/kg/day)	Elemental Calcium (gm/day PO)		
1	12	8.9	2.8	2000	N.A.	16	424	80	2	21	239
2	3	8.7	4	1906	74.4	14.1	574	73	2	12	265
3*	39	7.5	6.9	514	105	26.3	218	45	1.5	3	302
4	27	6.3	4.2	1700	110	26.1	467	66	1.25	16	557
5	24	7.3	2.7	3270	558	10.3	312	132	2.5	In follow up for 3 months	1406

\* Sibling of case 2

### TRACKING DIFFERENCES IN MORPHOLOGY AND REGULATION BETWEEN THE SPINE AND LONG BONES IN A PIG MODEL

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**Objectives:** The skeleton is not a single functional unit but consists of different, well-organized and mineralized compartments with specific functions, developmental aspects and regulations. Differences in the regulation of spinal and long bone elongation are mirrored clinically by the age course in body proportions. Whereas growth plates (GPs) in long bones can easily be discriminated, vertebral GPs are part of the cartilaginous endplate, which typically shows important species differences. This study aims to describe and compare histological, histomorphometric and regulatory characteristics in the GP of the spine and long bones in a porcine model.

**Methods:** 2- and 6-week-old piglet GP (GPs) of three vertebral segments (cervical, thoracic, lumbar) and eight long bones (proximal and distal radius, humerus, tibia, femur) were analyzed morphometrically. Further, estrogen receptor (ER), proliferation marker and growth factor expression was examined by immunohistochemistry.

**Results:** Individual vertebral GPs were smaller in width and contained fewer chondrocytes than long bone GPs, although their proliferation activity was similar. Whereas the expression pattern of growth hormone-associated factors such as Insuline-like Growth Factor (IGF-1) and IGF1-receptor was similar, ER $\beta$  and IGF-2 were distinctly expressed in the vertebral samples.

**Conclusions:** Vertebral GPs display differential growth, with measurements similar to the slowest growing GPs of long bones. Further investigation is needed to decipher the molecular basis of differential growth of the spine and long bones. Knowledge on the distinct mechanism will ultimately improve assessment of clinically essential characteristics of spinal growth, such as vertebral elongation potential and growth plate fusion.

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**Objectives:** The aim of this study was to analyse the incidence of cranial and craniovertebral anomalies in a series of children with X-linked hypophosphatemic rickets (XLHR).

**Methods:** Seventeen children (13 girls, 4 boys, mean age 7.3 years) followed for XLHR at the same center were included in the study.

On CT skull the patency of the sutures was noted. The position of the cerebellar tonsils was analysed in sagittal and coronal reconstructions. The importance of the subarachnoid spaces of the vault and the size of the ventricles were also assessed.

A Chiari type 1 malformation was considered when the cerebellar tonsils were lower than 5 mm from the foramen magnum edge on sagittal reconstruction.

**Results:** Craniostenosis was found in 12/17 children. It involved in all cases the sagittal suture. In 2/17 children the right coronal suture was also partially affected with a plagiocephalic deviation of the forehead and of orbital bandeau. In one child, a closure of both lambdoids was associated to the loss of the sagittal suture. In 1/17 child the fusion of the sagittal suture was partial and involved its posterior aspect.

On sagittal and coronal reconstructions, a clear descent of the cerebellar tonsils was found in 9/17 children. All of them presented also a fusion of the sagittal suture.

No child with an overt patent sagittal suture had a Chiari malformation. Closure of the sagittal suture was associated to the descent of the cerebellar tonsils ( $p=0.14$ ).

Children with Chiari malformation had a smaller cranial index compared to those without a descent of the cerebellar tonsils ( $p=0.021$ ).

**Conclusions:** This study highlights that the incidence of sagittal synostosis in patients affected by XLH is extremely high and that it has been probably underestimated in previous reports. As a result we now recommend clinical and X-ray screening for neurosurgical complications of XLHR in all children.

### CRANIAL SYNOSTOSIS AND CHIARI 1 MALFORMATION IN X-LINKED HYPOPHOSPHATEMIC RICKETS

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### STUDY OF ASSOCIATION OF VITAMIN D LEVELS WITH ASTHMA IN CHILDREN AGED 5-15 YEARS : A CASE CONTROL STUDY

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**Objectives:** To assess association of serum vitamin D levels in asthmatic children 5-15 years of age and the relation between Vitamin D levels with severity of asthma and frequency of attacks.

**Methods:** Study was carried out on children aged 5 to 15 years attending OPD and/or admitted in wards in department of Pediatrics in Manipal Hospital, Bangalore. Children with asthma were selected according to the GINA guidelines 2011. Period of study was between June 2013 to June 2016. Main outcome measures- Severity of asthma as defined in GINA guidelines, control of asthma as defined in GINA guidelines, serum vitamin D levels as defined in the endocrine society clinical practice guideline 2011.

**Results:** Total of 150 patients were studied of which 75 had asthma and 75 were non asthmatic healthy controls. Prevalence of vitamin D insufficiency among children with asthma was 18.7% and deficiency was 81.3%. Prevalence of vitamin D insufficiency among controls was 81.3% and deficiency was 12%. There was no significant difference in the vitamin D levels among and within the groups classified based on severity of asthma or among the groups classified based on the level of control of asthma.

**Conclusions:** There was a significant association between vitamin D deficiency and asthma. The chance of a vitamin D deficient child having asthma is 37.67 times more than that of a child with normal vitamin D level. There is no significant association between vitamin D deficiency and severity of asthma. There is an association between vitamin D deficiency and level of control of asthma.

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#### QUALITATIVE RESEARCH TO EXPLORE THE PEDIATRIC PATIENT EXPERIENCE WITH X-LINKED HYPOPHOSPHATAEMIA (XLH) AND TO EVALUATE THE CONTENT VALIDITY OF PROMIS® ITEM BANKS, FPS-R® AND POSNA-PODCI FOR USE AS CLINICAL TRIAL ENDPOINTS

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**Objectives:** XLH is a rare genetic disorder which leads to defective bone mineralization hypophosphatemia, and rickets in children. Published literature regarding pediatric XLH symptoms and impact on functioning is limited. This qualitative research study was conducted to increase understanding of the patient experience of XLH and to evaluate the content validity of the Faces Pain Scale - Revised®, selected items from the PROMIS® Pain, Fatigue and Physical Functioning Mobility item banks, and POSNA-PODCI for use as clinical trial endpoints in pediatric XLH.

**Methods:** Semi-structured telephone/Skype interviews were conducted with children with XLH (aged 8-12 years old) and parents/caregivers of children with XLH (aged 5-12 years old) in the US. Concept elicitation and cognitive debriefing techniques were used to spontaneously elicit concepts

relevant to the patient experience of XLH, assess the relevance of the PROMIS®, POSNA-PODCI and FPS-R items, and evaluate patient and caregiver understanding of item wording, recall period, and response options. Thematic analysis of verbatim transcripts was performed using Atlas.ti software.

**Results:** The most frequently reported symptoms were leg pain (notably in the knees, shins and ankles), bowing in the lower extremities and dental issues. Other symptoms included short stature, weakness, stiffness, fatigue, difficulty walking and unusual gait. Patients and their caregivers stated that the pain was considerably worse following physical activity, with some patients using the term 'bone pain' to describe the sensation. Patients were limited in doing activities such as sports and exercise, getting ready for school and boarding the school bus. The majority of the PROMIS®, POSNA-PODCI and FPS-R items were considered relevant and were well understood by most participants.

**Conclusions:** These findings support the content validity of the PROMIS® items, POSNA-PODCI and FPS-R® as assessments of the symptoms and impacts of pediatric XLH for use as endpoints in XLH clinical trials with children aged 5-12 years old. The next step is to perform psychometric validation of the instruments in a pediatric XLH population.

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#### FREQUENCY AND TIME OF CLINICAL SYMPTOM ONSET IMPACTING HEALTH-RELATED QUALITY-OF-LIFE DIMENSIONS IN PATIENTS WITH HYPOPHOSPHATASIA

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**Objectives:** Hypophosphatasia (HPP) is a rare, inherited, systemic, metabolic disease characterized by low serum alkaline phosphatase activity and poor skeletal mineralization. Little is known about health-related quality of life (HRQOL) in HPP patients (pts). Disease burden may be related to delayed developmental milestones, muscle weakness, ambulatory/functional difficulties, and pain. We assessed occurrence and timing of clinical symptoms impacting HRQOL of HPP pts.

**Methods:** A systematic review (MEDLINE, Embase; 1946-2016) was conducted of HPP cases with longitudinal ( $\geq 1$  y) follow-up. Data were extracted by age at onset (infancy, childhood, adolescence, adulthood). Frequency of clinical symptoms with HRQOL impacts (fractures, ambulation

difficulties, cranial abnormalities, surgeries, pain, premature tooth loss) and time to symptoms are reported.

**Results:** Of 3040 abstracts, 268 HPP cases were identified (age at presentation: in utero to 90 y). Median follow-up duration was 11 (9-15) years. 89.9% of pts experienced impact in  $\geq 1$  HRQOL dimensions, most frequently premature tooth loss (50.4%), fractures (35.4%; almost half had  $\geq 3$  fractures), ambulation difficulties (33.5%), pain (30.6%), cranial abnormalities (28.4%), and surgeries (23.9%). In infancy/childhood, cranial abnormalities, cranial surgery, premature tooth loss, and ambulation difficulties were most frequent; in adolescence/adulthood, fractures, extremity surgeries, pain, and ambulation difficulties were most frequent. Median (range) years to HRQOL impacts: respiratory difficulties, 0.3 (0-2); cranial abnormalities, 1 (0-12); premature tooth loss, 14 (1-60); pain, 44 (0-64); fracture, 46 (0-75); ambulation difficulties, 54 (0-90); surgery, 59 (0-83). Except for respiratory and cranial problems, risk of HRQOL impacts increased with age.

**Conclusions:** HPP has a significant impact on HRQOL across all ages. Cranial abnormalities and tooth loss were common among younger pts, fractures and pain were common among older pts, and ambulation difficulties and surgeries were common across all ages. These clinical symptoms are frequent and can have substantial HRQOL impacts that generally increase with age. The full burden of HPP as a systemic disease is yet to be fully understood.

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#### BONE MASS AND BODY COMPOSITION IN ADOLESCENTS WITH EXCESS WEIGHT

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**Objectives:** This study aimed to evaluate bone mass and body composition in overweight adolescents.

**Methods:** Cross-sectional study in 85 adolescents of both sex (41 males) aged 10 and 19 years with weight excess. Weight excess was categorized into overweight and obesity according WHO criteria using body mass index (BMI) Z-scores for age and sex. The presence of metabolic syndrome was evaluated according Cook *et al.* Dual X-Ray absorciometry (DXA) at lumbar spine (LS), total body (TB), femoral neck (FN) and total femur (TF) were performed (Explorer, Hollogic).

Anthropometry was performed before DXA examination. Bone mineral density (BMD) was expressed as Z-score. Lean mass index and fat mass index was calculated dividing kilograms per stature squared. Densitometric parameters were categorized by sex, age group (10-14 and 15-19 years), presence of metabolic syndrome and weight excess. Mean, standard deviation and relative frequencies with 95% confidence interval (CI) were used to describe data and Student's t-test to compare categories. It was considered significant a p value  $<0.05$ .

**Results:** Mean age was  $13.3 \pm 2.1$  (CI:12.8-13.7) and mean BMI was  $1.8 \pm 0.5$  (CI:1.6-1.8). The majority (72.9%) was in the age

group 10-14 years (CI:63.5-82.3%; n=62). Overweight was present in 64.7% (CI: 54.5-74.8%; n=55) and metabolic syndrome in 18.8% (CI:10.5-27.1%; n=16). Overweight adolescents presented lower bone mass in all sites (LS:  $0.0 \pm 1.1$  vs  $0.7 \pm 1.1$ ; FN:  $0.4 \pm 1.1$  vs  $1.5 \pm 1.1$ ; FT:  $0.1 \pm 1.1$  vs  $0.9 \pm 1.0$ ; TB:  $-0.2 \pm 1.1$  vs  $0.3 \pm 1$ ; p $<0.02$ ). Higher fat mass (%) and lower lean mass index ( $\text{kg}/\text{m}^2$ ) was observed in the group aged 10-14 years ( $37.0 \pm 6.3$  vs  $33.2 \pm 6.4$ ;  $17.6 \pm 2.8$  vs  $19.2 \pm 2.0$  respectively; p $<0.02$ ). The same occurred in female adolescents. They had higher fat mass (%), and lower lean mass index ( $39.2 \pm 4.0$  vs  $33.1 \pm 6.9$ ;  $17.0 \pm 2.8$  vs  $18.9 \pm 2.3$  respectively; p $<0.001$ ). The presence of metabolic syndrome was not associated to BMD or body composition parameters. There were no differences in fat mass index ( $\text{kg}/\text{m}^2$ ) considering sex, age group or metabolic syndrome.

**Conclusions:** Obesity was associated to higher bone mass in a group of adolescents predominantly 10-14 years old. Younger adolescents and female presented higher percentage of fat mass and lower lean mass ( $\text{kg}/\text{m}^2$ ).

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#### PREVALENCE OF FRACTURES IN INDIVIDUALS WITH TURNER SYNDROME IN THE UNITED STATES: RESULTS FROM A NATIONAL SURVEY

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**Objectives:** Common features of Turner Syndrome (TS) are estrogen deficiency and skeletal dysplasia, factors that may contribute to poor bone health. Prevalence of fractures in persons with TS in the USA is not well described. Our objective was to describe prevalence of fractures and identify risk factors in girls and women with TS.

**Methods:** Members of 3 national TS advocacy groups participated in an anonymous online survey (Nov. 2016 – Mar. 2017). Participants completed the survey on behalf of themselves or their child. Analyses were stratified by responder status as self-responders were older and medical care likely differed from current TS guidelines.

**Results:** 711 individuals completed the survey. Fractures occurred in 41%. Results are shown in Table 1. During childhood (0-12y), 22.8% reported at least one fracture; during puberty (13-20y), 16.3% and during young adulthood (21-50y), 36.3%. In women with TS age  $>50$ y (postmenopausal), 18.1% report at least one fracture during these years.

In individuals reporting a history of fracture, 27.9% reported a perceived balance problem compared to 19.8% of individuals without a fracture (p=0.01). Individuals with history of hearing loss (47.5%) were more likely to sustain fractures compared to individuals with normal hearing (36.9%); p=0.008. After controlling for age and hearing loss, odds of prior fracture in those with balance problems was still 49% more likely than for those without (p=0.04, 95% CI 1.02,



2.19). Individuals with TS reported physical activity a median of 3 days/week. Those without fracture reported more physical activity than those who had a history of fracture ( $p=0.01$ ).

**Conclusions:** This large survey of individuals with TS in the USA estimates the fracture prevalence at 41% with higher rates in self-responders likely due to older age and differences in estrogen replacement therapy, although more than a quarter of the younger population also reported fractures. Balance problems may be an unrecognized risk factor for fracture in individuals with TS. Further research is needed to investigate this and other factors contributing to impaired bone health in this population.

Table 1: Demographics, fracture history, and risk factors for fracture in persons with TS in USA

	Self-Responder (n=359)	Parent-Responder (n=352)
<b>Age - Individual with TS</b>	41.1 (13.8) [range: 13, 75]	12.7 (7.9) [range: 1, 48]
<b>Race (%)</b>		
- White	267 (74.4%)	247 (70.2%)
- African American	4 (1.1%)	6 (1.7%)
- Other	26 (7.2%)	35 (9.9%)
- Prefer not to answer	62 (17.3%)	64 (18.5%)
<b>Fracture History</b>		
Persons with at least 1 fracture (%)	200 (55.7%)	97 (27.6%)
Persons with multiple fractures (%)	92 (25.6%)	32 (9.1%)
Mean age at first fracture	19.8 (14.4)	7.4 (4.6)
<b>Location of 1<sup>st</sup> fracture (%)</b>	In 200 individuals with fracture	In 97 individuals with fracture
<i>Axial Skeleton</i>	23 (11.5%)	15 (15.5%)
- Head/face	9 (4.5%)	1 (1%)
- Clavicle	9 (4.5%)	11 (11.3%)
- Ribs	1 (0.5%)	1 (1%)
- Spine	3 (1.5%)	2 (2.1%)
- Pelvis	1 (0.5%)	0 (0%)
<i>Upper extremity</i>	80 (40%)	42 (43.3%)
- Upper arm/shoulder	5 (2.5%)	6 (6.2%)
- Elbow	2 (1%)	2 (2.1%)
- Forearm/Wrist	52 (26%)	34 (35%)
- Hand/fingers	21 (10.5%)	9 (9.3%)
<i>Lower Extremity</i>	65 (32.5%)	21 (21.6%)
- Hip	2 (1%)	0 (0%)
- Upper leg	2 (1%)	1 (1%)
- Knee	5 (1.4%)	1 (1%)
- Lower leg/Ankle	24 (12%)	12 (12.4%)
- Foot/toes	32 (16%)	7 (7.2%)
<b>TS diagnosis</b>		
- Prenatal	10 (2.8%)	78 (22.2%)
- Infancy	69 (19.2%)	95 (27.0%)
- Childhood	101 (28.1%)	114 (32.4%)
- Adolescence/teenager	111 (30.9%)	27 (7.7%)
- Adult	33 (9.2%)	2 (0.6%)
<b>Karyotype Distribution (%)</b>		
- 45X	94 (26.2%)	134 (38.1%)
- 45X, 46XX	89 (24.8%)	91 (25.8%)
- 45X, 46XY	18 (5.0%)	24 (6.8%)
- Other	17 (4.7%)	34 (9.7%)
<b>Growth and Pubertal Development</b>		
Age at breast development	14.8 (2.7)	12.7 (2.0)
Age at menses	15.2 (2.4)	13.6 (1.7)
Use of ERT (%)	293 (93.0%)	113 (37.7%)
- Age at start of ERT	15.8 (3.6)	13.4 (3.5)
- Age at stop of ERT	36.5 (12.5)	N/A
Use of GH (%)	159 (49.7%)	239 (79.4%)
<b>Report of Balance Problem (%)</b>	89 (27.3%)	76 (23.8%)
<b>Report of Hearing Loss (%)</b>	191 (60.8%)	106 (35.3%)

Results reported as mean and standard deviation unless otherwise noted. ERT: Estrogen Replacement Therapy; GH: Growth hormone

**Objectives:** The aim of this study was to detect and analyze PHEX gene mutations in 2 patients with X-Linked hypophosphatemic rickets, further to clarify the genetic etiology.

**Methods:** PCR-Sanger sequencing method was used to analyze the related gene mutations in 2 patients with X-Linked hypophosphatemic rickets from the genome level

**Results:** Two PHEX gene mutations, including 1 frameshift mutation c.931dupC and 1 abnormal splicing site mutation IVS14+1G>A, were found in 2 patients with X-Linked hypophosphatemic rickets, respectively, but the phenotype of their parents was normal.

**Conclusions:** Our study identified c.931dupC and IVS14+1G>A as 2 novel mutations in PHEX gene as the pathogenic mutations. This is important for understanding the genetic basis of X-Linked hypophosphatemic rickets and may provide new insights into the cause and diagnosis of XLH.

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## NEONATAL SEVERE HYPERPARATHYROIDISM IN A SUDANESE FAMILY : AN UNUSUAL PRESENTATION

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**Objectives:** Neonatal severe hyperparathyroidism due to Calcium Sensing Receptor mutation (CaSR) is rare. The heterozygous form has a benign presentation whereas the homozygous form is severe. In this report we present two siblings, one with a homozygous mutation of CaSR gene and the other heterozygous for the same mutation. Both presented with a severe phenotype. In addition both had hypercalciuria.

**Methods:** Case 1 : Female of seven months presented with a history of constipation, failure to thrive, hypotonia and global developmental delay. She was discovered to have hypercalcemia following multiple bone fractures. Both parents were first degree relatives. There was a family history of hyperparathyroidism in a maternal relative treated by parathyroidectomy. Our patient failed to respond to medical treatment (fluids and frusamide, bisphosphonates and calcitonin) and required parathyroidectomy.

Case 2 : Male of eight months presented with constipation, failure to thrive, hypotonia, polyuria and global developmental delay. He failed to respond to medical treatment and required parathyroidectomy.

**Results:** Case 1 : Serum Calcium was high (22.2 mg/dl). The parathyroid hormone was high (229pg/ml). Serum phosphate was low (1.4 mg/dl) Alkaline phosphatase 178 IU/L. The urinary calcium creatinine ratio was high 0.026 (>0.01). Bone X rays showed multiple fractures. Tissue biopsy of parathyroid gland showed parathyroid hyperplasia no evidence of adenomas. Currently she is asymptomatic with normal Calcium levels. Sequencing analysis revealed a heterozygous Missense mutation : c.2038 C>T p (Arg680Cys).

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## TWO NOVEL PHEX GENE MUTATIONS IN CHINESE PATIENTS WITH X-LINKED HYPOPHOSPHATEMIC RICKETS

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Case 2: Serum Calcium was high (19.5 mg/dl) . The parathyroid hormone was high (838.5pg/ml) . Serum phosphate was low ( 1.1mg/dl ) . Alkaline phosphatase was (235 IU/L) . The urinary Calcium- Creatinine excretion was high 4078.2 mg/gm ( 30-560 mg/gm ) . Bone X rays showed demineralization. Tissue biopsy of parathyroid gland showed parathyroid hyperplasia. Currently he is asymptomatic with normal Calcium levels . Sequencing analysis revealed a homozygous form of the same mutation. Genetic analysis of both parents is pending.

**Conclusions:** We report two siblings with an inactivating mutation of CaSR gene with hypercalciuria . We highlight that the heterozygous mutation can be severe.

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#### SEVERE HYPERCALCEMIA AFTER DISCONTINUATION OF LONG- TERM DENOSUMAB TREATMENT

*Pinar S Isguven, MD; Berat Sabit, MD; Ece C Okur, MD; Dilek Aydin, MD, University of Sakarya, Sakarya Medical School, Sakarya, Turkey*

**Objectives:** Denosumab is commonly used as an anti-resorptive agent for treatment of osteoporosis. Denosumab provides sustained suppression of bone turnover in osteolytic bone disease. We present a case report of hypercalcemia associated with discontinuation of treatment with denosumab.

**Methods:** A six-year-old boy was diagnosed with resectable giant cell tumor of bone (GCTB), which was an osteolytic, locally aggressive neoplasm in mandibular, and the tumor was surgically removed when he was 2.5 years old. He was operated 4 times until he was 5 years old because of local tumor recurrence. Administration of denosumab for 10 months showed good clinical response without any major complications. However 5 months after the last denosumab administration, he developed worsening nausea and fatigue and 4 days later he was admitted to an emergency clinic and diagnosed with severe hypercalcemia (15 mg/dl) accompanied by mild dehydration.

**Results:** Laboratory tests showed suppressed level of parathyroid hormone and 1-25-dihydroxy vitaminD3. Renal ultrasonography showed medullary nephrocalcinosis. The patient was treated with intravenous saline infusion along with furosemide and methyl prednisolone. However, the levels of serum calcium remained significantly elevated (13 mg/dl). Intravenous pamidronate in the dose of 1 mg/kg/day in a 3-hour infusion was given only once and the patient recovered from the life-threatening condition.

**Conclusions:** In conclusion, hypercalcemia may be an important side effect of denosumab treatment in pediatric patients. Most importantly, it is essential to provide intensive follow-up and careful monitoring during the use and after the discontinuation of denosumab therapy in pediatric patients.

P2-217

#### EFFECTIVENESS OF LOSARTAN ON BONE METASTASIS AND BODY MASS INDEX IN CAMURATI-ENGELMANN DISEASE

*Yoo-Mi Kim, MD; Su-Young Kim, MD, Pusan National University Children's Hospital, Yangsan, N/A, Korea, Republic Of; Chong Kun Cheon, MD, Pusan National University Children's Hospital, Yangsan, Korea, Republic Of*

**Objectives:** Camurati-Engelmann disease (CED) is a rare autosomal dominant genetic disorder caused by mutation of *TGFB1* on chromosome 19q13.1. TGFβ plays a role to inhibit adipogenesis and bone resorption and enhance bone formation and CED manifested with progressive bone thickness, muscle weakness, and low subcutaneous fat. Losartan as an anti-TGFβ effect have been introduced for CED patients to reduce bone pain and increase physical activity. In this study, we demonstrated the effectiveness of losartan in bone turnover and body mass index in CED patients.

**Methods:** We used losartan as a treatment for three related Korean CED patients including two siblings, a 10-year-old boy, a 6-year-old girl, and a 45-year-old mother. The heterozygote of p.R218C in *TGFB1* was identified in this family. After genetic confirmation, all subjects treated with losartan and the dose was gradually increased from 1 mg/kg/d to 1.5 mg/kg/d and 2 mg/kg/d every 3 months. Every 3 months, the body weight, height, body mass index (BMI) and pain score were measured and serum bone specific alkaline phosphatase (BAP), C-terminal telopeptide (CTX) or N-terminal telopeptide were performed before medication and CTX and BAP were follow-up every 6 months.

**Results:** All of the subjects had low BMI (mean -2.73 SDS) and diaphyseal thickening of long bone on X-ray. One year after losartan administration, not only reduced pain score but also weight gain was observed and the mean BMI was increased to -2.48 SDS. The Tanner stage was I in two siblings and mother was in menopausal state 2 years ago. The BAP level representing bone formation was decreasing (mean difference -12.9 μg/L) at last evaluation. In CTX level, older brother showed increasing CTX level (from 0.60 to 1.17 μg/L) but it was decreasing in a younger sister (from 1.52 to 1.01 μg/L) and a mother (from 0.91 to 0.48 μg/L) after losartan. Two children were tolerated with 2 mg/kg/d of losartan, but the mother complained of dizziness at dose of 100mg/d of losartan and reduced to 25mg/d at 12 months.

**Conclusions:** Three related CED patients showed improving BMI and decreasing BAP after one year of losartan. Beside steroid treatment, TGFβ antagonist may be an alternative and effective drug to modify the disease course including poor weight gain and progressive bone formation in CED patients.

P2-218

#### A HETEROZYGOUS FLNB MUTATION IN A JAPANESE BOY WITH SPONDYLOCARPOTARSAL SYNOSTOSIS SYNDROME AND HIS MOTHER WITH SHORT STATURE.

*Hitomi Shimizu, MD; Satoshi Watanabe, MD; Hiroyuki Moriuchi, MD; Koh-Ichiro Yoshiura, PhD; Sumito Dateki, MD, Nagasaki University, Nagasaki city, Japan*

**Objectives:** Spondylometaphyseal dysplasia (SMD), which is characterized by disproportionately short stature, progressive fusion of the vertebrae, scoliosis, lordosis, carpal and tarsal synostosis, and mild facial dysmorphism, is a rare autosomal recessive disease caused by *FLNB* mutations. We herein report the case of a Japanese SMD patient and his mother who displayed a heterozygous missense *FLNB* variant.

**Methods: Patients:** A Japanese male patient was born at 34 weeks of gestation with a body length of 43 cm (-0.7 SD) and a body weight of 2.35 kg (+0.3 SD). At 14 months of age, the patient was referred to our department due to severe short stature. The patient was 67.2 cm (-3.7 SD) in height, 7.8 kg (-2.2SD) in body weight, and had an OFC of 47 cm (+1.1SD). He also showed mild facial dysmorphism with frontal bossing and anteverted nares. A skeletal survey showed vertebral anomalies with block vertebrae, mild scoliosis and carpal and tarsal synostosis. On the last examination at 27 months of age, the patient was 72.4 cm (-4.3 SD) tall. His motor and mental development was normal. The parents were non-consanguineous. The patient's father and elder brother were phenotypically normal, while the mother showed short stature (147 cm, -2.2 SD).

**Results: Genetic analyses:** We performed whole-exome sequencing in the family, and identified a rare heterozygous missense variant in the *FLNB* gene (p.Ile160Met) in the patient and the patient's mother.

**Conclusions:** While the present patient showed the characteristic skeletal features and short stature of SMD, his mother only showed short stature. Homozygosity or compound heterozygosity for frameshift or nonsense mutations in *FLNB* has previously been reported to be associated with SMD. The present study suggests that SMD can be inherited in an autosomal dominant pattern with variable penetration. Further studies are needed to clarify the genetic mechanisms that lead to SMD.

P2-219

## NOVEL ACTIVATING MUTATION OF THE CALCIUM-SENSING RECEPTOR GENE

*Svetlana Ten, MD, Lutheran Medical Center, Brooklyn, NY, United States; Geoffrey N Hendy, PhD, McGill University, Montreal, QC, Canada; David E.C Cole, PhD, University of Toronto, Toronto, ON, Canada*

**Objectives:** Autosomal dominant hypoparathyroidism (ADH) is caused by activating mutations of the calcium-sensing receptor (CaSR). Here we report an Italian family with affected daughter and mother who were found to carry mutations in the CaSR gene.

**Methods: Case Report**

**Results:**

An 11-yr-old girl was seen because of fatigue and was found to have low calcium. She was born after normal pregnancy at 37 weeks, BW 6 lbs 4 oz. She developed seizures at 5 days of life and was treated with phenobarbital for 9 months. Later in life she had history of febrile seizures. Mother, maternal grandmother, maternal uncle and maternal aunt have low

calcium and low PTH and were treated with calcium and calcitriol. Maternal uncle was diagnosed at 39 yrs. of age and maternal aunt was diagnosed at 37 yrs. of age. Physical examination was normal. Laboratory tests revealed hypocalcemia (7.3 mg/dL; NL 9.1-10.5), hyperphosphatemia (8.8 mg/dL; NL 2.5-5.3), normal 1,25-dihydroxycholecalciferol ([1,25(OH)<sub>2</sub>D] 66 pg/mL; NL 15-90), low 25-hydroxycholecalciferol ([25(OH)D] 20.4 ng/mL; NL 30-100) and decreased iPTH (5.0 pg/mL; NL 15-65). The 24-hr urinary calcium excretion and kidney sonogram were normal. The patient was treated with calcium carbonate and calcitriol, dosages were adjusted to maintain a serum calcium level within the lower end of the normal reference range. Patient and her mother are heterozygous for a c.359T>C; p.I120T mutation in the CaSR gene. Both mother and daughter are also heterozygous for the R990G polymorphism.

**Conclusions:** It is important to analyze mutation of the CaSR gene in cases of acquired hypocalcemia with low iPTH. Patients with ADH can develop nephrocalcinosis and renal impairment during treatment with calcium and vitamin D. Mutational analysis of the CaSR gene can be considered to assess the risk of nephrocalcinosis during treatment of PTH-deficient hypoparathyroidism

## POSTER SESSION 2

**Friday, September 15, 2017, 11:30am-12:30pm**

### P2 - Ethics in endocrinology

#### P2-400 – P2-401

P2-400

#### PATIENT PORTALS MAY IMPROVE COMMUNICATION, BUT DO THEY WIDEN THE HEALTH DISPARITIES GAP?

*Kelsea Halpin, MD; Ryan McDonough, DO; Janelle Noel-Macdonnell, PhD; Yun Yan, MD, Children's Mercy Kansas City, Kansas City, MO, United States*

**Objectives:** Online Patient Portals are becoming increasingly popular in health care and have great potential to improve communication between patients and their providers. However, their use often requires that patients have an email account, internet access, and be literate in English. Therefore, this promising technology also has the potential to contribute negatively to inequities in health care. We sought to evaluate for disparities in Patient Portal use with a focus on obese pediatric patients with insulin resistance and/or type 2 diabetes, given the propensity of these diagnoses to disproportionately impact low-income, minority patients.

**Methods:** We retrospectively reviewed the records of patients 14 to 18 years of age, seen in Endocrine/Diabetes Clinic for insulin resistance and/or type 2 diabetes, following the implementation of a Patient Portal at our institution. There were 593 eligible patients seen between May 28, 2014 and August 30, 2016. Proportions of patients signed up for the Patient Portal were compared between populations based on race, primary language, gender, and insurance

provider. We also compared Patient Portal use between patients frequenting our 4 urban clinics vs. 8 rural outreach clinics. Data were explored using Chi-Square analyses.

**Results:** Statistically significant differences among Patient Portal use were found between White vs. Non-White (p 0.001), English speaking vs. Non-English speaking (p 0.013), private vs. non-private (Medicaid/self-pay) insurances (p 0.001), and urban vs. rural clinic patients (p 0.014). No differences in Patient Portal use were found between male and female patients (p 0.328).

**Conclusions:** These results demonstrate that Patient Portal access was more common among the parents of obese children with insulin resistance and/or type 2 diabetes from urban, white, affluent populations who speak English. Given low-income, minorities are disproportionately affected by obesity and type 2 diabetes, clinicians must be mindful to ensure that incorporation of Patient Portal technology does not contribute further to health inequities in these populations.

Patient Portal Use in Obese Youth with Insulin Resistance and/or Type 2 Diabetes									
	White	Non-White	English-Speaking	Non-English-Speaking	Private Insurance	Medicaid/Self-Pay	Urban Clinic	Rural Clinic	Male
Patients (n)	242	344	532	60	244	349	439	154	239
Patient Portal Access (%)	22.3	11.6	17.3	5	23.4	10.9	18.2	9.7	14.2
P-value	0.001		0.013		0.001		0.014		0.328

P2-401

**ETHICS IN PEDIATRIC ENDOCRINOLOGY: CURRICULUM DEVELOPMENT FOR FELLOWS AND FACULTY**

Rohan K Henry, MD, Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, OH, United States; Leena Nahata, MD, Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, OH, United States

**Objectives:** Pediatric endocrinologists frequently face ethical dilemmas in clinical practice. Concerns may arise in the use of medications to enhance an otherwise healthy child's height, hormone treatments in cognitively impaired youth, gender affirming therapy in youth with gender dysphoria, or new technologies such as fertility preservation. The objectives of this PES Ethics Committee initiative were to (a) examine whether fellows and faculty believe that "currently there is an effective ethics curriculum in place" and (b) assess whether a curriculum comprised of case-based modules created by the committee would be beneficial in learning about ethics.

**Methods:** Using 2 case-based modules: *Ethical Issues in Fertility Preservation in Klinefelter Syndrome* and *Ethical Principles Regarding Endocrine Care of Disabled Children*, pre- and post- surveys, geared primarily towards fellows, were distributed to 8 large pediatric endocrine programs (home programs and affiliates of PES Ethics committee members were invited to participate). Using a 5-point Likert scale, questions examined self-reported Knowledge (K) of the ethical pillars (beneficence, non-maleficence, autonomy and justice), Attitudes (A) regarding importance of these principles, and likelihood of applying these principles to clinical Practice (P), as well as perceived need/benefit of this curriculum.

**Results:** Surveys were completed by fellows (n=26) and faculty (n=6) at 6 of the 8 large pediatric endocrine programs (75% response rate). Only 24.2% of respondents felt that an effective ethics curriculum existed. KAP scores improved after participants completed the modules with knowledge scores showing the greatest improvement. 88% of respondents "strongly agreed" (n=17) or "agreed" (n=11) that the curriculum would be a helpful addition to pediatric endocrine fellowship training. Additionally, all faculty felt that the curriculum would be helpful for faculty to learn about ethical principles applicable to clinical practice.

**Conclusions:** These findings suggest that the modules were helpful in advancing knowledge of ethical principles, and that this curriculum could fulfill an unmet need for training fellows and faculty about ethical principles applicable to pediatric endocrinology practice.

**POSTER SESSION 2**  
**Friday, September 15, 2017, 11:30am-12:30pm**  
**P2 - Fetal and neonatal endocrinology and metabolism, including hypoglycemia**  
**P2-500 – P2-530**

P2-500

**HIGH AROMATASE TRANSCRIPT VARIANT EXPRESSION IN HUMAN PLACENTAL TISSUES FROM PRETERM AND TERM DELIVERIES OF LARGE FOR GESTATIONAL AGE NEWBORNS**  
Paula Aliberti, MS/MA, Hospital de Pediatria Prof. Dr. Juan P. Garrahan, Buenos Aires, Argentina; Romina Sainz, MS/MA; Andrea Servian, MS/MA, Hospital de Pediatria Garrahan, Buenos Aires, Argentina; Cristina Patricia Nemer, MD; Claudia Cannizzaro, MD, Hospital de Pediatria Garrahan y Hospital Materno Infantil Ramón Sardá, Buenos Aires, Argentina; Marco Aurelio Rivarola, MD, Hospital de Pediatria Garrahan, Buenos Aires, Argentina; Alicia Belgorosky, MD, PhD, Hospital de Pediatria Prof. Dr. Juan P. Garrahan, Buenos Aires, Argentina; Nora Saraco, PhD, Hospital de Pediatria Garrahan, Buenos Aires, Argentina

**Objectives:** Aromatase (Aro) is the key enzyme for estrogen biosynthesis from androgens and, in human placenta, it is expressed exclusively in the syncytiotrophoblast. It has been reported that in small and large newborns as well as in patients with Aro deficiency the prevalence of metabolic syndrome in adulthood tends to increase. We previously described a splicing variant of Aro mRNA (Intron9) that translates into inactive Aro enzyme. Our objective was to compare Aro mRNA variants expression in placenta from preterm (PT) (<35 weeks) and term large for gestational age (LGA) newborns to its expression in term adequate for gestational age (AGA) newborns. We propose that differential Aro mRNA variant expression relates to changes in Aro activity and hence to the regulation of the intrauterine estrogen-androgen balance.

**Methods:** Total RNA was extracted from placentas of PT (GA: 30-35 weeks, n=4), LGA (GA: 39-41 weeks, n=8) and two

subgroups of AGA: AGA1 (GA: 37-38 weeks, n=8) and AGA2 (39-41 weeks, n=11). Aro mRNA variants were analyzed by qRT-PCR with primers for total (TotAro, Ex2-Ex3), intron 9 (IN9, Ex8-In9) and active (ActAro, Ex9-Ex10) Aro, and Cyclophilin (PPIA) as housekeeping gene. Statistics (Student test) were performed on  $\Delta$ Ct data.

**Results:** TotAro was higher in PT than in AGA1 ( $8.91 \pm 3.35$  vs  $1.58 \pm 0.40$  AU, mean  $\pm$  SE), while it was lower in LGA than in AGA2 ( $0.81 \pm 0.36$  vs  $2.12 \pm 0.64$ ),  $p < 0.05$ . Analysis of each transcript variant related to total Aro showed that ActAro/TotAro ratio was higher in PT than in AGA1 ( $2.26 \pm 0.26$  vs  $0.66 \pm 0.20$ ) as well as in LGA than in AGA2 ( $2.42 \pm 0.31$  vs  $1.37 \pm 0.28$ ),  $p < 0.05$ . No significant difference was found for IN9/TotAro ratio when comparing LGA to AGA2.

**Conclusions:** The observed high Active Aro mRNA expression in preterm placentas coincides with reports of maternal salivary estriol and plasma estradiol increments in preterm parturition. These data suggest a role for placenta Aro in modulating local estrogen production associated to prematurity. In addition, the higher ActAro/TotAro ratio observed in LGA than in AGA suggests that the estrogen-androgen balance in placenta tissue might be involved not only in prematurity but also in fetal programming, determining disorders later on postnatal life.

P2-501

#### TRANSIENT NEONATAL DIABETES MELLITUS IN PATIENTS WITH MUTATION OF ABCC8 AND KCNJ11 GENES

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**Objectives:** Neonatal diabetes mellitus (NDM), characterized by hyperglycemia and the need for insulin treatment within the first 6 months of life. Approximately half of NDM cases are transient and resolve at a median age of 3 months (transient NDM: TNDM), while the remaining cases develop into a permanent form of diabetes. Most cases of TNDM (approximately 70%) are caused by abnormalities in chromosome 6q24. In a few patients, activating mutations in the genes, which encode the two subunits of the  $\beta$ -cell ATP-sensitive potassium channel, i.e. *ABCC8* and *KCNJ11*, have been reported to be associated with TNDM.

The aims of study was to describe clinical characteristics and genetic finding in 3 patients with TNDM due to ATP sensitive potassium channel: *ABCC8*, *KCNJ11*

**Methods:** Case series report. All exons of *KCNJ11*, *ABCC8* were amplified from genomic DNA and directly sequenced

**Results:** Three cases (one girl and two boys) onset at  $82.6 \pm 67.4$  days of age with gestation age of  $39.5 \pm 0.5$  weeks, birth weight of  $3200 \pm 700$ g. All cases admitted with the features of severe diabetes ketone acidosis, blood glucose levels of  $37.3 \pm 5.7$  mmol/l; HbA1C of  $8.8 \pm 4.4$  %; pH of  $6.99 \pm 0.09$ ;  $\text{HCO}_3^-$  of  $3.06 \pm 1.06$  mmol/l; BE of  $-27.6 \pm 1.4$  mmol/l. Sequence

analysis of coding and flanking intronic regions of the *KCNJ11* and *ABCC8* genes showed heterozygous mutation for the *KCNJ11* missense mutation p.E229K in patient 1, p.R50Q in patient 2 and heterozygous for the previously reported *ABCC8* missense mutation p.R1183W in patient 3. Patient 3 was stopped insulin injection at the age of 6 months of age. At his last examination at the age of 13 months, HbA1c was 5.8% with normal blood glucose. Patient 1 and 2 were transferred to sulfonylurea after of diagnosis 9 months and 14 months, they were stopped sulfonylurea after 2 months and 36 months respectively. After stop treatment 52 months and 2 months, HbA1C was 5,7% and 6,5% with normal blood glucose, respectively. All of them have normal motor and mental development.

**Conclusions:** It is important to perform screening gene mutation for patients with diabetes before 6 months of age to control blood glucose and follow up the patients.

P2-502

#### THE IMPACT OF GESTATIONAL ENDOCRINE DISORDERS ON BREAST MILK COMPOSITION AND INFANT GROWTH

Brigid Gregg, MD; Lindsay Ellsworth, MD; Emma Harman, BS/BA; Elizabeth John, Undergraduate ; Joanna Yeh, Undergraduate , University of Michigan, Ann Arbor, MI, United States

**Objectives:** Background: Maternal endocrine disorders are increasingly prevalent co-morbidities during pregnancy with the potential to impact maternal health, fetal development, newborn health and long-term childhood outcomes. Limited data exists on changes in breast milk composition associated with maternal metabolic disease in pregnancy. Based on existing data from animal models, we hypothesize that maternal metabolic disease results in alterations in insulin signaling. This then leads to changes in milk fat content and fatty acid profile.

Our study objective is to determine if maternal metabolic disease leads to changes in milk composition that then impact infant growth trajectory.

**Methods:** We are conducting a prospective cohort study of mothers with gestational diabetes mellitus (GDM), type 1 diabetes mellitus, type 2 diabetes mellitus, obesity, and polycystic ovary syndrome (PCOS) in comparison to healthy mothers. This study has been approved by the University of Michigan Institutional Review Board. We perform metabolomic analysis on human milk to evaluate fatty acid content through mass spectrometry. We will determine if maternal factors including metabolic disease diagnosis, body mass index, and glycemic control influence milk composition. We will then correlate infant growth trajectory with milk fat alterations. We also examine the levels of growth promoting hormones and putative obesity-associated microRNA species in the milk samples.

**Results:** We have enrolled 48 mother-baby pairs including 25 healthy, 10 obese, 8 PCOS, and 5 GDM mothers. Mothers had a mean maternal age of 30 years, mean gestation age of 40 weeks, and 31% delivered by C-section. In our existing cohort,

growth from birth to 2 months does not reveal a significant difference in weight or length however there is an indication that infant head circumference differs by maternal metabolic disease category by 2-way ANOVA testing. Breast milk composition analysis is underway.

**Conclusions:** Recruitment is ongoing with the goal of expansion of the diabetes mellitus cohorts in order to evaluate for significant differences in breast milk fat composition and infant growth trajectory in the setting of maternal metabolic disease.

P2-503

**MATERNAL STRESS DURING PREGNANCY IS ASSOCIATED WITH DECREASED CORTISOL AND CORTISONE LEVELS IN INFANT HAIR AND INCREASED LEVELS IN MATERNAL HAIR.**

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**Objectives:** Maternal stress during pregnancy has been associated with unfavorable infant neurodevelopment, possibly through increased placental transfer of maternal glucocorticoids (GCs). Infant hair GCs could reflect the intra-uterine GC regulation. We assessed whether maternal stress experienced prenatally and/or directly postpartum (pp) is associated with infant and maternal hair GCs pp.

**Methods:** Sixty-six mother-infant pairs that attended an outpatient psychiatric-obstetric-pediatric (POP) department and 107 control pairs donated hair pp. Hair cortisol and cortisone levels were determined by LC-MS/MS. Maternal stress was assessed with the Hospital Anxiety and Depression Scale (HADS) during the first (n=45) and third trimester (n=56) in POP mothers, and pp in all mothers (n=169). Linear regression was used to assess the effect of maternal stress during and/or after pregnancy, as well as antidepressant use on maternal and infant hair GCs.

**Results:** Maternal hair GCs were positively associated with elevated anxiety subscores pp (log. transformed  $\beta$  [95%CI]: cortisol 0.15 [0.00; 0.30], cortisone 0.17 [0.05; 0.29]). Maternal hair GCs were not associated with depression subscores pp or first and third trimester HADS-scores. Infant hair cortisol was negatively associated with elevated maternal stress during the first (-0.19 [-0.39; 0.00] and third trimester (-0.17 [-0.33; 0.00]) as well as pp (-0.10 [-0.21; 0.00]). A similar pattern was observed for infant hair cortisone. Elevated HADS-scores throughout the entire pregnancy showed the strongest negative association with infant hair GCs.

Antidepressant use was associated with elevated GCs, but did not affect GCs in infant hair.

**Conclusions:** Elevated maternal stress was suggested to suppress fetal HPA-axis activity, possibly through an increased maternal HPA-axis activity. Persistent maternal stress throughout pregnancy was associated with the most suppression of hair GC levels in infants. Studies on neurodevelopment are needed to estimate the clinical relevance of these findings.

P2-504

**DIFFERENCES IN GENE AND PROTEIN EXPRESSION OF KLOTHO IN HUMAN TERM (T) AND PRETERM (PT) SMALL (SGA) AND APPROPRIATE (AGA) FOR GESTATIONAL AGE PLACENTAS:EFFECTS OF KLOTHO ON IGF-I ACTIVITY.**

German Iñiguez, PhD, University of Chile/Faculty of Medicine, Santiago, Chile; Pedro Gallardo, BS/BA, University of Chile, School of Medicine, Santiago, Chile; René González, MS/MA, University of Valparaíso, School of Medicine, Valparaíso, Chile; Mirna García, MD; Elena Kakarieka, MD, Hospital Clínico San Borja Arriarán, Santiago, Chile; Sebastián San Martín, PhD, University of Valparaíso, School of Medicine, Valparaíso, Chile; María Cecilia Johnson, PhD; Verónica Mericq, MD, University of Chile, School of Medicine, Santiago, Chile; Fernando Cassorla, MD, School of Medicine, University of Chile, Santiago, Chile

**Objectives:** To determine Klotho gene expression and protein immunostaining in term (T-SGA y T-AGA) and preterm (PT-SGA y PT-AGA) human placentas. We also studied the effect of Klotho on the IGF-IR and AKT activation induced by IGF-I

**Methods:** We studied 117 placentas from 32 T-SGA (birth weight (BW) =  $-1.74 \pm 0.08$ SDS), 37 T-AGA (BW=  $0.12 \pm 0.12$  SDS) , 20 PT-SGA (BW=  $-2.08 \pm 0.14$  SDS),and 28 PT-AGA (BW=  $-0.43 \pm 0.13$  SDS) newborns. We determined mRNA expression by RT-PCR in the chorionic (CP) and basal (BP) plates of the placentas, and the presence of Klotho was evaluated by immunohistochemistry (integral optical density, IOD). We developed placental explants incubation with IGF-I in the presence or absence of Klotho. Protein activation was studied by Western immunoblotting. Results are shown in the table as mean  $\pm$  SEM, and the differences were analyzed by Mann-Whitney.

**Results:**

		T-SGA	T-AGA
Klotho mRNA	CP	$0.51 \pm 0.08^*$	$1.26 \pm 0.06$
	BP	$1.23 \pm 0.14^*$	$0.55 \pm 0.08$
Klotho IOD	CP	$6023 \pm 605^*$	$7131 \pm 553$
	BP	$7476 \pm 523$	$7548 \pm 588$

\*p < 0.05 T-SGA vs T-AGA ; \*\* p < 0.05 T-SGA vs PT-SGA or T-AGA vs PT-AGA.



We also observed a significantly reduction on IGF-IR tyrosine activation induced by IGF-I 10 nM ( 2.4±0.5 arbitrary units (AU)) when preincubated with 2.0 nM of Klotho 1.3±0.3 AU) , similar results we observed on AKT threonine activation (13.7±2.3 vs 3.6±0.6 AU respectively).

**Conclusions:** We describe for the first time that Klotho mRNA and protein expression varies according to fetal growth and gestational age. In addition, Klotho appears to down-regulate the activation induced by IGF-I on IGF-IR and AKT,suggesting that Klotho may be regulating IGF-I activity in human placentas in relationwith intrauterine fetal growth. Supported by Fondecyt 111 0240

P2-505

**EVALUATION OF NEWBORN SCREENING PERFORMANCE FOR 21-HYDROXYLASE DEFICIENCY CONGENITAL ADRENAL HYPERPLASIA (21-OHD CAH) USING GESTATIONAL AGE- AND BIRTHWEIGHT-STRATIFIED LOGIC.**

*Sarah E Lawrence, MD, University of Ottawa, Ottawa, ON, Canada; Emeril Santander, BS/BA, Newborn Screening Ontario, Ottawa, ON, Canada; Matthew Henderson, PhD; Pranesh Chakraborty, MD, University of Ottawa, Ottawa, ON, Canada*

**Objectives:** Newborn screening (NBS) for CAH using fluorometric immunoassay (FIA) 17OHP was implemented in Ontario, Canada in 2010 with the addition of second tier testing using LC-MS/MS in 2012. A positive steroid profile is indicated by elevation of both 17OHP and ratio ([17-OHP + androstenedione]/Cortisol of > 0.4). This successfully improved the sensitivity and positive predictive value (PPV), but false positive rates remained high, particularly for premature babies.The objective was to evaluate the impact of changing from birth weight (BW) to gestation age (GA) stratification for 17-OHP in the first tier on the PPV, sensitivity and specificity of NBS for CAH.

**Methods:** All dried blood spot samples obtained through population-based newborn screening in Ontario from Sept 1, 2012 to December 31, 2015 were reported using existing BW-stratified logic. Retrospective application of GA-stratified logic was applied to this cohort.

**Results:** 440,875 samples were received and analyzed with results as shown for each method of stratification. See Table – next column

Parameter	BW-stratification	GA-stratification
Number of positives on 17OHP FIA	2750	1407
Number of positives after 2 <sup>nd</sup> tier screening with LC-MS/MS	856	200
Number of true positives	18	18
Number of false negatives	1	1

Positive predictive value	2.2 %	9.3%
Sensitivity	95 %	95 %

Moving from weight based to GA cut-offs, reduced the number of samples requiring steroid profiling by 49% and the number of referrals by 77% while maintaining a high sensitivity of 95%. The proportion of retrievals in premature babies < 36 weeks GA decreased from 86% to 10.5% of the screen positives.

**Conclusions:** The use of gestational age based cut-offs for 17-OHP in newborn screening with second tier steroid profiling has a more favourable PPV with no loss of sensitivity when compared to weight based cut-offs. The major impact is on the rate of false positive screening tests in premature infants.

P2-506

**GLYCEMIC LEVELS IN NORMAL NEWBORN**

*Raphael DR Liberatore Junior, PhD; Carlos E Martinelli Junior, PhD; Jose S Camelo Junior, PhD; Nathalia Azevedo, Student, Ribeirao Preto Medical School, Ribeirao Preto, Brazil*

**Objectives:** We proposed to check glycemic interstitial levels in the first 24 hs in a group of normal newborns

**Methods:** We proposed to check glycemic interstitial levels in the first 24 hs in a group of normal newborns using a glycemic sensor (Medtronic IproII) implanted subcutaneously in the very first hour after born. All babies were born with more than 38 weeks of gestational age, with no medical problem, and Apgar Score of more than 8 in the first minute. The mothers were not in use of any medication and have no known medical condition. All babies received only breast milk from their own mother and nothing else, including water. The study was approved by ethical committee and the sensor was installed only after write permission from the mother and the father. The results were achieved and showed minimum, maximum, median and standard deviation.

**Results:** 200 normal babies with gestational age between 38 and 42 weeks were studied (Median: 39 2/7). The weight ranged between 2635 and 3980 grams. The glycemic levels ranged between 40 and 123 mg/dl, median 60,5 mg/dl. The glycemic value was equal or under 40 mg/dl in 17,8% of the babies. We haven't found any problem with the babies due the sensor. No baby had synthons of hypoglycemia.

**Conclusions:** The results show that interstitial glycemic levels in normal babies are very close to normal levels in older children. Those results would be very important to define normality of glycaemia.

P2-507

**LABOUR PHYSIOLOGY AND ITS RELATIONSHIP TO ARTERIOVENOUS UMBILICAL CORD GLUCOSE CONCENTRATIONS OF TERM NEONATES**

*Sinead Mcglacken-Byrne, MS/MA, Royal College of Physicians of Ireland, Dublin, Ireland; Tina Murphy, PhD; Michael Robson, MD; John Murphy, MD, National Maternity Hospital, Holles St, Dublin, Ireland*

**Objectives:** This study aimed to establish normative values of arteriovenous umbilical cord blood glucose concentrations in term neonates during labour.

**Methods:** This is a retrospective study of nulliparous non-diabetic women diagnosed in labour at term (>37 weeks) from April 2011 to January 2012 in a tertiary maternity centre. Paired arterial and venous cord blood glucose concentrations were tested using a blood gas analyser after delivery. ANOVA and Chi-square tests were used to compare mean glucose concentrations and demographic variables between groups. Glucose results are in mmol/L.

**Results:** Data from 358 women and babies were studied. 95.5% (n=342) delivered vaginally; 67% (n=240) were spontaneous. 28.5% (n=102) were instrumental deliveries; 4.5% (n=16) were emergency CS. Arterial glucose was significantly lower than venous glucose (5.3±1.2 vs 5.6±1.2, p<0.01). There was no significant difference between the arterial and venous cord glucose of babies delivered by spontaneous vaginal delivery, instrumental delivery, or emergency CS. Women who had a spontaneous rupture of membranes had higher arterial cord glucose concentrations than women who had an artificial rupture (5.5±1.2 vs 5.2±1.1, p=0.49). Cord glucose concentrations were significantly lower if an epidural had been used (arterial: 5.1±1.0 vs 5.9±1.4, p<0.01; venous: 5.4±1.0 vs 6.2±1.4, p<0.01). There were no significant predictive effects of maternal age, baby gender, birth weight, nor gestation on glucose concentrations.

**Conclusions:** This study offers normative values for arteriovenous cord glucose concentrations, and explores the interplay between labour physiology and cord glucose values. Higher cord glucose concentrations have been reported in infants delivered vaginally compared to by elective CS, with the catecholamine surge induced by labour likely explaining the rise. Our study found no difference between infants delivered vaginally or by emergency CS, suggesting that infants exposed to labour experience a catecholamine surge regardless of delivery method. Lower glucose concentrations associated with epidurals and artificial membrane rupture suggest that interruption of physiological labour may diminish this phenomenon.

P2-508

**IN UTERO EXPOSURE TO BPA ALTERS GENOME WIDE DNA METHYLATION AND GENE EXPRESSION IN FETAL STEM CELLS**  
Sara E Pinney, MD, The Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, United States; Sana Wajid, MS/MA; David Condon, PhD; Paul Z Wang, PhD, University of Pennsylvania, Philadelphia, PA, United States

**Objectives:** Background: Prenatal exposure to the endocrine disrupting chemical bisphenol A (BPA) have been linked to increased adiposity, changes in glucose metabolism and defects in insulin secretion in adult male offspring. These effects seen from prenatal exposure to BPA are more prominent in lower doses of BPA compared with higher doses of BPA exposure. Previously we reported that second trimester amniotic fluid BPA concentration is associated with decreased birth weight in term infants, but no sex-specific effect on birth weight was detected.

**Objective:** To measure changes in gene expression with RNA-Seq and genome wide DNA methylation in amniocytes, a fetal stem cell, exposed to BPA in utero.

**Methods:** Total RNA was extracted from amniocytes exposed to BPA in utero and RNA-Seq libraries were constructed and sequenced (n=4 per treatment, BPA vs. control, per offspring sex). Genomic DNA was extracted from amniocytes for Enhanced Reduced Representation Bisulfite Sequencing (ERRBS) to map genome wide DNA methylation (n=10 per treatment group per offspring sex). RNA-Seq differential expression was determined with EdgeR after alignment. Q<0.05 was considered significant for RNA-Seq. For ERRBS, differentially methylated regions (DMRs) were determined looking at sequential CpGs with significant change in DNA methylation >5%, with p<0.05 over the entire DMR.

**Results:**

	# of Differentially Expressed Genes (RNA-Seq) q<0.05	# of DMRs identified from ERRBS (Albert) p<0.05
Amniocytes from BOTH MALE and FEMALE offspring	22	9
Amniocytes from MALE offspring	245	199
Amniocytes from FEMALE offspring	13	46

**Conclusions:** Conclusion: Exposure to BPA *in utero* may have sex specific effects on gene expression and DNA methylation in amniocytes, a fetal stem cell.

P2-509

**TRANSIENT HYPOCORTISOLISM IN PRETERM BORN INFANTS – IS THERE A PREMATURE CRITICAL ILLNESS-RELATED CORTICOSTEROID INSUFFICIENCY SYNDROME ?**  
Felix Reschke, MD, Technische Universität Dresden, Dresden, Germany; Angela Hübner, PhD; Sebastian Brenner, PhD, Technical University of Dresden, Dresden, Germany

**Objectives:** The critical illness-related corticosteroid insufficiency (CIRCI) syndrome, which is well known in adults, describes the close association between the development of transient relative adrenal insufficiency (AI) in critical ill patients and increased morbidity. It occurs as a result of a decrease in cortisol production and peripheral resistance to cortisol. Preterm birth is often accompanied by critical illness (CI) and also can come along with transient AI, due to immaturity of the hypothalamic-pituitary-adrenal (HPA) axis. Regardless there is still no evidence about the existence of CIRCI in ill preterm infants

**Methods:** We report about 29 eutrophic, preterm born infants with good postnatal adaptation (5 min. Apgar  $\geq 7$ ), who all underwent at least one episode of a severe disease (secondary respiratory distress syndrome or neonatal sepsis) leading to a CI, which was defined by an impairment of at least three of the following symptoms: poor temperature regulation, dyspnea, oliguria or anuria, hypoglycemia or hypotension. During that period all infants were diagnosed suffering from an AI by blood tests. Afterwards all patients were treated with hydrocortisone as a substitution therapy additionally to fluid resuscitation and vasopressor agents. The clinical course was assessed using a standardized checklist. All infants were followed for at least one year focussing on the reconstitution of the HPA axis

**Results:** As a result of the initiation of the hydrocortisone therapy (mean starting dose:  $9.6 \text{ mg/m}^2/\text{d}$  – starting with a bolus of 5 mg) the blood pressure rapidly (mean 3.6 hrs) improved in all patients and the vasopressor dose could be reduced within 6 hrs after corticosteroid administration in all patients. The further symptoms also decreased continuously. However, a complete recovery of the HPA axis was found in all patients after survival of the crisis, after hydrocortisone therapy was stopped.

**Conclusions:** Because all patients showed a noticeable benefit of the hydrocortisone therapy we suggest, that CIRCI is a true entity in critical ill preterm infants. Typical symptoms should lead to the suspicion of CIRCI and a corticosteroid substitution should be considered early in the management strategy. It is important to remember, that CIRCI is usually reversible and the AI is transient.

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**Objectives:** Currently, the use of the 18F-DOPA PET/CT imaging is the most effective technique for identifying and locating focal lesions in patients with congenital Hyperinsulinism (HI). There are two ways to interpret the images; using standardized uptake values (SUV) or looking at the images and visually inspecting for altered areas of uptake (visual method). Data in the literature proposes that an SUV ratio of  $>1.3$  is indicative of focal disease and a ratio  $< 1.3$  suggests diffuse disease. Some surgical centers do not operate if the data suggests diffuse disease. Aim: To determine if using the SUV ratios of  $>1.3$  accurately differentiates focal from diffuse.

**Methods:** In the SUV method, readings are taken at 20, 30, and 40 minutes. Ratios are calculated by taking the max SUV value and dividing it by the second highest value. In contrast the visual method involves looking at the PET scan and determining visually if there is an area higher than all others.

**Results:** 33 patients underwent 18F-DOPA PET/CT scanning. We excluded 7 patients who did not have surgery, 3 atypical focal (focal lesions that covered  $>50\%$  of the pancreas) and 2 patients with LINE pathologies. Of the remaining 21 patients there were 15 focal and 6 diffuse based on final pathology. In 19 of 21 patients, the SUV value at all 3 time points were in concordance. In the 2 that were not, both discordant readings were at the 40 min scan. Of the 15 focal patients 7 had peak SUV ratio of 1.3 (1.61). The sensitivity of  $\text{SUV} \geq 1.3$  to detect focal disease is 53% with a specificity 83% and a positive predictive value 89%. On the other hand visual inspection allowed 93% of the focal lesions to be identified at surgery and cured with minimal resection. If a cutoff of  $\geq 1.2$  is used the sensitivity is 73%, the specificity is 50% and the positive predictive value is 79%.

**Conclusions:** Using the SUV value at a cutoff of  $\geq 1.3$  means that 47% of our patients would not have been operated on had if we made determination based on the SUV reading alone. Based on our results, we find visual PET read is superior to SUVmax ratio threshold for determining surgical intervention.

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P2-510

#### STANDARD UPTAKE VALUE RATIOS ARE NOT THE BEST TECHNIQUE TO DIFFERENTIATE FOCAL FROM DIFFUSE HI

*Paul Thornton, MD, Cook Children's Medical Center, Fort Worth, TX, United States; Rachid Nazih, PhD; Sudha Garg, PhD, Biomedical Research Foundation, Shreveport, LA, United States; Lisa Truong, CPNP; Larry Rodriguez, RN; Courtney L Reynolds, MPH; Jonathon NedreLOW, MD; John Uffman, MD;*

SUV Interpretation	Pathology	
	Focal	Diffuse
≥1.3	8	1
<1.3	7	5

SUV Interpretation	Pathology	
	Focal	Diffuse
≥1.2	11	3
<1.2	4	3

P2-511

# **PHYSICAL FITNESS, POWER AND PERFORMANCE IN MONOZYGOTIC TWINS WITH INTRA-TWIN BIRTH-WEIGHT-DIFFERENCES**

*Sandra Schulte, MD, University Children's Hospital Bonn, Bonn, Germany; Joachim Woelfle, MD, University of Bonn, Bonn, Germany; Peter Bartmann, PhD; Felix Schreiner, MD; Michaela Plamper, MD; Lioba Wimmer, MD, University Children's Hospital Bonn, Bonn, Germany; Bettina Gohlke, MD, University of Bonn, Bonn, Germany*

**Objectives:** Low birth-weight and unfavourable intrauterine conditions are associated with a subsequent impact on the endocrine system. In a longitudinal study we observed genetically identical twins with intra-twin birth-weight-differences from birth until adolescence to objectify the impact of a lower birth-weight on development and health in later life.

**Methods:** Birth-weight-difference of <1SDS was defined concordant (n=13), birth-weight-difference >1SDS discordant (n=14). Single two leg jump with Leonardo GRFP Mechanography Measurement Report was performed at a mean age of 14.6 yrs. Best jumps Esslinger fitness index (EFI), efficiency, maximum total power and maximum total performance were analysed.

**Results:** Best jumps Esslinger fitness index (EFI), efficiency and maximum total power did not show any significant differences. However, in all twin pairs, a significant intra-twin difference was represented concerning maximum total performance (p=0.023; 2.33 kW vs 2.13 kW) with the former smaller twins showing an impaired muscular performance in comparison to the co-twin. A significant difference for BMI-SDS at the age of 14.6 years was observed in the concordant (p=0.039) and the discordant (p=0.007) pairs, the former smaller twins had a lower BMI than their co-twins in either groups. Only in the discordant twin pairs with a greater birthweight difference, a highly significant intra-twin difference for height SDS remained up to the age of 14.6 years (p<0.001), the smaller twin was an average of -0.53 SDS shorter than the co-twin.

**Conclusions:** In this special group of monozygotic twins with intra-twin birth-weight-differences, we could show that birth-weight has a long-lasting impact not only on growth and body weight, but as well on physical performance. The former smaller twins showed significantly lower maximum total performance, suggesting differences in muscle work or body composition. Further analyses are necessary.

P2-512

# **FUNCTIONAL MATURATION OF PANCREATIC BETA CELLS DURING HUMAN DEVELOPMENT**

*Diana E Stanescu, MD, University of Pennsylvania, Philadelphia, PA, United States; Changhong Li, PhD; Daphne Yau, MD, Children's Hospital of Philadelphia, Philadelphia, PA, United States; Doris A Stoffers, MD, PhD, University of Pennsylvania, Philadelphia, PA, United States; Charles A. Stanley, MD, Children's Hospital of Philadelphia, Philadelphia, PA, United States*

**Objectives:** The transient hypoglycemia of normal newborns in the first 72 hours of life seems to be due to insulin release at low concentrations of glucose and possibly in response to other stimuli. During the intra uterine period, insulin is crucial for growth and maintaining fetal insulin secretion, irrespective of maternal plasma glucose variations, appears to be the result of a maturational islet adaptation, which can persist during the first days of extrauterine life. We aimed to determine the stages of functional maturation of human fetal beta cells in order to delineate normal versus pathologic patterns of insulin release with potential impact on the evaluation and treatment of neonatal hypoglycemia.

**Methods:** We performed perfusions on human fetal islet samples at 17-20 weeks gestation.

**Results:** Fetal islets at 17 weeks did not secrete insulin in response to glucose but did respond to KCl, indicating that the secretory machinery is functional. By 18-20 weeks gestation, fetal islets released insulin in response to very low glucose concentrations (1-2 mM glucose). These findings indicate that the maturation of glucose responsive insulin secretion begins between 17 and 19 weeks gestation. We found that these islets also release insulin in response to aminoacids. Preliminary experiments also suggest that fetal human islets respond to a lactate/pyruvate stimulus. Ongoing experiments will further define the timing of stimulus-induced insulin secretion in parallel with the characterization of fetal beta cell transcriptomic maturation at the single cell level.

**Conclusions:** Understanding the functional maturation of  $\beta$  cells during the fetal and neonatal period, coupled with the insight into the molecular mechanisms responsible for this maturation, will positively impact the care of newborns. It can lead of the development of molecular markers of a dysregulated  $\beta$  cell function that is likely to persist beyond early neonatal period. It can also guide specific interventions to manage hypoglycemia or limit the persistence of fetal pattern of  $\beta$  cell response in the neonatal period.

# RELATIONS OF BIRTH HEAD CIRCUMFERENCE / BIRTH CHEST CIRCUMFERENCE RATIO TO CIRCULATING INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN-3 IN THE NOT-LIFE-THREATENED NEWBORN: ROLE OF BIRTHWEIGHT AFTER CONTROLLING FOR PRETERM BIRTH, RESPIRATORY SUPPORT MEASURES AND CALORIC INTAKE

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**Objectives:** The ratio of birth head circumference(HC) to birth chest circumference(CC)(HC through CC; HC/CC) is related to birth gestational age(GA) in the human newborn(NWB). We intended to evaluate the relevance of birthweight(BW) to correlations of HC/CC with blood serum Insulin-like Growth Factor Binding Protein-3(IB3) after control for gender(SEX), preterm birth(birth at  $\leq 36$  completed weeks GA; PTB), postnatal age(PNA), respiratory oxygen supplementation(O2S), assisted ventilation of any kind(AV) and caloric intake(KT) in not-life-threatened NWBs.

**Methods:** NWBs with any among total parenteral nutrition, life-threatening disease, diabetes mellitus(DM), endocrine diagnosis out of DM, malformation, clinically relevant trunk trauma, and mother with DM were excluded. Each of 78 included NWBs had available data for: 1) SEX, GA(range=28-42 completed weeks), BW(range=1200-4150g), HC(range=27.0-36.0cm), CC(range=22.0-39.0cm), HC/CC(range=0.82-1.28cm/cm) and a BW $\leq$ 10th centile for GA(SGA) and 2) same-day records at one of the first 5 postnatal days(x), 5 days after x(y) and 10 days after x(z) for PNA(unit:day), O2S, AV, KT(as KCal/kg/24h or, for PNA $<$ 24h, KCal/kg/PNA) and IB3 RIA measurements(unit: uM/dl)(male SEX, n, 43; PTB, n, 46; SGA, n, 20; O2S, n, x=22, y=11, z=1; AV, n, x=8, y=4, z=1). Natural log-transformed IB3(IB3-LN) was near-normally distributed. Multiple Linear Regression(MLR) was used to predict IB3-LN at x-y-z (computations; male SEX, PTB, O2S, AV, condition present=1, condition absent=0).

**Results:** MLR showed 1) a significant partial correlation(PC) coefficient(r) of HC/CC PCs with outcome IB3-LN at y-z when including together as predictors O2S-AV-KT-PNA chronologically corresponding to IB3-LN, as well as SEX, PTB and HC/CC(HC/CC vs IB3-LN; y,  $r=-.385$ ,  $p=.0008$ ; z,  $r=-.477$ ,  $p<.0001$ ) but 2) no significant HC/CC PC with outcome IB3-LN when including together as predictors O2S-AV-KT-PNA chronologically corresponding to IB3-LN, as well as SEX, PTB,

HC/CC and BW(each considered MLR model was significant; MLR R2 range=.32-.57).

**Conclusions:** BW could be involved in negative HC/CC relations to IB3-LN not explained by SEX, PTB, PNA, O2S, AV and KT in the not-life-threatened NWB.

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# DIAZOXIDE SIDE EFFECTS IN THE TREATMENT OF CHILDREN WITH CONGENITAL HYPERINSULINISM

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**Introduction:** Congenital Hyperinsulinism (CHI) is a rare disease which causes excessive insulin secretion resulting in profound hypoglycemia putting the child at risk for permanent brain damage, seizures, and mental retardation if poorly treated. There are two type of CHI, transient disorders due to perinatal stress hyperinsulinism (PSHI) or genetic (GHI) forms which are cause from mutations in the ABCC8, KCNJ11, Glud-1, and GK genes. Diazoxide is the first line treatment for children with CHI. There are known side effects of diazoxide therapy such a hypertrichosis, pulmonary hypertension, neutropenia, and anorexia however the incidence of the severe adverse events (SAE) is unknown.

**Aim:** To determine the incidence of SAE with the treatment of diazoxide in patients with PSHI and GHI

**Methods:** A retrospective chart review was conducted on 171 patients with CHI who attended the Cook Children Hyperinsulinism Center to determine if they had side effects from diazoxide therapy.

**Results:** There were 70 patients with PSHI and 101 patients with GHI treated with diazoxide therapy. Dose ranged from 5 mg/kg/day to 15 mg/kg/day. SAE occurred in 9 patients overall (5%), 8 of the 9 (88%) had PSHI giving a SAE rate of 11.4 % in this population. 4 patients developed neutropenia and 5 patients developed pulmonary HTN. Symptoms resolved after discontinuing the diazoxide. A retrial of diazoxide was not performed in the pulmonary hypertension patients due to the risks. However, 2 out of the 4 patients that developed neutropenia had a retrial and recurrence of the neutropenia occurred once again causing discontinuation of the medication.

**Conclusions:** The frequency of serious adverse advents associated with diazoxide therapy is 5%. However, they occurred predominantly in the PSHI patients at a frequency of 11.4%. We recommend that patients who are starting Diazoxide therapy start a diuretic therapy at the same time, in addition to having a baseline CBC and echocardiogram done before starting the treatment. After being on the medication for 5 days we recommend a repeat CBC and echo to evaluate for any changes. Particular caution should be taken with infants treated for PSHI.

# INCIDENCE AND PATTERN OF HYPOGLYCEMIA AMONG AT-RISK NEWBORNS IN A COMMUNITY HOSPITAL SETTING

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**Objectives:** Background: Hypoglycemia is frequent in at-risk neonates. Despite recommendations by the American Academy of Pediatrics to screen newborns with known risk factors, implementation is not universal, and little is known about the incidence and pattern of hypoglycemia in this population.

**Objective:** To describe hypoglycemia incidence among at-risk newborns in a community hospital, and to describe barriers to implementation of screening guidelines. We will subsequently use this data as our baseline for a quality improvement (QI) project, with the goal of minimizing recurrent hypoglycemia.

**Methods:** Retrospective cohort study. Hypoglycemia was defined as plasma glucose less than 45 mg/dL (less than 4 hours of life) or less than 50 mg/dL (four hours of life or older). Incidence of hypoglycemia was determined for the cohort and compared across risk categories using Fisher's exact test. Balancing metrics included rates of formula supplementation and transfer to the neonatal intensive care unit for hypoglycemia management, which were determined through chart review. Interviews of nursery nurses were conducted to assess barriers to timely screening and treatment of hypoglycemia.

**Results:** In one 3-month period in 2016, 166 newborns were screened for hypoglycemia at our hospital. Fifty-two percent (52%) of screened at-risk newborns became hypoglycemic; 33% had recurrent hypoglycemia prior to discharge. Rates of initial or recurrent hypoglycemia did not differ significantly across risk groups ( $p>0.05$ ). Approximately 2% of screened infants required transfer to the neonatal intensive care unit for glucose management. Approximately 72% of newborns at our hospital in this time period received at least one formula supplementation prior to discharge. Nurses reported difficulty in monitoring multiple newborns at once due to the competing desires for on-demand breast feeding and pre-prandial glucose value.

**Conclusions:** Hypoglycemia among at-risk newborns is common in this community hospital setting. As a QI project, we will introduce dextrose gel; this will be used with breast feeding to treat hypoglycemia during this transitional period in otherwise healthy newborns, with the goal of reducing formula supplementation

# MOLECULAR CHARACTERISTICS OF 107 VIETNAMESE PATIENTS WITH CONGENITAL HYPERINSULINISM

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**Objectives:** Hyperinsulinemic hypoglycemia (HH) is a consequence of unregulated insulin secretion by pancreatic  $\beta$ -cell. Congenital HH is caused by mutations in genes involved in regulation of insulin secretion (*ABCC8*, *KCNJ11*, *GLUD1*, *CGK*, *HADH*, *SLC16A1*, *HNF1A*, *HNF4A* and *UCP2*). Severe forms of congenital HH are caused by inactivating mutations in *ABCC8* and *KCNJ11*, which encode the two components of the pancreatic  $\beta$ -cell ATP-sensitive potassium channel.

Our aim is to identify mutations in the *ABCC8* and *KCNJ11*, *HNF4A* and *GLUD1* genes, and to describe genotype and phenotype correlations of Vietnamese children with congenital HH.

**Methods:** A prospective study was conducted on 107 cases with congenital HH diagnosed and treated at the National Children's Hospital from January 2007 to February 2017. Patients were selected by using inclusion criteria of Hussain K (2008). All exons of *ABCC8*, *KCNJ11*, *HNF4A* and *GLUD1* were amplified from genomic DNA and directly sequenced.

**Results:** Mutations were identified in 57 cases (53.3%) including mutations of *ABCC8* gene (51 cases; 47.7%), among them 29 with homozygous/compound heterozygous of *ABCC8* and 22 cases with one paternal/maternal mutation of *ABCC8* gene; mutations of *KCNJ11* (5 cases; 4.7%); and *HNF4A* (1 case; 0.9%). 98.2% of cases with homozygous/compound heterozygous recessive mutations or one paternal dominant mutation of *ABCC8* gene did not respond to diazoxide treatment and required 95% pancreatectomy or octreotide injection. Other cases without identified mutations responded to diazoxide and/or glucose infusion.

**Conclusions:** Children with congenital HH should be performed mutation analysis which helps in making diagnosis and treatment decision. Families of children with congenital HH should be given genetic counseling. Prenatal diagnosis should be performed as well as follow up and treatment should be given to children with congenital HH immediately after birth.



# **ALTERED EXPRESSION OF HEXOKINASE ISOFORMS MAY MEDIATE A LOW GLUCOSE THRESHOLD FOR INSULIN SECRETION IN THE PERINATAL PERIOD**

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**Objectives:** Insulin release at low glucose concentrations appears to underlie the transient hypoglycemia occurring in the first 24-72h in normal neonates. This likely reflects the role of insulin for growth in utero. Although usually uneventful, permanent neurologic injury can occur as a consequence of the hypoglycemia, particularly when risk factors are present. Given the potential for adverse outcomes, we sought to understand the mechanisms underlying the regulation of insulin secretion during the transition from fetal to post-natal life.

**Methods:** Insulin responses to fuels were examined in perfused minced rat pancreas and isolated islets. Rat islet gene expression was analyzed by RNA sequencing.

**Results:** The glucose threshold for insulin secretion was markedly lower in the perinatal period compared to mature islets. Insulin release was stimulated by 3mM glucose from gestational day E21 through post-natal day 3 (P3). By P7, the threshold had shifted upward to 5-10 mM, similar to adult islets. Maximal GSIS also increased with age. At P1, the maximal response was reached at 3mM glucose and increasing glucose to 25mM did not stimulate secretion further. However, at P3, 10 mM glucose stimulated a 3-fold increase in secretion compared to 3mM glucose (n=4, p less than 0.01 vs. P1). This increase was also seen in P7 and P14 animals. Increasing the glucose concentration further from 10mM to 25mM stimulated an additional increase in secretion in P7 and P14 but not P3 animals. Analysis of gene expression in fetal islets showed a 67% reduction in glucokinase expression (n=3, p<0.05) with a 3-fold increase in hexokinase 2 expression versus adult islets (n=3, p<0.01).

**Conclusions:** These data show that perinatal maturation of islet function involves a progressive increase in both threshold and maximal responsiveness of GSIS. The low glucose threshold in the perinatal period appears to reflect increased expression of the low Km hexokinase 2 and reduced expression of the high Km glucokinase. We speculate that signals generated through metabolism of glucose may be responsible for the increase in maximal GSIS. Future pharmacological targeting of these different hexokinase isoforms in the beta-cell may represent a unique way to treat neonatal hypoglycemia.

# **EARLY-LIFE BODY COMPOSITION AND METABOLIC MARKERS IN OFFSPRING OF OVERWEIGHT/OBESE WOMEN FOLLOWING ANTENATAL EXERCISE: A RANDOMISED CONTROLLED TRIAL**

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**Objectives:** To determine effects of antenatal exercise on fetal and neonatal body composition and early life metabolic markers in offspring of overweight and obese women

**Methods:** A parallel two-arm community-based randomised controlled trial was conducted on 75 non-smoking women (baseline BMI >25 kg/m<sup>2</sup>) with a singleton pregnancy, in Auckland, New Zealand. Participants were randomised to either an intervention arm (I) who followed a home-based moderate-intensity stationary cycling program between 20-36 weeks of gestation or control arm (C) without an exercise intervention. Offspring outcomes included fetal growth (3-D ultrasonography), birth weight, neonatal body composition (whole body DXA scanning) and cord blood metabolic markers. Maternal fitness (submaximal test on a cycle ergometer) habitual physical activity (PA), diet and metabolic markers were monitored. Analysis of covariance regression models adjusting for pre-specified confounders were used to evaluate intervention effects, and model-adjusted means and their difference between two groups (aMD) were estimated and tested. Further *post hoc* gender-based sub-analysis on offspring outcomes was performed.

**Results:** Maternal fitness improved between 20 to 36 weeks of gestation in the I arm, while it declined in the C arm. Maternal diet, habitual PA and metabolic markers were similar. Fetal growth, birth weight, lean mass and fat mass were similar between offspring groups. I offspring had increased bone mineral content (BMC) (adjusted mean difference (aMD) 9.1 g; p=0.01) and a lower cord blood interleukin-6 level (aMD -13.97 pg/ml; p=0.03), while other metabolic markers including insulin, IGF I and II and lipids were similar. On gender- based sub-analysis, female I offspring had higher BMC (aMD 8.3 g; p=0.046) and lower IL-6, but male I offspring had increased adiposity (fat mass aMD 110 g; p=0.017, % body fat aMD 1.6%; p=0.044).

**Conclusions:** Non-weight-bearing antenatal exercise in overweight/obese women improved maternal fitness, increased offspring bone mass and lowered fetal IL-6 levels. Female offspring appeared to benefit from maternal antenatal exercise, while male offspring showed increased adiposity, suggesting gender-based differences in fetal response to antenatal exercise.

**DELAYED ONSET HYPOGLYCAEMIA IN A CHILD WITH GLICLAZIDE POISONING**

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**Objectives:** To describe the presentation of delayed onset hypoglycaemia in a child secondary to sulphonylurea ingestion

**Methods:** Case summary:  
A 22 month old child presenting with seizures was found to have hypoglycaemia, which persisted despite 10% dextrose infusion and frequent feeding. Urine ketone bodies were negative. On repeated inquiry for possible accidental drug ingestion, it was disclosed that the child had been found chewing gliclazide (80 mg) tablets at her grandmother’s house, 5 days prior to presentation. Her blood sugar stabilized over the next 48 hours and she was discharged after strict advice on child safety.

**Results:** Discussion:  
Refractory and rebound hypoglycaemia is known to occur following sulphonylurea ingestion but onset of hypoglycaemia more than 72 hours after ingestion is rarely reported. Gliclazide is a second generation sulphonylurea which can cause delayed onset of symptomatic hypoglycaemia due to differences in pharmacokinetic properties of children and adults.

**Conclusions:** Ingestion of oral hypoglycaemic drugs such as gliclazide, can cause delayed and prolonged hypoglycaemia, and need to be considered in the evaluation of a child with refractory and rebound hypoglycaemia, even when the presentation is be delayed.

**NO EFFECT OF GREEN TEA POLYPHENOLS OR CARBAGLUMIC ACID IN HYPERINSULINISM/HYPERAMMONEMIA SYNDROME**

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**Objectives:** To test potential new treatments of hyperinsulinism/hyperammonemia (HI/HA) syndrome, a variant of congenital hyperinsulinism (CHI) caused by a *GLUD1* mutation, as 1) epigallocatechin gallate (EGCG), a polyphenol found in green tea, allosterically inhibits the glutamate dehydrogenase enzyme, which is activated in HI/HA syndrome; and 2) carbaglumatic acid is used for treatment of hyperammonia, which is not otherwise treated (e.g. by diazoxide) in this CHI subtype.

**Methods:** Prospective patient evaluation.

**Results:** A 4 month old Kazakhstani girl with HI/HA syndrome presented with persisting hypoglycemia down to 1.3-1.4 mmol/L, and delayed psychomotor development with a Bayley III test equaling <5<sup>th</sup> percentile. The patient tolerated fasting, but by leucine test (150mg/kg of leucine in 20% solution), protein-induced hypoglycemia was overt. Concentrated green tea (20mL) by nasogastric tube prior to another leucine test did not prevent hypoglycemia. A short trial of carbaglumatic acid failed to normalize her hyperammonemia and no improvement in neurological symptoms was detected.

**Conclusions:** In this to our best knowledge first reported standardized test the effect of concentrated green tea in HI/HA syndrome, the lack of response discouraged the further use of commercially available green tea. The lack of any convincing effect from carbaglumatic acid on the elevated ammonium or neurological symptoms likewise discouraged further use of carbaglumatic acid in HI/HA syndrome patients.

Table 1. Biochemical results from 6-hour fasting and two leucine tests; with and without prior oral green tea.

	6h-fasting	Postprandial	Leucine test without green-tea		Leucine test with green tea		References (fasting)
			0min	60min	0min	60min	
p-glucose	3.9	3.1	5.2	3.8	6.0	2.3	3.5 – 5.5 mmol/L
p-Insulin	24	53		215		91	18 - 173 pmol/L
p-C-peptide	208	603		1035		735	370 - 1470 pmol/L
p-proinsulin	4			26		16	2-23 pmol/L
p-ammonium				208		224	< 49 µmol/L

Leucine stimulation test: 150mg/kg leucine given orally in a 20% solution. A positive test is a drop in plasma glucose concentration of minimum 50%.

**USE OF LONG-ACTING SOMATOSTATIN ANALOGUE (LANREOTIDE) IN A CHILD WITH CONGENITAL HYPERINSULINISM DUE TO PATERNAL HETEROZYGOUS ABCC8 MUTATION AND A FOCAL LESION IN THE HEAD OF THE PANCREAS.**

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**Objectives:** Long-Acting Somatostatin Analogue (Lanreotide) has been reported in the management of patients with diffuse form congenital Hyperinsulinism (FCHI) unresponsive to Diazoxide. However, there is no report of Lanreotide use in FCHI. This is the first case report of FCHI with known genetic mutation responsive to Lanreotide.

**Methods:** Prospective follow up of a child with CHI with paternally inherited heterozygous nonsense mutation, p.Gln822Ter (c.2464C>T) in *ABCC8* gene causing focal lesion in the head of pancreas; which was difficult to remove surgically due to its adherence to surrounding structures.

**Results:** A paternal heterozygous mutation in *ABCC8* gene was identified in a diazoxide-unresponsive CHI neonate. 18F-

DOPA-PET/CT scan revealed a focal lesion in the head of the pancreas. He showed partial response to 6-hourly subcutaneous(sc) octreotide injections, with 3-hourly nasogastric tube feeds. Surgical removal of the focal lesion was attempted, but intraoperative biopsies from the pancreatic head showed that the lesion was extensive, therefore, conservative treatment was chosen. Sirolimus (mTOR inhibitor) was tried simultaneous to 6-hourly octreotide sc injections, with frequent feeds. Whilst establishing sirolimus treatment, he developed a life-threatening infection. As a result, sirolimus was stopped in accordance with parents' wishes.

At the age of 12 months, the patient was started on Lanreotide (Somatuline autogel) 30mg 4-weekly. Octreotide injections were stopped after 8 weeks. Over the last 6 months, he has been on Lanreotide 30mg 4-weekly, with three-hourly oral feeds during the daytime and continuous overnight feeds via gastrostomy. Currently, his blood glucose is stable on the above regime and has demonstrated no side effects. Significant improvement in the quality of life for the family has been noted.

**Conclusions:** CHI patients with focal lesions in the pancreatic head are challenging especially if not amenable to surgery. Conservative treatment is preferable and Lanreotide might be an option. The therapeutic impact of Lanreotide treatment in CHI patients with focal lesions should be confirmed in prospective studies and the side effects must be monitored closely.

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#### **SIROLIMUS THERAPY FOR PERSISTENT HYPOGLYCEMIA FOLLOWING NEAR-TOTAL PANCREATECTOMY IN AN INFANT WITH CONGENITAL HYPERINSULINISM**

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**Objectives:** Persistent hypoglycemia may occur in up to 60% of patients with congenital hyperinsulinism (CHI) following near-total pancreatectomy. Additionally, nearly all develop insulin-dependent diabetes later in life. Hence, as an alternative to surgery, Seniappan et al introduced sirolimus, a mammalian target organ receptor inhibitor, in the management of medically unresponsive patients with CHI. This report highlights the use of sirolimus as a rescue therapy in an infant for persistent hypoglycemia following surgery for CHI.

**Methods:** A term female infant with a birth weight of 4.85kg presented with persistent hypoglycemia from day 1 of life due to CHI and was unresponsive to medical therapy with both diazoxide and octreotide. She had the same homozygous *ABCC8* (*p.Arg837*) mutation as her two siblings

who required pancreatectomy for management; the second sibling developed insulin dependent diabetes at 2 years of age. Our patient also had a near-total pancreatectomy at 1 month of age and a re-resection at 2 months of age. However, hypoglycemia persisted necessitating a glucose infusion rate of 10mg/kg/min. Diazoxide was not effective and was ceased post re-resection. Sirolimus was commenced at 5 months of age at a dose of 0.5mg/m<sup>2</sup>/day.

**Results:** There were no documented episodes of hypoglycemia (<4mmol/l) after 7days of sirolimus therapy. Octreotide was ceased at 4 weeks with reduced dependence on continuous high calorie feeds. She was discharged at 6 months. Continuous glucose monitoring (Dexcom G4) at 6 and 8 months demonstrated similar profiles with only 6% and 8% of sensor glucose levels below 3.9mmol/l respectively. There were no reported side-effects and she continues under regular surveillance and demonstrates appropriate growth for age.

**Conclusions:** Our case demonstrates that sirolimus offers a medical alternative in patients with persistent hypoglycemia following surgery for CHI. The long-term utility, efficacy and safety of this agent is unknown and international registries prospectively collecting outcomes of sirolimus therapy in CHI are warranted.

P2-523

#### **RESOLUTION OF HYPOGLYCAEMIA IN A PATIENT WITH HYPERINSULINISM-HYPERAMMONEMIA (HI/HA) SYNDROME DUE TO *GLUD1* MUTATION**

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**Objectives:** The hyperinsulinism/hyperammonemia (HI/HA) syndrome is the second most common form of congenital hyperinsulinism (CHI) characterised by fasting and protein induced post-prandial hypoglycaemia and persistently elevated ammonia concentration. Gain of function mutations in *GLUD1* that encodes the mitochondrial enzyme, glutamate dehydrogenase (GDH), is responsible for HI/HA syndrome. The hypoglycaemia in HI/HA is responsive to diazoxide and patients are expected to require treatment for life in view of the underlying genetic disorder.

**Methods:** A Caucasian female infant born to non-consanguineous parents presented with persistent hypoglycaemia and seizures at 7 months of age. Subsequent investigations showed an inappropriately raised plasma insulin concentration (80pmol/L) with a suppressed beta hydroxy butyrate and free fatty acids confirming the diagnosis of CHI. She also had persistently high serum ammonia concentration [90-100µmol/L(normal<70µmol/L)]. A protein load test (using Vitapro) demonstrated hyperinsulinaemic hypoglycaemia (blood glucose<2.6mmol/L). Genetic analysis confirmed a heterozygous mutation in *GLUD1*. Diazoxide was commenced with a good response. She initially required anticonvulsants,

which was subsequently weaned and stopped. At 8 years of age, following excellent glycaemic control and some high blood glucose readings (up to 11mmol/L), diazoxide was gradually weaned and stopped. A 20-hour controlled fast [off diazoxide] and an oral protein load test did not show any hypoglycaemia.

**Results:** The patient is currently 9 years old and continues to stay off diazoxide with no documented pre and post-prandial hypoglycaemic episodes.

**Conclusions:** GDH is expressed in liver, kidney, brain, and pancreatic  $\beta$ -cells and therefore patients with HI/HA syndrome are characterised by seizures and persistent hypoglycaemia. We report, for the first time, the resolution of hypoglycaemia with age in a patient with HI/HA syndrome. This might possibly reflect the normalisation of GDH activity in the pancreatic  $\beta$ -cells but the underlying mechanism(s) is yet to be understood. A careful monitoring of blood glucose will still be required in the long term in these patients.

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#### **DIAZOXIDE RESPONSIVENESS IN A NEONATE WITH CONGENITAL HYPERINSULINAEMIC HYPOGLYCAEMIA DUE TO HOMOZYGOUS ABCC8 MUTATION**

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**Objectives:** We report a case of diazoxide responsiveness in a child with severe hyperinsulinaemic hypoglycaemia due to a homozygous *ABCC8* mutation.

**Methods:** A term baby (birth weight +0.52 SDS), born to consanguineous parents, presented with hypoglycaemia on day 1. Hypoglycaemia screen confirmed hyperinsulinism and diazoxide was commenced on day 7 due to ongoing elevated glucose requirements (15mg/kg/min). The diazoxide dose was escalated to 15mg/kg/day and he was then transferred to a specialist centre due to ongoing intravenous (IV) glucose requirement (13mg/kg/min).

**Results:** Genetic testing confirmed a homozygous *ABCC8* splicing mutation (c.2041-1G>C), consistent with diffuse hyperinsulinism, and diazoxide treatment was stopped. A subcutaneous (SC) octreotide infusion was commenced and increased to a maximum dose of 40mcg/kg/day. Despite this, SC glucagon and IV glucose (3.5mg/kg/min) were required to prevent hypoglycaemia. Further options including a trial of sirolimus and near-total pancreatectomy were considered. However, the proband was noted on pre-treatment screening to have post-natally acquired CMV infection, precluding the use of Sirolimus. Due to the potential complications of near-total pancreatectomy, a further trial of diazoxide was commenced. At a dose of 10mg/kg/day of diazoxide, both IV glucose and SC glucagon were stopped as normoglycaemia was achieved.

The baby was discharged at 3.5 months of age on 10mg/kg/day diazoxide and 40mcg/kg/day octreotide, with 3 hourly bolus feeds during the daytime and overnight continuous feeding. Blood glucose was stable on this regimen and fasting tolerance to 6 hours was demonstrated.

**Conclusions:** Congenital hyperinsulinaemic hypoglycaemia due to homozygous *ABCC8* mutation poses management difficulties if the somatostatin analogue octreotide fails to prevent hypoglycaemia. Diazoxide unresponsiveness is often thought to be a hallmark of this mutation. This patient was initially thought to be non-responsive, but this case highlights that a further trial of diazoxide may be warranted, where other available treatments are associated with a significant risk of morbidity. This patient has currently avoided surgical management and treatment with immunosuppressive therapy.

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#### **A CASE OF NEONATAL DIABETES ASSOCIATED WITH NOVEL MUTATION IN PTF1A GENES**

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**Objectives:** Diabetes that occurs within the first six months of life is called neonatal diabetes (NDM). There are two different clinical courses, temporary (TNDM) and permanent (PNDM). Transient neonatal DM cases constitute 50-60% of cases and most commonly are due to sixth chromosome anomalies. Permanent NDM cases constitute 40-50% of cases and are most commonly associated with *KCNJ11* mutations. The less frequent *PTF1A* encodes the pancreatic transcription factor 1A protein, and the mutations of this gene usually result in pancreatic hypoplasia or aplasia-associated PNDM. We aimed to present this case because of the newly identified mutation in the *PTF1A* gene and its very rare occurrence.

**Methods:** Three days old girl when she was followed up for infantile prematurity, and respiratory distress, was consulted for the detection of infantile blood glucose 651 mg/dL. She was born with normal vaginal route at 33 gestational week. Her parents were first-degree cousins but no any known disease in the family. Laboratory investigation; Insulin 0.8  $\mu$ U / ml, C-peptide 0.01 ng / ml, Anti-GAD <5, thyroid function tests and cortisol were normally. There was no acidosis in the blood gas. Regular insulin was started as an infusion of 0.05 U / kg / h. Subsequently, NPH insulin was administered subcutaneously in 3 doses. Daily insulin dose was up to 3 U / kg, but the blood glucose was partially stable with 1 U / kg / day. In the genetic analysis, a previously unidentified homozygous g.23508336G>T mutation in the *PTF1A* gene was detected. Neurodevelopmental disorders can also be seen in PNDM cases due to *PTF1A* gene mutations. However, she has been in our clinic for nine months and the developmental stages are normal and the blood sugars are partially stabilized with NPH insulin.

**Results:** Infants with neonatal diabetes mellitus are usually born with low birth weight. Insulin deficiency in these cases

results in IUGR due to its effect on growth in the intrauterine period.

**Conclusions:** It is known that half of the cases are transient, and fewer parts are permanent DM. PTF1A gene mutations are known to be very rare and are known to cause PNDM due to pancreatic hypoplasia or aplasia.

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#### **DIAZOXIDE-UNRESPONSIVE CONGENITAL HYPERINSULINISM CAUSED BY DE NOVO GERMLINE GCK I211F MUTATION: REPORT OF TWO CASES**

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**Objectives:** Congenital hyperinsulinism (CHI) is a rare disorder of dysregulated insulin secretion resulting in severe hypoglycemia in affected children. Mutations in *ABCC8*, *KCNJ11*, *GLUD1*, *GCK*, *HADH*, *SLC16A1*, *HNF4A*, *HNF1A* and *UCP2* genes are currently known as the genetic etiologies of CHI. Patients with *ABCC8/KCNJ11* mutations are often unresponsive to diazoxide treatment and need pancreatectomy to ameliorate hypoglycemia while patients carrying mutations in other CHI-related genes are often diazoxide-responsive. We report two cases with diazoxide-unresponsive CHI caused by germline *GCK* mutation.

**Methods:** Genomic DNA was extracted from peripheral blood of patient and parents. Direct sequencing of all known CHI-related genes was performed. Whole exome sequencing (WES) was applied in patients without mutation identified in known CHI-related genes by Sanger sequencing. The variants produced from WES with allele frequencies  $\leq 0.5\%$  in both the 1000 Genomes Project and NHLBI-ESP 6500 exome project were filtered. PolyPhen2/SIFT scores were used to predict functional effect of missense variants. A set of 316 genes implicated in pancreatic islet beta cell function was used to prioritize the variants. The final candidate variants were verified by direct sequencing and co-segregation analysis.

**Results:** The first case, born at full term with birth weight 5840 gram, was diagnosed due to persistent asymptomatic hyperinsulinemic hypoglycemia since the age of 2 days. Near-total pancreatectomy was performed at the age of one month after failure of diazoxide treatment. Sanger sequencing revealed a de novo heterozygous *GCK* I211F mutation. The second case, born at full term with birth weight 4300 gram, experienced several seizure episodes since the age of 4 months and was diagnosed as CHI at the age of 11 months. Near-total pancreatectomy was done at the age of one year due to diazoxide treatment failure. WES identified a de novo *GCK* I211F mutation present in 7 of 58 (12%) reads which was missed in initial Sanger sequencing. *GCK* I211F

mutation has been reported to be the most active variant identified to date.

**Conclusions:** *GCK* mutation should be considered a cause of diazoxide-unresponsive CHI. De novo germline *GCK* I211F mosaicism is a novel cause of CHI. WES is valuable for the genetic diagnosis of CHI with mosaicism.

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#### **CONGENITAL HYPERINSULINISM: MANAGEMENT CHALLENGES AND RESPONSE TO LOW DOSE SIROLIMUS**

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**Objectives:** Congenital hyperinsulinism (CHI) is the most common cause of persistent severe hypoglycaemia in neonates. It can be focal, diffuse or atypical in nature. Diffuse form of CHI are generally unresponsive to medical therapy requiring near total pancreatectomy. Recently, Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, was shown to be effective in diffuse CHI but clinical experience is limited with only few cases reported to date. We report our experience of managing a diffuse form of CHI with Sirolimus.

**Methods:** We describe a 15 month old girl with CHI due to homozygous *ABCC8* mutation who responded to a low dose Sirolimus with concomitant octreotide therapy.

**Results:** A 38 week, large for gestational age, neonate presented with recurrent severe hypoglycaemia from day two of life. A critical blood sample collected at the time of hypoglycaemia (blood glucose level 0.7mmol/L) confirmed the diagnosis of hyperinsulinism with elevated serum insulin level and suppressed beta hydroxybutyrate. A homozygous *ABCC8* mutation was confirmed, consistent with diffuse form of CHI. The patient was unresponsive to a maximal diazoxide, glucagon and octreotide therapy.

Sirolimus was commenced at 7 weeks of age with improved glycaemic control and ability to change continuous enteral feeds to bolus feeds. Patient was discharged at 11 weeks of age on Sirolimus and octreotide via continuous subcutaneous infusion. At 15 months of age, glycaemic control remains stable on Sirolimus (mean trough level maintained at 6.1ng/ml, Target 5-9ng/ml) and Octreotide. She has maintained age appropriate growth and developmental milestones. Except for mild hypertriglyceridemia, no other adverse events were noted. Management challenges include feeding issues with oral aversion and dependence on nasogastric feeds.

**Conclusions:** Treatment with Sirolimus, at relatively low trough levels, together with octreotide was safe and effective in our case. This is the first case report showing long term efficacy and safety of Sirolimus in CHI due to a homozygous *ABCC8* mutation. This case adds to growing evidence of published literature of Sirolimus use in unresponsive diffuse CHI. However, Long term studies are required to monitor its ongoing efficacy and safety.

## DIAGNOSIS AND PRENATAL DIAGNOSIS OF CBLA PATIENTS WITH METHYLMALONIC ACIDEMIA

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**Objectives:** The cblA complementation class of inborn errors of cobalamin metabolism (MIM# 251100) is a rare type of methylmalonic acidemia (MMA) with prevalence rate <1/1,000,000. The purpose of study is to investigate the clinical characteristics and diagnosis of cblA and pay attention to the importance of prenatal diagnosis.

**Methods:** There is a four months old cblA patient in China, the clinical progress was recorded, metabolite levels were analyzed by tandem mass spectrometry (MS/MS) and gas chromatography-mass spectrometry (GC-MS), and vitamin B12 loading test was done with hydroxocobalamin. MMAA gene mutation was detected in the proband by next-generation sequencing. His mother underwent amniocentesis and amniotic fluid extraction at 16th week of pregnancy.

**Results:** The clinical manifestations of this patient were recurrent vomiting, diarrhea, cough and infection. Blood MS/MS analysis showed that the level of propionylcarnitine (C3) increased significantly to 6.83 (0.2~5.0)  $\mu\text{mol/L}$ , the ratio of C3/ acetylcarnitine (C2) was 0.43 (0.03~0.20) slightly increased. Urine methylmalonic acid level was 206.89 (0.2~3.6) mmol/mol creatinine and its metabolites were also increased. The result of vitamin B12 loading test was effective. Gene analysis showed that he had c.365T>C (p.L122P) homozygous MMAA mutation, a novel pathogenic mutation, and his parents carried same heterozygous mutation respectively. After the treatment with B12, oral L-carnitine and proper control of diet protein, his symptoms had improved, metabolite levels were lower than before, but still higher than normal. During the follow-up, his psychomotor development was normal when he was 2 years and four months old.

His mother did amniocentesis at 16th week of pregnancy, the level of C3, C3/ C2, methylmalonic acid were significantly higher than normal. We found fetus had a same homozygous mutation of p.L122P as the proband by amniotic fluid cells mutation detection.

**Conclusions:** CblA is a rare type of methylmalonic acidemia, vitamin B12 effective patient had mild symptom, and the prognosis is good. However, due to lack of specific symptoms, the diagnosis should depend on metabolite analysis and gene mutation detection. The technology of next-generation sequencing is the first choice for MMA. Prenatal diagnosis is conducive to eugenics.

## THE USE OF OXYTOCIN TO IMPROVE FEEDING AND SOCIAL SKILLS IN INFANTS WITH PRADER-WILLI SYNDROME

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**Objectives:** Patients with Prader-Willi syndrome (PWS) display poor feeding and social skills as infants and a decreased number of hypothalamic oxytocin (OXT) - producing neurons was documented in adults. Animal data demonstrated that early treatment with OXT restores sucking after birth. Our aim is to reproduce these data in infants with PWS.

**Methods:** We conducted a phase 2 escalating dose study of a short course (7 days) of intranasal OXT administration. We enrolled 18 infants with PWS under 6 months old (6 infants in each step) who received 4 IU of OXT either every other day, daily or twice daily. We investigated the tolerance and the effects on feeding and social skills and changes in circulating ghrelin and brain connectivity by fMRI.

**Results:** No adverse events were reported. No dose effect was observed. Sucking assessed by the neonatal oral motor scale (NOMAS) was abnormal in all infants at baseline and normalized in 88%. The scores of NOMAS and videofluoroscopy of swallowing significantly decreased from 16 to 9 ( $p < 0.001$ ) and from 18 to 12.5 ( $p < 0.001$ ), respectively. Significant improvements in Clinical Global Impression scale, social withdrawal behaviour (Alarm Distress BaBy scale) and mother-infant interactions (Coding Interactive Behaviour scale) were observed. We documented a significant increase in acylated ghrelin and connectivity of the right superior orbitofrontal network that correlated with changes in sucking and behaviour. The follow-up until 2 to 3 years documents the excellent tolerance and possible long-lasting effects of early OXT treatment on social skills, relationship and psychomotor development.

**Conclusions:** OXT is well tolerated in infants with PWS, improves feeding and social skills. These results open perspectives for early treatment in neurodevelopment diseases with feeding problems.



# CLINICAL CHARACTERISTICS OF TURKISH CHILDREN AND ADOLESCENTS WITH TYPE 2 DIABETES

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**Objectives:** The prevalence of type 2 diabetes (T2D) is increasing in children and adolescents along with obesity and insulin resistance. This study aimed to investigate the clinical features of a large pediatric Turkish population with T2D.

**Methods:** Our retrospective study included 255 children and adolescents with T2D who were evaluated in 37 different centers in Turkey. Clinical and laboratory findings and treatment regimens at the time of diagnosis were analysed.

**Results:** The mean age at diagnosis was  $13.7 \pm 2.2$  (range, 6.56-18.8) years. Only 6.7% (17 patients) were younger than 10 years old. The majority was female (69%) and had a family history of T2D (80%). The most common symptoms at the time of diagnosis were weight gain (54%), polyuria-polydipsia (26.7%), remaining of the participants was diagnosed incidentally. Only 4.2% of the cases had diabetic ketoacidosis, however 11% had ketonemia and/or ketonuria. The mean body mass index (BMI) z-score was  $2.39 \pm 0.83$  (range: 1.01-5.9). The mean HbA1C level was  $9.7 \pm 2.78$  (range: 5.19-18.4), 14 (5.5%) of the cases had an HbA1C  $< 6.5\%$ . The cases whose HbA1C  $< 6.5\%$  had glucose values confirmatory of diabetes, the mean fasting glucose level of these cases was  $171.7 \pm 57.7$  (range 128-277) mg/dl. Forty one percent (41%) of the cases were treated with metformin, 32% with combination of insulin and metformin, 13% with insulin and 13% with lifestyle modification alone.

**Conclusions:** This is the largest group of children with T2D reported from Turkey. Most of the children diagnosed with T2D required medical treatment. T2D should be taken into consideration in obese children with typical symptoms of diabetes.

## POSTER SESSION 2

Friday, September 15, 2017, 11:30am-12:30pm

### P2 - Global health

#### P2-700 – P2-704

P2-700

#### ACCESS TO FLUDROCORTISONE AND TO ORAL AND INJECTABLE HYDROCORTISONE FOR THE MANAGEMENT OF CONGENITAL ADRENAL HYPERPLASIA IN THE WHO EASTERN MEDITERRANEAN REGION

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**Objectives:** Most countries maintain a National List of Essential Medicines (EML). It is based on two non-binding EMLs (children and adults) published by the World Health Organisation (WHO). The WHO EML includes 3 medicines that are essential for the management of congenital adrenal hyperplasia (CAH): fludrocortisone (F), oral (OH) and injectable (IH) hydrocortisone. Information on the true access to F, OH and IH by the patient is not readily available. We aimed at determining 1. Whether F, OH and IH are included in the National EMLs for the WHO Eastern Mediterranean Region (EMR) (+ Algeria) and 2. To which extent inclusion in the National EMLs is associated with patient access to the medicines (registration, availability, manufacturer, cost to patient).

**Methods:** We analysed the published National EMLs for the EMR countries + Algeria and surveyed pediatric endocrinologists in each country to assess true access to F, OH or IH.

**Results:** EMLs were published by 18/23 countries (Income group: low [n=3], lower-middle [n=6], upper-middle [n=3] and high [n=6]). Information on true access was provided by pediatric endocrinologists from 19/23 countries. Cinq countries offered CAH screening to part or all of the population. F was listed in the EMLs of 9/18 (=50%) countries and was officially registered in 12/19 countries (NOT Algeria, Bahrain, Djibouti, Lebanon, Morocco, Pakistan, Sudan). Registration was associated with access (from at least 6 pharmaceutical companies) most or all of the time. OH was listed in the EMLs of 11/18 (=61%) countries, was registered in most countries (NOT Djibouti, Pakistan) and routinely available (from at least 9 pharmaceutical companies) in most countries except Djibouti and Egypt. IH was listed in all EMLs, registered in all countries and almost always available at least

in hospitals (from at least 9 pharmaceutical companies). Financial support to families for accessing each medicine in each country varied from no subsidization to full governmental coverage.

**Conclusions:** True access to F and OH for the management of CAH is uneven in the EMR where CAH is common (consanguinity) and cost varies greatly between countries. Potential reasons include country's income group and differences in health policies. Understanding system differences may lead to new avenues that promote better access.

P2-701

#### **EFFECTIVENESS OF A TARGETED EDUCATIONAL INTERVENTION IN A PEDIATRIC DIABETES PROGRAM FOCUSED PREDOMINANTLY ON ACUTE CARE IN HAITI**

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**Objectives:** Patients affected by Type I diabetes (T1D) need ongoing education and self-management skills to survive. In resource-limited countries such as Haiti, many families struggle to meet their daily needs for food and shelter. The healthcare system is oriented towards acute care. Consequently, children diagnosed with T1D have high morbidity and mortality despite access to insulin due to significant gaps in self-management skills. We report our experience in assessing patient knowledge as well as conducting an educational intervention in a pediatric T1D program, started in 2013, in northern Haiti. This study evaluates a targeted educational intervention in a pediatric diabetes program focused predominantly on acute care.

**Methods:** We conducted an interventional pre and post-assessment of patients age  $\geq 18$  currently enrolled in the Pediatric T1D Program ( $n=14$ ) at the Hôpital Sacré Coeur in Milot, Haiti. Individual education sessions using a "T1D toolkit" were delivered in creole by an investigator.

Participants completed linked assessments composed of 9 questions before and after the educational intervention. Primary outcomes included 1) # of participants with a satisfactory performance on the pre-assessment ( $\geq 65\%$  score), and 2) trajectory of individual performance on post-assessment. Secondary outcomes included identification of knowledge gaps defined as  $\geq 50\%$  of participants with incorrect answer for question.

**Results:** Eight participants were male. Mean duration of diabetes was 32 mos (IQR 6,48). Pre-assessment mean score was 31% with only 1 participant scoring  $\geq 65\%$ . On post-

assessment, mean score was 35%; 5 participants (35%) had improved scores. One participant scored  $\geq 65\%$  although 3 participants scored  $\geq 50\%$ . Knowledge gaps in disease management, hypoglycemia and DKA prevention were apparent.

**Conclusions:** This study revealed substantial knowledge gaps among patients with T1D despite being part of an established pediatric T1D program in Haiti for several years. Targeted education was marginally effective in improving knowledge as measured. Possible reasons include assessment tool efficacy, low literacy, and need for continual reinforcement. The program is now developing its own chronic care service model and has hired a local diabetes nurse educator to provide ongoing education.

P2-702

#### **EARLY GROWTH IN RELATION TO FAMILY SIZE AND BIRTH ORDER**

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**Objectives:** Among the most important environmental cues to child growth is the family structure. The disadvantages of having a large family include financial stress, a missed connection with some of the children and emotional stress put on the family by the problems that others in the unit are experiencing. Here, we framed the hypothesis that family size and birth order impact infantile (I) and childhood (C) growth, and the transition age between them (ICT).

**Methods:** Among the most important environmental cues to child growth is the family structure. The disadvantages of having a large family include financial stress, a missed connection with some of the children and emotional stress put on the family by the problems that others in the unit are experiencing. Here, we framed the hypothesis that family size and birth order impact infantile (I) and childhood (C) growth, and the transition age between them (ICT).

**Results:** The study group subjects were shorter than control at birth and at C ( $p5^{th}$ ) in large families were short at birth ( $-0.3$  SDS) and at infancy ( $-0.4$  SDS) and they lost additional  $0.3$  SDS at ICT age as compared to  $0.03$  SD in small families ( $p=0.029$ ). Family size correlated negatively with birth ( $r=-.112$ ,  $p=.022$ ), I ( $r=-.141$ ,  $p=0.004$ ) and C length ( $r=-.263$ ,  $p<0.01$ ), and the birth rank correlated negatively with I ( $r=-.149$ ,  $p<0.0001$ ) and C length ( $r=-.208$ ,  $p<0.0001$ ) and positively with ICT age ( $r=.146$ ,  $p<0.001$ ). The ICT age correlated strongly with the loss of height from I to C ( $r=-.627$ ,  $p<0.0001$ ) and with C length ( $r=-.361$ ,  $p<0.0001$ ).

**Conclusions:** 1. Prenatal, infantile and mostly childhood length are compromised in children from large families. 2. As the family grows larger the younger children get shorter. 3. Delayed ICT is a central mechanism for short stature in large families; each month of delayed ICT was associated with a loss of  $0.19$  SDS at C.

# EARLY LIFE STRESS INDUCES GLUCOSE INTOLERANCE AND INSULIN SECRETION FAILURE IN ELDER FEMALE MICE

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**Objectives:** The incidence of metabolic disorders is increasing worldwide. Besides diet and life style habits, epidemiological studies highlighted an association between post-traumatic stress and metabolic disorders. Based on the concept of Developmental Origins of Health and Diseases our study aimed to investigate whether early life stress can trigger metabolic disorders and associated key feature i.e. low-grade inflammation.

**Methods:** Maternal separation (MS) is an established model of early life stress in rodent. C3H/HeN mice pups were separated from their dam and the rest of the litter 3 hours per day during 10 days starting at post-natal day 2 (PND2). All experiments were carried out in female offspring aged of PND350 on standard diet. Metabolic state was evaluated by oral glucose tolerance test (OGTT) and intraperitoneal insulin tolerance test (ITT). Cellular immune response was analyzed by primary cell culture of spleen, *lamina propria* (LP) and mesenteric lymph nodes. Immune state of liver and pancreas were evaluated through cytokine measurements by ELISA.

**Results:** MS decreased body weight of female mice at PND350. MS mice developed glucose intolerance, measured during OGTT. The area under the curve (blood glucose mg/dL/2h) during OGTT was significantly increased by MS. MS did not induce a loss of insulin sensitivity measured by ITT. Instead, MS decreased fed plasma insulin levels and insulin secretion during OGTT without any modification of cytokine signature in pancreas. MS increased TNF $\alpha$  and TGF $\beta$  concentrations in the liver. Furthermore, MS increased anti-CD3/CD28 induced secretion of IL17 and IL22 by LP cells and IFN $\gamma$  by splenocytes.

**Conclusions:** For the first time, this study showed that early life stress induces glucose intolerance associated with a loss of insulin secretion in mice non-genetically predisposed to metabolic disorders or type 1 diabetes and fed with standard diet. Interestingly, glucose intolerance is associated with local (Th17 and Th22 in small intestine LP) and systemic (Th1 spleen) low-grade inflammation.

# SEDENTARY BEHAVIOR ASSOCIATED WITH METABOLIC SYNDROME AMONG KOREAN ADOLESCENTS

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**Objectives:** Sedentary behavior may be a contributor to various health outcomes. We aimed to investigate the relationships between daily sitting time and the risk of metabolic syndrome in Korean adolescents.

**Methods:** Data for a total 486 adolescents aged 12 to 18 years was obtained from the Korea National Health and Nutrition Examination Survey 2014. Sitting time was defined as time spent in a seated or reclined position except sleep. Sitting time was divided into three groups: <8 hours; 8-12 hours;  $\geq 12$  hours. We analyzed the association between sitting time with multiple variables. Logistic regression analysis for risk of having metabolic component associated with sitting time was assessed.

**Results:** Mean age was  $15.1 \pm 0.1$  years, 53% were male and 45.5% resided in metropolitan area. Mean daily sitting time was  $620.9 \pm 9.9$  minutes/day, sleeping time was  $7.1 \pm 0.1$  hours/day, prevalence of positive metabolic component was  $45.5 \pm 2.7\%$ . Sitting time was positively correlated with female, metropolitan area and less sleeping time. Overweight youth were not more sedentary than lean youth. In multivariate logistic regression analysis, adolescents who did more sitting were more likely to have metabolic component independently of age, gender, area of residence, sleeping time and body mass index.

**Conclusions:** Longer daily sitting time seem to be associated with an increased risk of having metabolic component in adolescents. These findings highlight the need to focus on decreasing sitting time in all youth, rather than focusing on only with obesity.

## POSTER SESSION 2

Friday, September 15, 2017, 11:30am-12:30pm

### P2 - Growth and GH/IGF Axis

P2-800 – P2-857

P2-800

### POSTNATAL GROWTH OF VERY LOW BIRTH WEIGHT (VLBW) PRETERM INFANTS WITH DIFFERENT RISK FACTORS

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**Objectives:** The aim was to evaluate the effect of different risk factors on the postnatal growth of preterm very low birth weight infants (VLBW) in the first 18 months following birth including : the severity of bronchopulmonary dysplasia (BPD) presence of sepsis, necrotising enterocolitis, periventricular hemorrhage, patent ductus arteriosus.

**Methods:** The anthropometric data for sixty nine (39 F, 30 M) preterm born infants with a gestational age =  $26.5 \pm 1.7$  weeks and birth weight =  $920 \pm 183$  g with BPD were recorded at birth and at  $8 \pm 2$  months and  $16 \pm 3$  months postnatally. 45 had culture-proved sepsis, 14 had PVH, 14 had NEC, and 36 had PDA.

**Results:** At birth, the majority of those preterms 66/69 (96 %) were appropriate for gestational age (AGA). Only 3/69 (4%) preterms had birth weight SDS < -2 for GA, and 3/69 (4%) had length SDS < -2 for GA. At 16 +/- 3 months of age preterms with severe BPD were shorter and had smaller HCSDS compared to those with moderate severity (P < 0.0001 and p 0.045 respectively). Preterms who were part of twins remained shorter at 8+/- 2 months of age compared to singleton preterms but not at 16+/-3 months of age. They had smaller head size compared to singletons at 16+/- 3 months. Preterms with proved sepsis and those with NEC required significantly longer mechanical ventilation and were shorter at 16+/- 3 months of life compared to those without sepsis or NEC. Preterms with BPD and PVH > 2 required more prolonged MV and O2 therapy ( p < 0.01)and were shorter (p = 0.05) and had smaller HCSDS ( p <0.01) at 16 +/- 3 months compared to those without PVH . Preterm infants with BPD who presented with PDA (confirmed by Echocardiography) had significantly longer duration of mechanical ventilation and O2 therapy as well as smaller HCSDS at 16 +/- 3 months of age compared to those without PDA.

**Conclusions:** Most (84%) of preterm infants with VLBW infants show normal or above normal length growth velocity postnatally compared to full term infants. The degree of severity of the BPD, and the presence of sepsis, NEC, PDA and PVH ominously affects postnatal somatic growth in these infants.

Growth Data of VLBW infants at 18 months of life in relation to different risk factors

	Sepsis	No Sepsis	NEC	No NEC	PDA	No PDA	PVH>2	No PVH
Number	45	24	14	55	36	33	14	55
LSDS	-1.5	-0.8	-2.1	-1.1	-1.2	-1.3	-1.7	-1.2
HCSDS	-1.7	-1.1	-1.8	-1.3	-1.9	-0.9	-2.6	-1.1
BMISDS	-0.1	0.3	-0.2	0.1	0.2	-0.2	-0.3	0.1

NEC = necrotising Enterocolitis, PDA = patent ductus arteriosus, PVH = periventricular hemorrhage.  
LSDS = length SDS, HCSDS = head circumference SDS, BMISDS = body mass index SDS

P2-801

PROFILING THE EFFECTS OF PAPP-A2 DEFICIENCY ON THE HUMAN SERUM METABOLOME

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**Objectives:** Mutations in the PAPP-A2 gene, which encodes for the pregnancy-associated plasma protein-A2 (PAPP-A2), a metalloprotease highly specific for IGFBP-3 and -5, have

recently been reported to cause a novel syndrome of progressive growth failure that is characterized by increased circulating IGF-I and IGF-II and decreased IGF bioactivity. The analysis of the serum metabolome by gas chromatography - mass spectrometry was employed to investigate the metabolic effect of PAPP-A2 deficiency.

**Methods:** Serum samples from a Spanish family consisting of two parents and four children, two (a 10.5-year-old girl and a 6-year-old boy) with a homozygous loss-of-function mutation in the PAPP-A2 gene (p.D643fs25\*) and undetectable PAPP-A2 activity, were studied by untargeted metabolomics. Principal component analysis (PCA) and descriptive statistics were employed to explore the effect of the mutation on the metabolism of carbohydrates, proteins and lipids.

**Results:** PCA showed the naïve clustering of the samples according to the presence/absence of the mutation, with polyols (myo-inositol and ribitol), organic acids (pyruvate and 3-hydroxybutyrate) and amino acids (tryptophan, serine, ornithine and lysine) being the metabolites that mainly contributed to the separation showed by the model. Noteworthy changes were further observed using descriptive statistics to compare the relative abundance of the metabolites among the four siblings. A marked decrease of amino acids, free fatty acids, polyols and sugars was observed, suggesting reduced protein synthesis and altered lipid and carbohydrate metabolism likely related to the reduced bioactivity of IGF-I.

**Conclusions:** New insights into the metabolic effect caused by the loss of PAPP-A2 function have been provided in the study; this allows depicting a wider picture of the effect of the PAPP-A2 mutation not only related to the growth failure, but also to its action on crucial metabolic pathways. Metabolic analysis in response to rhIGF-I treatment is forthcoming.

P2-802

SERUM STANNIOCALCIN (STC)2 LEVELS ARE INCREASED IN PREPUBERTAL OBESE CHILDREN

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**Objectives:** Obese patients are generally taller than their peers, although GH secretion is reduced. These patients present an increase in circulating insulin-like growth factor I (IGF-I) levels, although this augment does not necessarily imply that bioactivity of this growth factor is increased. New

members of the IGF system have been identified including stanniocalcins (STCs), which modulate the activity of IGFs. Our aim was to analyze the novel component of the IGF axis, stanniocalcin-2, in obese prepubertal children.

**Methods:** Serum samples of 33 prepubertal (Tanner stage I) control and 60 obese children [(BMI>+2 SDS, 50% non-insulin-resistant (NIR), 50% insulin-resistant (IR)]. IGF-I, IGFBP-3 and insulin were measured by chemiluminiscent assays, STC2 by ELISA and IGF bioactivity by a quantitative kinase receptor activation assay (IGF-KIRA). HOMA index was also determined.

**Results:** There was an increase in serum IGF-I, IGFBP-3 and STC2 levels in obese children, with a higher increase of IGF-I in IR patients. When IGF-KIRA was determined, obese children presented no differences in IGF-I bioactivity with respect to controls or between IR and non-IR groups. There were no significant correlations of IGF-KIRA or STC2 with HOMA index.

**Conclusions:** As total IGF-I levels are increased in obese children but IGF-I bioactivity is not, stanniocalcin-2 could act to inhibit the peripheral GH-IGF axis to avoid over activation of IGF-I bioactivity.

	Control	Obese NIR	Obese IR
IGF-I (µg/L)	96 ± 35	190 ± 57***	221 ± 66*** #
IGFBP-3 (mg/L)	3.09 ± 0.78	4.12 ± 0.75***	4.50 ± 0.76***
IGF-KIRA ((µg/L)	1.74 ± 0.89	1.46 ± 0.54	1.67 ± 0.76
STC-2 (µg/L)	14.2 ± 3.2	17.6 ± 3.22**	16.5 ± 3.3**

Table 1. Serum levels of insulin-like growth factor I (IGF-I), IGF binding protein-3 (IGFBP-3), IGF- kinase receptor activation assay (IGF-KIRA) and stanniocalcin (STC)2 levels in control children, obese non-insulin-resistant (NIR) and obese insulin-resistant (IR). Significant:\*\* p<0.01, \*\*\*p<0.001 vs control group; #p<0.05 vs. NIR.

P2-803

**AARSKOG SYNDROME – PERSPECTIVES ON GROWTH HORMONE THERAPY**

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**Objectives:** The etiology of short stature is diverse and it varies from the classic provable GH deficiency to idiopathic causes, some in the context of dysmorphic syndromes. Aarskog syndrome (AS) is an X-linked inherited disease characterized by short stature, facial, skeletal, and genital anomalies, with ophthalmic, dental, and cardiac defects rarely seen. We report the case of 10 years 10 months old boy diagnosed with AS that benefited of growth hormone therapy.

**Methods:** Clinical and paraclinical evaluations were performed periodically (6 months).  
**Results:** We report the case of 10 years 10 months old boy, diagnosed at 2 months with AS (due to specific phenotype). He was born at term, naturally, with SGA (birth weight of 2400g), the only child of a nonconsanguineous couple, but with a family history of 5 cases on the mother's sides with AS. Medical history revealed atrial septal defect diagnosed at birth and congenital bilateral undescended testis, for which the corrective surgical intervention was performed at age 2. At age 3 he was evaluated at the Endocrinology Department due to significant growth retardation (height -4.5SD, weight -3.5SD), associating delayed bone age (1 year) and low IGF-1 (40.8 ng/ml, normal=49-289). In the context of SGA, with accentuated growth retardation until the age of 3, GH administration was considered and started. After approximately 7 years of treatment (with a medium dose of 0.041 mg/kg/day, varying between 0.026-0.048mg/kg/day) the patient gained 47.5 cm, with an improvement of 1.77 SD (currently height at -2.73SD), gaining 5cm in predicted final height (currently 162.4±3.3cm). No side-effects were reported.

**Conclusions:** When reviewed the literature, the incidence of AS is exceedingly rare in clinical practice and experience with GH treatment is exceptionally limited (31 cases cumulated from case series and case reports). We presented the case of boy diagnosed with AS, born SGA and treated with GH therapy for 7 years, with a very good growth response, especially in the context of early treatment initiation. Although final height data for all these patients are still awaited, the present results support the use of GH to promote growth in children with AS.

P2-804

**THE ROLE OF BASAL BIOCHEMICAL TESTS IN THE DIAGNOSTIC WORK-OUT OF GROWTH HORMONE DEFICIENCY (GHD) IN THE NEWBORN PERIOD**

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**Objectives:** GHD diagnosis represents a challenge in neonates in whom provocative tests are difficult to implement. The accuracy of basal GH-IGFs biomarkers in the diagnostic work-out of GHD in neonates is still controversial. To assess the diagnostic accuracy of basal GH/IGF-I/IGFBP3 concentrations for GHD diagnosis and to evaluate serum GH usefulness under hypoglycemia in neonates.  
**Methods:** Retrospective case-control study of 25 full-term neonates [median age (m): 25 days] with confirmed GHD based on growth retardation, stimulated GH<4.7 µg/L, other pituitary hormone deficiencies and brain MRI. GHD group was compared with 22 neonates (m: 22 days) referred to the Endocrinology Division with clinical suspicion of GHD, in

whom endocrine disorders were ruled out (non-GHD group) and with 52 healthy neonates (m: 18 days). Main outcome measures by receiver operating curve were sensitivity (S), specificity (Sp) and diagnostic efficiency (DE) of random basal GH/IGF-I/IGFBP3 (Siemens), expressed as value (95 IC%).

Critical GH samples under hypoglycemia in 8 GHD, 6 non-GHD and 8 neonates with congenital hyperinsulinism (m: 17 days) were compared to current guidelines reference of 5.0 µg/L\*.

**Results:** To exclude GHD, basal GH  $\geq 6.5$  µg/L showed S: 0.84 (0.60-0.97), Sp: 0.61 (0.50-0.72) and DE: 70%; IGF-I  $\geq 30$  µg/L had S: 0.91 (0.70-0.99), Sp: 0.71 (0.58-0.81) and DE: 76%; and IGFBP-3  $\geq 0.8$  µg/mL had S: 0.30 (0.06-0.65), Sp: 0.97 (0.89-1.0) and DE: 87%. When GH and IGF-I were considered together, Sp and DE improved [S: 0.91 (0.60-0.99); Sp: 0.94 (0.84-0.99); DE: 94%], with a negative predictive value of 0.98 (0.89-1.0). In hypoglycemia, GH concentration did not reach the cutoff level in 5/8 GHD (63%), 2/6 non-GHD (33%) and 4/8 (50%) neonates with congenital hyperinsulinism.

**Conclusions:** In neonates with clinical suspicion of GHD, the coexistence of GH  $\geq 6.5$  µg/L and IGF-I  $\geq 30$  µg/L excludes GHD diagnosis with high diagnostic accuracy. IGFBP-3 seems to be a highly specific biomarker for GHD diagnosis in newborns. Since hyperinsulinemic neonates may present a lack of GH response to hypoglycemia, metabolic disorders should be ruled out to further interpret GH results.

\*Grimberg A. et al. *Horm Res Paediatr*. 2016.

P2-805

#### NEAR ADULT HEIGHT (NAH) IN GIRLS WITH TURNER SYNDROME (TS) TREATED WITH GROWTH HORMONE (GH) FOLLOWING EITHER INDUCED OR SPONTANEOUS PUBERTY

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**Objectives:** Background: Girls with TS who experience spontaneous puberty (SP) often have a milder phenotype than those who require induction of puberty (IP), and are predicted to have better growth on GH supplementation. Aim: To determine if girls with TS with SP respond differently to GH therapy than those with IP.

**Methods:** Within the 25 years of cumulative data in the Pfizer International Growth Database (KIGS), 772 girls with TS were treated with GH and followed to NAH (near adult height). Puberty was induced in 627 subjects while 145 experienced spontaneous puberty. The Wilcoxon rank sum test was performed and median values are presented. \* =  $p < 0.05$ .

**Results:** Weight SDS at birth (-1.1/-1.0), and age (7.4/8.0 yrs), weight SDS (-1.9/-1.7), and BMI SDS (0.1/0.1) at GH start were similar in SP and IP groups, respectively. At GH start, girls with SP were a bit shorter than those with IP (Ht-SDS TS -0.2/-0.0\*; Ht-SDS: -3.3/-3.1\*), but median Ht-SDS-MPH SDS (-

2.8/-2.8) were similar when mid parental height (MPH) was taken into consideration. GH doses (0.3/0.3 mg/kg/wk) during therapy were similar. At the beginning of puberty, the SP group was younger (12.4/13.3 yrs\*) but its Ht-SDS TS (1.8/1.8) and  $\Delta$ Ht SDS (Pub-GH start) TS (2.0/1.8) were not significantly different than those in the IP group. Duration of puberty before reaching NAH was comparable between groups (3.0/2.8 yrs). Girls with SP reached NAH at earlier ages (15.8/16.8 yrs\*) and grew more between the onset of puberty and NAH (10.7/8.5 cm\*) than those in the IP group. Ultimately, however, Ht-SDS TS at NAH were similar in both groups (1.8/1.7).

71.4% of subjects with IP had a 45,X karyotype versus 43.1% of those who experienced SP but subsequently arrested, and 17.8% of those with SP who continued pubertal progression on their own.

**Conclusions:** Girls in the spontaneous puberty group tended to grow more during puberty than those in the induced group, but not enough to make a difference in NAH SDS TS. Therefore, spontaneous puberty is unlikely to be associated with a better growth outcome.

P2-806

#### PREDICTORS OF GROWTH RESPONSE IN SHORT CHILDREN BORN SMALL FOR GESTATIONAL AGE (SGA) TREATED WITH RHGH.

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**Objectives:** The aims of this study were to evaluate various criteria of good response, validate the KIGS mathematical model and develop prediction models for adult height (AH) and height gain.

**Methods:** Longitudinal, retrospective growth study of short SGA children treated with rhGH (n=103) or combined rhGH + GnRH analogue (n=36). Criteria for first-year good response included height increase  $\geq 0.5$  and  $\geq 0.3$  SDS, growth velocity increment (GV)  $\geq 3$  cm/yr and GV  $\geq 1$  SDS. Good long term response criteria was defined when AH was higher than target height (TH). Prediction models were developed by multiple regression analysis and STEPWISE method.

**Results:** The percentage of patients with first-year good response varies between 46.6% (height increase  $\geq 0.5$  SDS) and 81.6% (GV  $\geq 1$  SDS). The criteria that best correlates with good long-term response is the increment in GV  $\geq 3$  cm/yr since 48% reached their target height and this criteria showed the greatest correlation with height gain ( $r=0.47$ ,  $p=0.026$ ). The KIGS mathematical models predicts adequately the first-year GV (studentized residual (SR) = 0.063), AH (SR=0.4) and AH gain (SR= 0.6) but not the second year GV (SR=-1.5). Table 1 shows 4 prediction models created for AH and height gain. TH and distance to TH at start of treatment, birth length and rhGH dose are direct predictors of AH. For patients treated with rhGH, AH gain is predicted through distance with TH at start, birth length and weight SDS at onset, which is also a

predictor for the combined rhGH+GnRHa treatment group, in addition with the second year GV.

**Conclusions:** Growth velocity increment  $\geq 3\text{cm/yr}$  is the best short-term criteria of good response. KIGS prediction models are valid and applicable to our population. Adequate adult height prediction models have been developed and show that long-term response depends mainly on intrinsic pretreatment factors and on the first 2-year growth response.

Table 1. Prediction models for rhGH and combined rhGH/GnRHa treatment in short SGA children.

	rhGH		rhGH + GnRHa	
	R <sup>2</sup>	Equation	R <sup>2</sup>	Equation
Adult Height SDS	0,49	$-0,059 + [0,492] \times \text{Target height SDS} + [0,252] \times \text{Birth length SDS}$	0,58	$-3,13 + [0,737] \times \text{Height-TH at start SDS} + [64,29] \times \text{Second-year rhGH dose} + [1,15] \times \text{First-year height gain SDS}$
Height Gain SDS	0,61	$0,328 - [0,318] \times \text{Height-TH at start SDS} + [0,258] \times \text{Birth length SDS} - [0,447] \times \text{Weight at start SDS}$	0,57	$-0,232 + [0,294] \times \text{Second-year growth velocity SDS} - [0,452] \times \text{Weight at start SDS}$

P2-807

**GROWTH PATTERNS OF CHILDREN WITH SICKLE CELL ANEMIA EXPOSED TO HYDROXYUREA THERAPY**

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**Objectives:** Sickle cell anemia (SCA) is an inherited disorder of hemoglobin associated with poor growth, altered body composition, and delayed skeletal maturation. Increasingly used in SCA, hydroxyurea (HU) is an oral medication that causes increased fetal hemoglobin and reduction in many acute complications of SCA. Little is known about the effect of HU upon growth, particularly when initiated at an early age. We aimed to describe the effect of short-term HU treatment on growth in children with SCA. We hypothesized that patients treated with HU will have improved linear growth compared to untreated children.

**Methods:** A retrospective study of patients at our institution with SCA born between 1993 and 2016 was conducted. Data included laboratory parameters (hematologic and endocrine values when available), anthropomorphic data from birth through present, and treatments (primarily HU and chronic blood transfusion therapy). Height for age Z-scores (HAZ) were recorded using the appropriate WHO or CDC growth curves.

**Results:** Of 160 total patients with SCA, 108 were treated with HU alone or prior to any additional therapy, and 55% were male. Median age at HU start was 5.6 years, and the median duration of use was 3.4 years. HAZ was calculated for 2 years pre-treatment, at treatment initiation, and after 2 years on treatment in a total of 35 patients with available data. We found that there appears to be a statistically significant reduction in HAZ after 2 years of HU treatment (median HAZ -0.27 at baseline, -0.56 after 2 years of HU therapy,  $p<0.0001$ ).

**Conclusions:** HU is associated with a number of salutary effects but its effect upon growth is poorly described. In this study, we have a large amount of growth data for children who have been treated and untreated for many years. Ongoing additional analyses to account for patient age, sickle cell-related comorbidities, growth velocity, pubertal/bone age status, and medication adherence are actively underway and are needed to further delineate the effect of HU on linear growth. We recommend that families receive counseling on the risks and benefits of HU therapy prior to treatment initiation.

P2-808

**PHARMACOKINETICS OF RECOMBINANT HUMAN IGF-1 IN PATIENTS WITH PAPP-A2 GENE MUTATION, GROWTH RESPONSE TO THERAPY, AND EFFECTS ON GLUCOSE METABOLISM AND BONE DENSITY**

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**Objectives:** PAPP-A2 is a protease which cleaves IGFBP-3 and -5, thereby releasing free IGF-I. This study seeks to describe the 24-hour PK profile of free and total IGF-I to a single dose of rhIGF-1 in 3 short statured siblings with a homozygous mutation in PAPP-A2, compared to heterozygous relatives and healthy controls. We also describe the growth response and effects on glucose handling and bone mineral density (BMD) with one year of IGF-1 therapy.

**Methods:** Three affected siblings (P1, P2 and P3), their heterozygous parents (M and D) and two healthy adult controls (C1 and C2) participated. The subjects received a single SC dose of rhIGF-1 (120  $\mu\text{g/kg}$ ), followed by serial blood samples collected over a 24-h period. The two younger siblings (P2 and P3) were started on rhIGF-1 treatment. An oral glucose tolerance test (OGTT) and dual X-ray absorptiometry (DXA) scan were obtained at baseline and after one year of treatment. Non-compartmental PK analysis was performed.

**Results:** SC administration of rhIGF-1 increased the concentration of free and total IGF-I in patients with PAPP-A2 deficiency. The PK profile and parameter estimates were comparable in the affected patients, heterozygous carriers and healthy controls (Table 1). On day 51 after initiation of therapy, P2 developed pseudotumor cerebri (LP opening pressure of 52 mm H<sub>2</sub>O). Therapy discontinuation resulted in resolution of symptoms. P2's height further decreased by 0.1 SD despite being in mid-puberty (Table 2). Treatment with rhIGF-1 is ongoing in P3, who is currently prepubertal. His height velocity improved from 3.0 to 6.2 cm/year in the first



year of treatment (? height SD +0.4). At baseline, the affected patients had an abnormal glucose metabolism with marked insulin resistance, as well as mildly decreased to low-normal size-corrected BMD (Table 2). In P3, the insulin resistance resolved after one year of IGF-1 therapy and total body BMD increased significantly.

**Conclusions:** rhIGF-1 at standard doses resulted in similar PK characteristics in patients with PAPP-A2 deficiency, heterozygous relatives and healthy controls. The youngest affected patient experienced a modest response to therapy with rhIGF-1, as well as beneficial effects on glucose metabolism and bone mineral density.

**Table 1** Pharmacokinetic analysis

	P1	P2	P3	M	D	C1	C2
Age (years)	19	14	10	47	40	20	29
Dose (µg)	5000	6600	2700	9400	8600	8800	6500
C <sub>max</sub> (µg/L)	235	254	186	283	203	291	278
T <sub>max</sub> (h)	4	5 (7)†	3.5 (5)†	3	3.5 (8)†	6	5
AUC <sub>0-12h</sub> (µg·h/L)	2406	2346	1602	2742	2068	3002	2755

Baseline-corrected concentrations were used in this analysis.  
†Profiles with multiple 'peaks'; for T<sub>max</sub> estimation the time of first peak was used.  
Robust estimation of half-life not possible due to missing later data points (12 and 24h).

**Table 2** Anthropometric characteristics and results at baseline and 12 months

	Baseline			12 months	
	P1	P2	P3	P2	P3*
Age (years)	19	14	10	15	11
Height (cm)	138	142	122	147	128.2
Height SDS	-3.8	-2.9	-2.9	-3	-2.5
BMI (kg/m <sup>2</sup> )	21	27	14	27	16
Height velocity (cm/year)	NA	4.2	3	5	6.2
Bone Age (years)	18	13	9	14	10
BMD Z-score corrected for height					
Whole Body	-0.5	-2.5	-0.7	-2.2	-0.1
Lumbar Spine	-1	-1.3	-0.1	-1.9	0.3
Hip	-0.03	-1.6	-0.5	-2	-0.4
Forearm	-0.04	-1.7	-0.5	-1.8	0
BMD % increase from baseline					
Whole Body				9.9	13.6
Lumbar Spine				5.4	12.9
Hip				5.9	6.1
Forearm				7.6	8.5
OGTT (Glucose mg/dL/ Insulin µU/mL)					
0 minutes	98/23	100/35	111/18	90/60	84/4
30 minutes	160/96	144/223	194/88	117/205	114/38
60 minutes	200/64	176/145	204/113	93/110	78/11
90 minutes	176/147	166/188	157/132	110/128	96/22
120 minutes	152/95	141/244	128/107	106/124	90/22

\* P3 was treated with rhIGF-1  
Abbreviations: BMI, body mass index. BMD, bone mineral density. OGTT, oral glucose tolerance test

P2-809

**GROWTH HORMONE NEUROSECRETORY DYSFUNCTION: PART OF THE SPECTRUM OF GROWTH HORMONE DEFICIENCY DISORDERS WHICH BENEFIT FROM GROWTH HORMONE TREATMENT**

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**Objectives:** None of the current provocative tests for GH deficiency (GHD) achieve 100% sensitivity and specificity. GH

neurosecretory dysfunction (NSD) is a term used to describe children with growth failure, normal stimulated GH responses, but impaired spontaneous overnight GH secretion. We describe our experience in diagnosing and treating GHNSD between 2013-2016.

**Methods:** We reviewed a cohort of 73 children admitted for 12-hour overnight GH profiles (with 20-minute sampling) over 4 years. Auxological and biochemical data were collected at the time of profiling, and, where available, at 1-year follow-up. GHNSD was defined when the overnight profile showed <3 spontaneous peaks of GH ≥6.7 µg/L. In the subcohort fulfilling this criterion, we compared auxological outcomes between those who did and did not receive GH therapy.

**Results:** GH profiles were performed on 52 boys and 21 girls presenting with growth failure at a median age of 8.1 (IQR 5.1-10.3) years, with a median height of -3.3 (-3.7 to -2.4) SDS and a median height velocity (HV) of -2.1 (-2.8 to -1.0) SDS. All had low IGF-1 concentrations with 46.6% below the reference range, but normal (≥6.7 µg/L) GH peaks to provocation (median GH peak 10.6 (9.1-13.5) µg/L). 55 patients had GHNSD, and 1-year auxological outcome data were available for 24 (13 treated with GH). Absolute height SDS was not significantly different between the treated and untreated groups (-2.8 (-3.4 to -2.4) vs. -3.0 (-3.2 to -2.4)), but HV and HV SDS were significantly increased in the GH-treated group (HV: 7.6 (6.8-8.3) vs. 4.5 (3.6-5.2) cm/year, p=0.001; ΔHV +3.8 (3.2-4.9) vs. +0.3 (0.1-1.2) cm/year, p<0.001; HV SDS: 1.5 (0.6-3.0) vs. -1.2 (-1.4-0.3), p=0.01). There was a positive correlation between the maximal GH amplitude observed on an overnight profile and the GH peak to provocative testing (β=0.28 (95% CI 0.06-0.64, p=0.02).

**Conclusions:** Children with abnormal auxology and a normal GH peak to provocative testing may warrant an overnight GH profile to identify GH NSD. Children with GH deficiency secondary to NSD display similar responses to GH replacement as in frank GHD, and therefore should be considered part of the spectrum of GHD disorders.

P2-810

**LONG-TERM GROWTH IN PATIENTS BORN SMALL FOR GESTATIONAL AGE WITHOUT CATCH-UP GROWTH TREATED WITH GROWTH HORMONE FROM PREPUBERTAL AGE TO ADULT HEIGHT**

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**Objectives:** To evaluate in a cohort of children born Small for Gestational Age (SGA) without catch-up growth treated with Growth Hormone (GH) (30mcg/kg/day) from prepubertal age to adult-height: height gain, height gain variability and changes in the metabolic profile.

**Methods:** Longitudinal and retrospective study in 78 SGA children (51 boys, 27 girls); 18% preterm babies; GH was started at mean age of 6.98+/-2.1 years (boys) and at 5.94+/-

1.7 years (girls). The response to two GH release stimuli were: deficient (n=39;50%), dissociated (n=25, 32%), and adequate (n=12;15%). Mean parental height was -1.09 SD. Reference Pattern: Spanish Growth Study (SGS 2010).

**Results:** Heights: at start of GH -3.35+/-0.7 SD, at pubertal growth spurt (PGS) onset -1.75+/-0.7 SD, adult-height -1.73+/-0.8 SD. PGS and distribution in the five pubertal maturation groups were similar to SGS 2010. Mean age of menarche was 13.04+/-1.1 years.

Depending on the individual height gain from the start of treatment until adult-height, patients were divided into five groups: 1: <0.5 SD (n=10;13%); 2: 0.5-1 SD (n=10; 13%); 3: 1-2 SD (n=31; 39%); 4: 2-3 SD (n=20;26%); 5:>3 SD (n=7;9%). A negative correlation was observed with weight (r=0.47,p<0.001) and height (r=0.51, p<0.001) at the start of GH therapy and positive with growth velocity rate during the first year of treatment (r=0.41, p<0.001). There were no statistically differences in height gain in relation to prematurity, neonatal anthropometry and response to GH release stimuli.

IFG-I increased progressively during treatment (always within normal limits). There were no pathological changes in glycemia, insulinemia or lipid metabolism profiles.

**Conclusions:** SGA patients without catch-up growth treated with GH from prepubertal age reached adult-height less than <-2 SD, but lower than their mean parental height.

Height gain was heterogenous and the greatest height gain was during the prepubertal period. The age of pubertal growth spurt onset and distribution in pubertal maturation groups were similar to the reference population. Height gain was related to growth velocity rate during the first year of therapy, but not to the response to GH release stimuli. No pathological changes were reported in the metabolic profile.

P2-811

#### PHENOTYPIC SPECTRUM AND RESPONSES TO RECOMBINANT HUMAN IGF-I (RHIGF-I) THERAPY IN PATIENTS WITH HOMOZYGOUS GH RECEPTOR PSEUDOEXON DEFECTS

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**Objectives:** Patients with homozygous *GHR* pseudoexon defects (6Ψ) have GH insensitivity and a spectrum of phenotypes, from severe to mild growth failure. We previously described 11 6Ψ patients and now report 9 additional patients. No data exist on response to rhIGF-I therapy.

**Methods:** 20 6Ψ patients (12M, 11 families), mean age 4.9yr (0.7-13.0) were diagnosed genetically in our centre. Variables are stated as mean±SD. Continuous parametric variables were compared using student t-test or ANOVA with bonferroni correction for multiple comparisons. p values <0.05 were statistically significant (SPSS V.23).

**Results:** 10/20(50%) patients had facial features of Laron syndrome. 19/20(95%) were from consanguineous families and 18/20 (90%) of Pakistani origin. Mean height was -4.3SDS (-5.6 to -3.0), IGF1 -2.1SDS (-6.8 to +3.0), IGFBP3 -3.0SDS (-8.9 to -0.6) and mean peak GH level 45.2 mcg/l at diagnosis. Twelve patients had IGF-1 generation test (IGF1G). 11/12 showed no response (IGF-1 rise <15 ng/ml), 1 responded (132 to 255 ng/ml).

17/20 (85%) (11M) had rhIGF-I therapy. Mean age at initiation was 8.8±2.8yr and duration of treatment 4.4±2.4yr. In the treated group, 11/17 (9 naive) completed linear growth, mean final height (FH) -3.7SDS (-5.7 to -1.8) compared to -4.2SDS (-5.9 to -3.1) at start. Height at latest assessment (LH) in remaining 6/17 (4 naive) was -3.1SDS (-5.5 to -2.1) compared to -4.1SDS (-4.7 to -3.7) at start. In 3 untreated patients, FH was -3.5 and -5.0 and LH was -5.0 SDS. Baseline HV SDS (-1.4±2.1 cm/yr) increased after 1<sup>st</sup> year (2.2±2.3 cm/yr; p=0.011) and 2<sup>nd</sup> year (1.9±2.6; p=0.036) of treatment. Mean Δ height SD score at year 5 of rhIGF-1 was 1.3±0.7 and significantly higher than the Δ height SD score at year 1 (0.38±0.5; p=0.01). Difference between target height (TH) SDS and FH/LH SDS was less than that of TH SDS and pretreatment height SDS (4.3±1.2 vs 5.1±0.7; p=0.048). There was no correlation between sex, age at initiation of rhIGF-1, baseline height SDS or baseline IGF-1 SDS and 1<sup>st</sup> year HV SDS.

**Conclusions:** We report a spectrum of phenotypes even within the same family. Majority of patients did not respond in the IGF1G. RhIGF-1 treatment improved height outcomes and responses seem comparable to those seen in patients with other homozygous *GHR* mutations.

P2-812

#### E74 LIKE ETS TRANSCRIPTION FACTOR 4 (ELF4) IS A CANDIDATE GENE FOR X-LINKED FAMILIAL ISOLATED GROWTH HORMONE DEFICIENCY BY WHOLE EXOME SEQUENCING

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**Objectives:** Defects in genes encoding growth hormone (GH1) or the receptor of growth-hormone-releasing hormone (GHRHR) are the most common genetic causes of IGHD. Our aim was to identify mutation in genes causing IGHD using the whole exome sequencing (WES) in two brothers in which mutations in genes classically associated with IGHD were ruled out.

**Methods:** WES was performed in the Illumina HiSeq 2500 platform. Variants located in exonic and consensus splice site regions with minor allele frequency (MAF) <0.1% in public databases and in house Brazilian database were selected.

**Results:** This is a nonconsanguineous pedigree of two siblings with IGHD without hypogammaglobulinemia or any other immune problem. Patient 1 presented at 5 years of age with short stature 96.5 cm (-2.5 SDS). IGHD was diagnosed based on low basal IGF1 levels and lack of GH response to clonidine stimulation test. Small anterior pituitary, absent stalk, and ectopic posterior pituitary was present at MRI. After 8 years of GH treatment the patient was 169 cm tall (+ 1.5 SDS) at 13.5 years of age. His younger brother had IGHD diagnosed at 4 years of age, based on short stature (height = 93.2, -2.0 SDS), very low basal IGF1 levels (18 ng/ml) and lack of GH response to hypoglycaemia. Neuroimaging revealed small anterior pituitary, absent stalk and a partially descended posterior pituitary. GH treatment began at 4 years of age and at 11 years old his height is 142.5 (0 SDS). WES found the variant (c.C1499T: p.Ala500Val, rs145281864) in the ELF4 gene that is present in the X chromosome. The segregation of the variant reveals a heterozygous mother and hemizygous affected brothers. The father and the unaffected brother do not have the variant. The frequency of this variant is < 0.08% in all public databases checked (1000Genomes, ESP, ExAC and gnomAD). A single mutation in ELF4 has been associated with X-linked hypogammaglobulinemia and isolated growth hormone deficiency (MIM #307200) in one family.

**Conclusions:** WES identified a novel variant in ELF4 gene in two brothers with isolated GH deficiency not associated with immune disorders. This finding suggests a role of this protein in the development of somatotrophs and can provide novel insights in the genetic diagnosis of familial cases of IGHD.

P2-813

## EXPERIENCE OF USE OF THE SAIZENPREP™ RECONSTITUTION DEVICE IN HUMAN FACTORS STUDIES

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**Objectives:** Human factors studies were done to assess the safety and ease of use of the new saizenprep™ device to reconstitute Saizen® (somatotropin [rDNA origin] for injection) 8.8 mg and the associated instructions for use (IFU). Saizenprep™ was recently approved by the FDA and will replace the clickeasy® device.

**Methods:** Twenty-one and seven adolescents, 26 and six adults, and 16 and six healthcare providers (HCPs) participated in the summative and supplemental summative studies, respectively. In both studies, after a pre-test interview, experienced and naïve participants reconstituted Saizen®, once with the IFU as an option and then with the IFU as a requirement, and located and interpreted the Saizen® vial inspection instructions in the IFU. Objective performance measures included observed and reported use errors, close calls, operational difficulties, and instances where assistance was requested. Participants' impressions of the safety and ease of use of the device were collected in a post-test interview.

**Results:** In the summative study, four main safety-related use errors (three maintaining sterile technique and one interpreting the vial inspection instructions) and four operational difficulties (identifying the sharps container, removing the sterility seal from packaging, drawing reconstituted Saizen® into the cartridge, and determining if Saizen® and diluent were mixed) were identified. Four simulated helpline calls were made (3/63 participants observed bubbles in the liquid and 1/63 was unable to depress the plunger). 90% (55/61) thought the device safe to use and 79% (48/61) thought the IFU clear and easy to follow (two were excluded owing to time limits). In the supplemental summative study, only one use error (sterility-related) and two operational difficulties (removing the seal from packaging and determining the medication is appropriate for use) were reported, and one call to the simulated helpline was made (liquid appeared cloudy). Eighteen participants (95%) considered the device safe to use and 16 (84%) considered the IFU clear and easy to use.

**Conclusions:** In summary, the IFU led to few safety-related use errors and the saizenprep™ device was rated easy to learn to use by >80% of users.

# GH TREATMENT EFFECTIVENESS IN SHOX-D SHORT STATURE

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**Objectives:** To determine the efficacy of growth hormone therapy in treating short stature associated with shox-D in a group of pre-pubertal children.

**Methods:** Eight pre-pubertal patients (3 males, 5 females; aged between 2-11 ys) with a molecularly proven shox gene defect, height below the third percentile for age and gender and height velocity below the 25th percentile, received a GH treatment for one year. Three of them completed the second year of treatment.

**Results:** We observed a greater first and second year height velocity ( $m + 1.5$  SDS) with a greater height SD score at first ( $m + 0.5$  SD) and second year ( $m + 0.3$  SD) of treatment.

Compliance affected one patients height velocity with no catch up after four years of follow up without treatment.

**Conclusions:** Our study confirms the effectiveness of GH treatment in SHOX-D patients in promoting linear growth, as described in previous studies.

P2-815

# RADIAL EPIPHYSEAL DYSPLASIA IS A COMMON FINDING IN CHILDREN WITH HETEROZYGOUS AGGRECAN MUTATIONS

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**Objectives:** Heterozygous mutations in the Aggreacan gene (ACAN) cause autosomal dominant short stature with accelerated skeletal maturation. In most affected individuals, no obvious skeletal dysplasia is detected on skeletal surveys. In order to investigate if subtle signs of skeletal dysplasia is common in this condition, bone age (BA) radiographs from an international cohort of ACAN patients were reviewed.

**Methods:** BA radiographs of 20 children (9M:11F), average age 7y3m (range 2y to 15y) with confirmed heterozygous ACAN mutations (8 truncating, 6 missense) were studied.

The radiographs were assessed by one pediatric endocrinologist and one pediatric radiologist specialized in skeletal dysplasias. Both were blinded to the age and identity of the individuals. BA was assessed by the Greulich and Pyle method.

**Results:** In most children, skeletal maturation was advanced (BA-CA: median 15months, range: 0 to 43 months). Subtle skeletal abnormalities were identified in 14 out of 20 radiographs.

The most common finding was a low height of the radial epiphysis (8 out of 20), followed by uneven radial growth plate (8 out of 20) and defects of the radial contour of the radial epiphysis (6 out of 20). In two radiographs short, cone-shaped epiphyses in distal phalanges of the thumb were also observed.

**Conclusions:** Our data suggest that a mild epiphyseal dysplasia of the radial epiphysis is a frequent finding on BA radiographs of children with heterozygous ACAN mutations. This report may thus provide diagnostic clues to the pediatric endocrinologist evaluating a child with idiopathic short stature and a normal or advanced BA.

P2-816

# RACIAL/ETHNIC DISPARITIES IN U.S. PEDIATRIC GH TREATMENT

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**Objectives:** To compare racial/ethnic proportions of GH registry subjects to those expected based on U.S. Census and differences in growth rates, and secondarily, to assess racial/ethnic differences in other subject characteristics at initiation of GH treatment.

**Methods:** Race/ethnicity-based relative risks for height  $<-2.25$  SD (i.e. short enough to qualify for GH treatment of idiopathic short stature [ISS]) were calculated from a heterogeneous regional population of 189,280 pediatric primary care patients (*Sci Rep.* 2015;5:11099). Race/ethnicity-based expected frequencies of height  $<-2.25$  SD were calculated from the relative risks for short stature and 2011 U.S. Census data, and compared by Chi-squared test to the racial/ethnic proportions of U.S. subjects enrolled in the Pfizer International Growth Study (IGS) database, for all combined and individual indications. Characteristics of the white and black subjects at start of GH treatment were presented as medians and compared by Wilcoxon rank sum test (significant P-value  $<0.01$ ).

**Results:** White subjects exceeded the expected frequency (63%) for all indications (83%) and each separately, ranging from 73% for congenital GHD to 85% for ISS (every  $P<0.001$ ). Comparing the white and black subjects in U.S. KIGS, baseline characteristics did not differ significantly among those treated for ISS, while black subjects in the idiopathic GHD group had greater height deficits relative to the population ( $-2.97$  vs  $-2.56$  SD) and their mid-parental heights ( $-2.47$  vs  $-1.89$  SD), lower GH peak levels on provocative testing (4.85 vs

6.0 ng/ml), and lower birth weights (-0.86 vs -0.48 SD). Black subjects with congenital GHD had lower GH peaks on testing (2.1 vs 3.2 ng/ml) and started GH treatment at younger ages (2.91 vs 4.8 yrs), while those with acquired GHD had lower birth weights (-1.12 vs -0.08 SD). Male predominance did not differ by race for any or all of the indications.

**Conclusions:** Over-representation of white children among those receiving GH treatment in the U.S. reflects racial/ethnic treatment biases and not just differences in growth rates.

P2-817

#### THE EFFECT OF RECOMBINANT GROWTH HORMONE TREATMENT ON INTRAOCULAR PRESSURE IN CHILDREN WITH GROWTH HORMONE DEFICIENCY

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**Objectives:** Recombinant growth hormone (rhGH) treatment is indicated for growth hormone deficiency (GHD), idiopathic short stature, chronic renal failure, SGA, and some genetic disorders such as Turner and Prader Willi syndrome. The most frequently reported side effects of rhGH treatment include headache, nausea, vomiting, vision problems, arthralgia, myalgia, paresthesia, fluid retention, and reaction at the injection site. Less frequent side effects are increased intracranial pressure, slipped capital femoral epiphys and Perthes disease. There are many articles in the literature that increase intraocular pressure (IOP) in cases of endogenous growth hormone increase such as acromegaly, but not enough information about the effect of the intake of exogenous growth hormone (rhGH) on IOP.

**Methods:** An observational cohort study was conducted in children with GHD. To evaluate the effect of rhGH treatment on IOP, baseline IOP values were compared with between 6th and 12th months of rhGH treatment. A total of 20 patients (14 female, 6 male) with a mean age of  $12.3 \pm 1$  years were included in the study. IOP measurements were performed with Goldmann applanation tonometer in all patients. In addition, ultrasonic pachymetry was performed to calculate corrected IOP. Baseline IOP values of the patients were compared with the control group ( $11.4 \pm 2$  years). A dose of 27 µg/kg/day rhGH treatment was applied to all cases for the GHD diagnosis for 12 months, and the IOP values of patients were measured at 6th and 12th months of treatment.

**Results:** The mean IOP before treatment was 12.6 mmHg, whereas the control group was 13.2 mmHg ( $p > 0.05$ ). The mean IOPs of the patients treated with rhGH at 6th and 12th months were 14.4 mmHg ( $p > 0.05$ ) and 15.5 mmHg ( $p = 0.04$ ), respectively.

**Conclusions:** At the end of one-year follow-up, rhGH treatment led to an increase in IOP. The results showed that IOP seems positively correlated with the treatment duration. This suggests that the follow-up of IOP before and during the

treatment of rhGH may be beneficial for early detection of IOP increase without glaucoma.

P2-818

#### THE GROWTH PARAMETERS OF CHILDREN WITH IDIOPATHIC SHORT STATURE WERE COMPARABLE TO THOSE WITH GROWTH HORMONE DEFICIENCY DURING 3 YEARS' TREATMENT OF DIFFERENT GH DOSE

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**Objectives:** Growth hormone (GH) treatment significantly improves the growth velocity and the adult height of children with idiopathic short stature (ISS). Nevertheless, the use of GH has remained controversial, because of the modest benefit and high cost. Many studies used GH dose of 0.16 to 0.26 mg/kg/wk, with improved adult height of less than 4 cm, whereas other studies used higher dose of 0.32 to 0.4 mg/kg/wk with dose-dependent benefit. To investigate the effect of GH, we retrospectively compared the growth parameters of children with ISS and idiopathic GH deficiency (GHD).

**Methods:** Among the short children with normal birth weight and height below -2 standard deviation score (SDS), they were divided into two groups by GH stimulation tests [ISS (N=26) and GHD (N=30)]. They were followed for 3 years with GH dose of 0.175 to 0.245 mg/kg/wk for GHD (standard of national insurance), and 0.253 to 0.370 mg/kg/wk for ISS. The GH dosage in ISS were adjusted to maintain IGF-1 level not to exceed +2 SDS. Growth parameters were checked every 6 months.

**Results:** At the beginig of treatment, chronologic age [CA, mean(sd) 9.4(2.7) vs. 8.5(3.2)], height SDS [HSDS, -2.4(0.4) vs. -2.5(0.5)], and mid-parental height [MPH, -1.0(0.6) vs. -0.9(0.6)] were not different between ISS and GHD group. However, bone age (BA, 8.9(2.8) vs. 7.2(3.0)), BA/CA ratio [0.94(0.12) vs. 0.85(0.13)], and IGF-1 SDS [-0.5(0.9) vs. -1.1(0.8)] were significantly lower in GHD group, and predicted adult height (PAH) SDS [PSDS, -2.9(1.4) vs. -2.2(0.8)] was significantly lower in ISS group. At each 3 year, CA, BA, BA/CA ratio, HSDS, PSDS, IGF-1SDS were not different between the two groups. Though the annual HSDS increments were not different, annual PSDS increments were higher in ISS group as a result of lower annual BA increments. At 3rd year of treatment, HSDS [-1.2(0.7) vs. -1.6(0.7)] and PSDS [-1.2(0.8) vs. -1.7(1.0)] were not different. The GH dosage was significantly higher in ISS group during 3 years of treatment.

**Conclusions:** With higher GH dose in ISS group, initially different growth parameters of high BA, BA/CA ratio and lower PSDS became not different from those in GHD group including HSDS at 3rd year of treatment.

### THE RELATIONSHIP BETWEEN IGF-I AND -II CONCENTRATIONS AND BODY COMPOSITION AT BIRTH AND OVER THE FIRST 2 MONTHS OF LIFE

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**Objectives:** Insulin-like growth factors (IGF)-I and -II play an important role in prenatal growth and concentrations at birth are associated with infant birth weight. During the first 2 months of life, body fat doubles while lean mass remains constant relative to body size. Rapid weight gain during this time increases future risk of cardiometabolic disease. The aim of this study was to describe the association between IGF-I and -II concentrations at birth and body composition at birth, and the trajectory of changes in fat mass (FM) and fat free mass (FFM) over the first two months of life in a large healthy birth cohort.

**Methods:** IGF-I and -II concentrations were measured by liquid chromatography/tandem mass spectrometry in umbilical cord samples in term healthy infants enrolled in the Cork BASELINE Birth Cohort Study. Air displacement plethysmography (ADP) was performed at birth and approximately 2 months later (between 49 and 86 days). FM and FFM were corrected for infant length (L) and age- and sex-specific Z-Scores for FM/L<sup>3</sup> and FFM/L<sup>2</sup> were generated using previously described methodology.

**Results:** IGF-I and -II concentrations were measured in 601 (317 male) term infants who had ADP performed both at birth and 2-months of age. Increased IGF-I concentrations were associated with higher FM/L<sup>3</sup> and FFM/L<sup>2</sup> Z-Scores at birth ( $R^2=0.05$ ,  $P<0.001$  and  $R^2=0.02$ ,  $P=0.016$  respectively) while IGF-II concentrations at birth were associated with FFM/L<sup>2</sup> Z-Score at birth ( $R^2=0.01$ ,  $P=0.014$ ). Higher IGF-I or IGF-II concentrations at birth were associated with a reduction in FM/L<sup>3</sup> Z-Score in the first 2 months of life, although the association was stronger for IGF-I than for IGF-II concentrations ( $R^2=0.04$ ,  $P<0.001$ , and  $R^2=0.007$ ,  $P=0.04$  respectively).

**Conclusions:** IGF-I concentrations at birth are strongly associated with adiposity and lean mass at birth and inversely related to the trajectory of FM and FFM accumulation over the first 2 months of life. The association of body composition

was weaker for IGF-II than IGF-I concentrations at birth. It is not clear if this association is due to IGF-I reflecting prenatal nutritional status or if the growth hormone/IGF-I axis plays a critical role in regulating the significant changes in body composition during early infancy.

P2-820

### REASSESSMENT OF IGF-1 VALUES IN THE DIAGNOSIS OF GROWTH HORMONE DEFICIENCY

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**Objectives:** IGF-1 is an indirect biomarker of the GH secretion and a useful screening tool for the appraisal of the GH-IGF-1 axis. They are influenced by age, pubertal status and several other factors. Previous studies of these peptides have compared their serum concentrations with reference values for chronological age, although in clinical practice it is also evaluated by bone age and pubertal status. This study aims to compare IGF-1 standard deviation scores (SDS) for chronological age (CA), bone age (BA) and pubertal status, with regards to its accuracy in the diagnosis of growth hormone deficiency (GHD).

**Methods:** It is a retrospective, transversal study with children with growth disorders evaluated at our service. The patients were classified as GHD and non GHD based on GH stimulation test, clinical features, pituitary MRI and response to rhGH treatment. The immunoassay IMMULITE was used to measure IGF-1 serum concentrations and their SDS were calculated accordingly.

**Results:** Data from 286 patients were included, with a predominance of the male gender (60.5%), the average age of the patients was  $9.6\pm 4.2$  years and 45 patients had GHD. The IGF-1 SDS was lower among patients with GHD ( $p<0.05$ ). The sensitivity for the IGF-1 SDS for CA and BA was 93.3% and 80.6%; the specificity was 75.9% and 88.5%; and accuracy of 78.7% and 87.4%, respectively. Considering a prevalence of GHD of 5% among short children, the positive and negative predictive value are 16% and 100% for CA and 27% and 99% for BA, respectively. Although the higher accuracy of IGF-1 SDS for BA, its discriminatory performance was similar (area under the curve (AUC) of 0.900;  $p=0.961$ ). When only patients in pubertal age were analyzed, the AUC of IGF-1 SDS for CA, BA and pubertal status were 0.884; 0.834 and 0.823, respectively, with p-value of 0.227 CA vs. BA and 0.381 for CA vs. pubertal status.

**Conclusions:** The IGF-1 serum concentrations are an inexpensive and effortless tool for the initial evaluation of the somatotrophic axis of a child with short stature. Our data does not demonstrated beneficial to assess IGF-1 SDS based on bone age or pubertal status in comparison with chronological age.

### SHORT STATURE IN PEDIATRIC CANCER SURVIVORS

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**Objectives:** Describe the repercussion on growth and final height of childhood cancer and its treatment.

**Methods:** Retrospective review of medical records of 117 pediatric cancer survivors currently without oncological treatment with endocrine complication followed in pediatric endocrinology department outpatient unit. We evaluated their initial and final Z score of stature, gender, age, time of follow-up, use of recombinant growth hormone (rGH), oncological diagnosis and its treatment.

**Results:** Of the 117 patients, 20 had short stature (Z-SCORE < -2SD) at initial evaluation. Ten were females, the mean age at their first visit was  $9.0 \pm 4.1$ SD years and the mean follow-up time was  $8.9 \pm 4.2$ SD years. Medulloblastoma (25%), Wilms Tumor (11%) and Acute Lymphoblastic Leukemia (10%) were the most prevalent oncological diagnosis among them. Cranial radiotherapy were performed in 50% of this group, 80% of them had chemotherapy treatment and only 1 patient was submitted to allogeneic stem cell transplant. Mean initial Z-score height was  $-2.81 \pm 0.41$ SD and mean final z-score was  $-2.18 \pm 0.97$ SD. Growth hormone deficiency was found in 40% of the patients established from stimulation tests (clonidine, insulin or glucagon) with a peak of less than 5ng/mL. rGH was introduced in 52% of the short stature patient with mean time of use of 2.39 years. Only one patient had tumor recurrence after 5 month of use of rGH.

Ten patients with z-score of height between -1.5 and -2.0 were also followed in our unit. Seven of them were female, the mean initial age was  $9.1 \pm 3.5$ SD years and the mean follow up time was  $8.5 \pm 5.6$ SD years.

Sixty percent of them received rGH for 3.75 years. Their mean z score of height at first and last visit was  $-1.7 \pm 0.13$ SD and  $-1.51 \pm 0.68$ SD respectively.

**Conclusions:** Short stature is a common endocrine complication of childhood cancer and its treatment. Therefore, early screening and early treatment of this condition is very important for better outcome. In our study, 40% of patients with short stature presented deficiency of growth hormone which drew the attention of its prevalence in pediatric cancer survivors with height impairment.

P2-822

### RELIABLE MONITORING OF WEEKLY IGF-I LEVELS DURING LONG-ACTING GROWTH HORMONE THERAPY WITH SOMAPACITAN

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**Objectives:** Reliable monitoring of IGF-I levels is essential for ensuring the correct dose during treatment of growth hormone deficiency (GHD). Correct assessment of weekly IGF-I levels during treatment with long-acting growth hormone must account for fluctuations in IGF-I over a dosing interval. This study characterized the variability in IGF-I response and evaluated if reliable estimates of weekly mean and peak IGF-I can be obtained from a single IGF-I sample taken during weekly dosing with somapacitan, a long acting growth hormone.

**Methods:** Full time-profiles of pharmacokinetics (PK) and IGF-I (ng/ml and SDS) from three clinical phase 1 studies with somapacitan were included: From 73 healthy volunteers (0.01-0.32 mg/kg single and weekly dosing), from 26 adults with GHD (0.02-0.12 mg/kg weekly dosing) and from 23 children with GHD (0.02-0.16 mg/kg single dosing). A semi-mechanistic non-linear mixed effects model was fit to PK and IGF-I profiles. Linear models were used to predict mean and peak IGF-I SDS from observed IGF-I SDS on day 1-7 after dosing.

**Results:** The PK and IGF-I profiles were well described with a non-linear PK/IGF-I model. Accurate description of individual PK and IGF-I profiles were obtained with estimates of variability between GHD subjects in IGF-I production rate (37% CV), IGF-I turn-over rate (26% CV), IGF-I response to somapacitan (31% CV) and PK parameters describing absorption, distribution and elimination of somapacitan (40-76% CV). Body weight could account for substantial parts of variability in IGF-I levels and PK. Mean IGF-I were well predicted by observed IGF-I levels on any day (1-7) in children and adults with GHD. Peak IGF-I was best predicted from IGF-I levels observed day 1-4 in both children and adults.

**Conclusions:** The observed IGF-I time-profiles following somapacitan dosing were well characterized in children and adults. Reliable estimates of weekly mean and peak IGF-I SDS can be made from a single IGF-I SDS measurement. The developed models were integrated into software that allows real-time illustration of the likely IGF-I profile given the dose, body weight, age, gender and the IGF-I SDS monitored anytime during weekly treatment with somapacitan.

P2-823

### CHANGES IN COAGULATION AND FIBRINOLYSIS PARAMETERS DURING GH TREATMENT IN PREPUBERTAL GROWTH HORMONE DEFICIENT CHILDREN

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**Objectives:** To evaluate whether prepubertal GH deficient (GHD) children showed any impairment in coagulation- and



fibrinolysis-related parameters and the effect of GH therapy on these parameters

**Methods:** Fifteen prepubertal children (10 girls and 5 boys) of a mean (sd) age of 9.8 (0.4) yrs and GH deficiency participated in this hospital based prospective study. Serum levels of PT, APTT, fibrinogen, VII, VIII, AT, PC, D-dimers, Plg, and PAI-1 were measured before and after 6-12 months of GH treatment.

**Results:** At baseline all studied parameters were within normal ranges. A significant increase in PT values was noted after a mean (sd) interval of 9.3(0.4) months of treatment: 12.46 (0.2) sec vs 12.1(0.15)sec,  $p=0.045$ . A significant decrease in PAI-1 levels (3.04 (0.1) U/ml vs 2.28 (0.3) U/ml,  $p=0.018$ ) was noted at the same time. No significant changes in the rest of parameters were found during the study period

**Conclusions:** GH replacement therapy for 6-12 months led to a significant increase in PT values, while fibrinogen levels did not change. Moreover, GH treatment reduced PAI-1 levels in GHD children, suggesting a beneficial effect of GH treatment on possible risk of future atherothrombosis. Further evaluation of the clinical significance of these changes is needed.

P2-824

#### CHANGE IN BODY MASS INDEX DURING SOMAVARATAN THERAPY IN PEDIATRIC SUBJECTS WITH GROWTH HORMONE DEFICIENCY IN THE VISTA LONG-TERM SAFETY STUDY

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**Objectives:** Somavaratan is a long-acting rhGH fusion protein under study as a twice-monthly alternative to daily rhGH for pediatric growth hormone deficiency (PGHD). We have assessed the changes in body mass index (BMI) of subjects completing 3 years of protocol-specified treatment in the VISTA long-term safety study.

**Methods:** Pre-pubertal PGHD subjects were initially treated with weekly, twice-monthly or monthly somavaratan, transitioning to 3.5 mg/kg twice monthly by the 2<sup>nd</sup> treatment year. Height (HT) and weights were recorded at each 3-month interval. The CDC Growth Chart percentile tables for HT and BMI of US children were used to compute standard deviation scores (SDS). Multiple regression analyses were used to assess possible effects of baseline characteristics on subsequent changes in BMI SDS from 0 to 3 years. Data cutoff date was December 8, 2016.

**Results:** 45 subjects (21 male, 24 female) have completed all HT and weight measurements through 36 months. At start of treatment, the mean ( $\pm$ SD) age was  $7.8\pm 2.4$  years, HT SDS was  $-2.60\pm 0.60$ , BMI SDS was  $-0.07\pm 0.88$ , maximally stimulated GH was  $5.57\pm 2.53$  ng/mL and IGF-I SDS was  $-1.74\pm 0.77$ . The overall range for baseline BMI SDS was -1.67 to 2.11. By Year 3, mean BMI SDS had increased to 0.56

(range, -0.69 to 2.01) with mean increase of 0.64 SDS. Mean HT SDS increased by 1.45 to -1.16. Change in BMI SDS over 3 years was greater in boys than in girls (increase of 0.82 SDS vs. 0.48 SDS) and was inversely related to baseline values of BMI SDS. Forty-two of 45 subjects had BMI SDS values in the normal range of -2 to +2 before treatment and at the end of each of the three years of somavaratan treatment. There was no relationship between change in IGF-I SDS and change in BMI SDS at the end of Year 3 ( $r^2 = 0.06$ ).

**Conclusions:** The higher SDS for BMI than HT at baseline (-0.07 vs. -2.60, respectively) suggests that weight growth exceeded statural growth before treatment. The greater change in SDS values for HT than BMI after three years (increase of 1.45 vs. 0.64, respectively) suggests this trend is reversed during somavaratan treatment. The greatest changes in BMI SDS were observed in those with lower baseline BMI SDS.

P2-825

#### EVALUATION OF BONE AGE USING GREULICH-PYLE METHOD AND SAUVEGRAIN METHOD IN GIRLS WITH PRECOCIOUS PUBERTY

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**Objectives:** There are several methods of bone age(BA) assessment. Although evaluation of bone age using the Greulich-Pyle (GP) method has been the most widely used, it is difficult to assess BA in adolescents during puberty. Sauvegrain (SV) method is known to be useful alternative tool during puberty to determine BA from elbow radiograph. The aim of this study was to compare the differences of BA assessment by using GP method, SV method, olecranon maturation (OM) method in girls with central precocious puberty (CPP)

**Methods:** Between September 2014 and September 2016, A total of 63 CPP girls were included in this study. BA of all patients was evaluated periodically by GP, SV, and OM methods respectively. Two professional investigators evaluated BA of all patients according to each method of bone age measurement. The gap between GP and OM methods was classified into 6 months or less (Group 1) and 6 months or more (Group 2). Factors affecting to bone age maturation were analyzed in 2 groups with CPP girls.

#### Results:

1. While 60 patients (95.2%) were able to be assessed bone age using SV methods, 28 patients (44.4%) were able to be assessed Bone age using OM method.
2. There was significant inter-variation between two investigators about BA Assessment using only GP methods, not SV or OM methods.
3. There was no significant differences in the age, gender, body mass index standard deviation score, peak LH

level, and estradiol values between two groups (group 1 and group 2) ( $P = 0.044$ ).

4. The average changes of bone age during 6 months follow-up period were 3 months and 9.5 months in group 1, 2, respectively ( $p = 0.044$ )

**Conclusions:** It is difficult to assess BA through only GP method in CPP girls. Several method such as GP, SV or OM method are complementary each other. Further study is needed to evaluate the effectiveness of BA assessment using SV or OM method during puberty.

P2-826

#### GH TREATMENT ADHERENCE IN CHILDHOOD AND ADOLESCENCE IMPROVES USING EASYPOT<sup>TM</sup> DEVICE: DATA DEMONSTRATION IN AN ITALIAN CENTRE

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**Objectives:** Poor adherence to GH treatment is one of the pitfalls affecting the treatment efficacy. This study evaluates the GH treatment, using easypod<sup>TM</sup> in young patients over 6 months of therapy and describes the relationship between treatment efficacy and adherence.

**Methods:** We collected the retrospective data registered in the electronic device easypod<sup>TM</sup> in 40 patients treated with GH. Number and doses of injection were used to calculate the percentage of treatment adherence. The inclusion criteria were: GH deficiency and the existence of one of the clinical condition in which GH is available: GHD, SGA, chronic renal failure, Turner syndrome. The GH efficacy was evaluated using the height gain in SD.

**Results:** adherence was 92.20%, inversely related to patients' age ( $p=0.023$ ), significantly higher in patients with age 10-13 y. Adherence was inversely related to the y of therapy ( $p=0.003$ ) and to the number of GH doses/week ( $p=0.012$ ). Treatment efficacy did not correlate with adherence. Adherence showed a statistically significant correlation with IGF-1 ( $p=0.032$ ). 35% referred discomfort at site of injection, 5% referred pain. The adherence was significantly lower in patients who self-injected GH (80.91%), compared to those treated by parents (95.2%) ( $p=0.002$ ). 37.5% used all sites of injection, 32.5% refused 1 site, 12.5% 2, 17.5% used 1 site. The number of refused sites was inversely related to the adherence ( $p=0.011$ ). The parents' "level of education" did not show a statistically significant correlation with the adherence and data registered by the electronic device demonstrate that 35% of patients erroneously report their treatment adherence.

**Conclusions:** Childhood and adolescent patients with GH deficiency show a high adherence to GH treatment monitored by easypod<sup>TM</sup>. Treatment adherence is inversely related to patients' age, confirming the difficulties to treat chronic diseases especially in adolescence. The study suggests the importance of an electronic device able to measure adherence and easypod<sup>TM</sup> represents one of the most recent

advances obtained in this field. This electronic device could represent a system to monitor patients' adherence in chronic treatments, especially if they are expensive and self-managed by the family.

P2-827

#### SERUM IGF-I AND IGFBP-3 CONCENTRATIONS ARE SENSITIVE MARKERS OF TRAINING STATUS AND PREDICTORS OF STRENGTH AND SPEED PERFORMANCE IN YOUNG SOCCER PLAYERS DURING A CHAMPIONSHIP

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**Objectives:** Soccer is one of the most popular sports in the world. Growth, maturation and muscle gain provide advantages in performance. Exercises are related to the anabolic actions of GH/IGF axis; however, few reports are available on the changes in GH/IGF-I axis as markers of training status during a soccer championship. **Aim:** To evaluate GH, IGF-I, and IGFBP3 serum concentrations; strength; and speed in young soccer players during a 7 month-championship.

**Methods:** Eleven male soccer players aged <15yrs and from a Local League were included in the study. Maturation was accessed by an equation that takes into account: leg length, sitting height, age, weight and height. Blood samples to determine GH, IGF-I, and IGFBP-3 levels were collected before and after a standard training session (STS) at the beginning (T0), middle (T4, 4th month) and end (T7, 7th month) of the Championship. Strength (RAST test) and speed were evaluated at T0, T4, and T7; 48hs before blood sampling.

**Results:** Serum IGF-I levels increased after STS at T4 ( $460 \pm 68$  vs.  $519 \pm 115$  ng/ml,  $P=0.05$ ) and decreased after STS at T7 ( $461 \pm 95$  vs.  $429 \pm 87$  ng/mL,  $P=0.04$ ). IGF-I variation ( $\Delta$ IGF-I) after STS was higher at T4 than at T7 ( $59 \pm 95$  vs.  $-32 \pm 49$  ng/ml,  $P=0.04$ ). Serum IGFBP-3 levels were higher at T4 than at T7, before ( $4.9 \pm 1.0$  vs.  $4.6 \pm 1.0$  mg/l,  $P=0.03$ ) and after ( $5.5 \pm 1.7$  vs.  $4.5 \pm 0.8$  mg/l,  $P=0.04$ ) STS. Serum GH levels did not vary significantly during the study. Strength and speed values followed the chronic changes in IGF-I and IGFBP-3, with higher scores observed during the anabolic phase (T4), which was characterized by increasing IGF-I and high IGFBP-3 levels. Strength values (mean, peak, and minimum; W) were higher at T4 than at T0 (mean.Str:  $458 \pm 100$  W vs.  $409 \pm 87$  W,  $P=0.007$ ; peak.Str:  $563 \pm 35$  W vs.  $508 \pm 27$  W,  $P=0.03$ ; min.Str:  $377 \pm 25$  W vs.  $306 \pm 29$  W,  $P=0.007$ ) while the values at T7 were in between those at T4 and T0. Speed was greater at T4 than at

T0 ( $4.29 \pm 0.14$  vs.  $4.47 \pm 0.17$  sec/30m,  $P < 0.05$ ). Maturation was higher at T7 ( $0.85 \pm 0.49$ ) than at T4 ( $0.48 \pm 0.61$ ) and T0 ( $0.43 \pm 0.6$ ).

**Conclusions:** Serum IGF-I concentration was a sensitive marker of acute and chronic training status and strength/speed performance in young soccer players while IGFBP-3 was sensitive only to chronic stimulus.

P2-828

#### FINAL HEIGHT IN TURNER SYNDROME CONSIDERING RECOMBINANT HUMAN GROWTH HORMONE SUPPLEMENTATION.

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**Objectives:** Short stature is one of the most prominent features of Turner Syndrome (TS) and it is not due to growth hormone secretion deficiency, but rather to haploinsufficiency of the pseudo-autosomal gene SHOX. Recombinant human Growth Hormone (rhGH) have demonstrated to increase final height in TS girls with short stature, but requires an expensive treatment with daily subcutaneous injections for many years. Even though rhGH supplementation appears to be safe, there are still no evidence of the consequences of the treatment in long term. The objective of this study was to add more information on the decision to initiate rhGH in TS, a theme that is still scarce and controverse in the literature.

**Methods:** Analytical study based on a retrospective cohort. Data were collected from records of 110 TS patients in final height and evaluated by Epiinfo 3.5.1. Significance level accepted was  $p < 0.05$ . The patients were classified according to the use or not of rhGH. Following variables were also evaluated: karyotype and rhGH treatment regularity and duration.

**Results:** Final adult height in rhGH group did not differ from the untreated group (mean  $\pm$  SD:  $144.82 \text{ cm} \pm 6.97$  vs.  $143.46 \text{ cm} \pm 6.81$ ,  $p = 0.319$ ), the same result was found when final height z score was analyzed (mean  $\pm$  SD:  $-2.76 \pm 1.05$  vs.  $-2.958 \pm 1.03$ ,  $p = 0.357$ ). There was also no difference between the karyotypes in regards of final height (mean  $\pm$  SD: structure x abnormalities  $139.86 \text{ cm} \pm 8.7$  vs. monosomy  $144.25 \text{ cm} \pm 6.73$  vs. mosaic  $147.37 \text{ cm} \pm 6.22$ ,  $p = 0.927$ ) and final height z score (mean  $\pm$  SD: structure x abnormalities  $-2.5 \pm 1.67$  vs. monosomy  $-3.11 \pm 0.97$  vs. mosaic  $-2.99 \pm 0.90$ ,  $p = 0.348$ ).

In the rhGH group, regularity of treatment (mean  $\pm$  SD: regular rhGH  $-2.78 \pm 0.66$  vs. irregular rhGH  $-2.76 \pm 1.2$ ,  $p = 0.9515$ ) did not improve final height z score or final height (mean  $\pm$  SD: regular rhGH  $144.89 \text{ cm} \pm 7.9 \text{ cm}$  vs. irregular rhGH  $144.67 \pm 4.42$ ,  $p = 0.927$ ). No significant correlation in terms of final adult height or final height z score was found when start age or duration of treatment was taken into consideration.

**Conclusions:** The present study concluded that supplementation of rhGH had no impact on final adult height in our patients with TS.

P2-829

#### CATCH UP GROWTH- DO LEPTIN AND AROMATASE LIMIT ITS EFFICIENCY?

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**Objectives:** Malnutrition in childhood leads to growth stunting; usually when food intake is corrected spontaneous catch-up growth (CUG) occurs, bringing the child back to its original growth curve, however, sometimes CUG is incomplete, leading to permanent growth deficit and short stature.

The aim of this study was to investigate the mechanisms that limit the efficiency of CUG. Specifically, we studied the cross talk between leptin, increased by re-feeding and sex hormones, increased with age.

**Methods:** *In-vivo* studies were performed in young male Sprague Dawley rats fed *ad libitum* (AL group) or subjected to 36 days of 40% food restriction followed by three months of re-feeding (CU group). Studies were done in normal and castrated rats. *In-vitro* studies were performed in ATDC5 cells incubated with leptin; mRNA and protein analysis of estrogen and leptin receptor and of aromatase were performed by qPCR and western blot respectively.

**Results:** The *in-vivo* studies showed that sex hormones are responsible for the incomplete CUG, therefore we focus on a potential interaction between leptin, increased by refeeding and aromatase that converts testosterone, also increased by refeeding in this model, to estrogen, that inhibits growth. *In-vitro* studies demonstrated that leptin significantly increased the expression and protein levels of estrogen and leptin receptors as well as aromatase in a dose and time-dependent manner. The effect on aromatase was direct and through the *PI3K*, *MAPK* and *STAT3* pathways.

**Conclusions:** We have shown that *in-vitro*, leptin increases the level of aromatase, and estrogen receptor, therefore may increase *in situ* estrogen production and activity, suggesting that when re-feeding occurs during puberty, it will lead to increased estrogen level and activity, and irreversible shrinkage of the EGP.

Our results suggest a crosstalk between leptin and aromatase in linear growth regulation. These results may have significant implications in the understanding of the mechanisms that limit CUG and may pave the way for new strategies in treatment of short stature.

# MICROSCOPIC HEMATURIA FOLLOWING AMBULATORY PROVOCATIVE GROWTH HORMONE STIMULATION TESTING IN CHILDREN

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**Objectives:** Provocative growth hormone (GH) testing is used to assess growth hormone secretory reserve in children with short stature or growth failure. While insulin-induced hypoglycemia is considered the gold-standard for GH testing, it is rarely used in practice. Sequential testing with two agents, including either L-arginine, clonidine, or glucagon, is used to determine GH sufficiency. Isolated idiopathic macroscopic hematuria has been reported following GH stimulation testing and is thought to be associated with L-arginine. The risk of microscopic hematuria in patients undergoing GH testing is not known. This study was designed to assess the risk of micro- and macroscopic hematuria following GH testing.

**Methods:** Children scheduled to undergo GH testing were recruited from our outpatient Endocrine clinic. Those with significant renal disease were excluded. After signing informed consent/assent, auxiologic data including height and weight were collected. Blood pressure was taken before and after and urinalysis performed prior to testing. Families were provided urine dipsticks and asked to check the child's urine for the presence of blood on days 1, 2, 3 and 7 following testing. The results were returned to the investigators. Families were to notify the investigator of any abnormal urine findings. Additional data collected included the provocative agents used for testing, IGF-1 levels, and GH levels following stimulation.

**Results:** The study enrolled 24 children. The mean age was  $10.9 \pm 3.0$  years. All but five subjects were Tanner stage 1 for puberty and 95.8% were male. Height Z-score was  $-2.06 \pm 0.87$ . Sequential testing with clonidine/arginine was the most commonly used provocative agent (54.2%) followed by clonidine/glucagon (37.5%) and arginine/glucagon (8.3%). No subject had hematuria at baseline. Two subjects developed hematuria on Day 1 following testing; provocative agents were clonidine/arginine for both. One subject had microscopic hematuria, while the other had macroscopic hematuria. The hematuria resolved by day 7 after testing for both subjects.

**Conclusions:** Provocative GH testing is used as a tool in the evaluation of children with short stature and growth failure. This study in 24 patients suggests that while hematuria may occur after GH testing, it is a transient adverse effect.

# HEIGHT REFERENCES' EVOLUTION FOR ROMANIAN CHILDREN IN THE LAST 40 YEARS

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**Objectives:** Recently Romania has published new synthetic growth references. The aim of this study was the comparison of the new growth charts with previously reported growth references from 20 and 40 years before.

**Methods:** The three growth references (synthetic 2016, 1999 and 1974) provide means and standard deviations for ages between 3 and 18 years. For each of the 3 growth references, mean height and standard deviations were computed for each month using linear interpolation. The differences between the three references were calculated. Statistical analysis used MedCalc v. 14.8.1. with a level of significance  $\alpha=0.05$ .

**Results:** For boys, the mean difference between the new synthetic growth reference and the 1999 one was 2.71cm (95%CI 2.60-2.81), with a minimum of 0.64cm for the final height (216 months) and a maximum of 4.25cm at 172 months of age. When comparing the synthetic with the 1974 reference, the mean was 3.67cm (95%CI 3.5-3.83), with a minimum of 0.64cm at 36 months and a maximum of 6.21cm at 180 months of age. For girls, the mean difference between the new synthetic growth reference and the 1999 one was 1.52cm (95%CI 1.41-1.64), with a minimum of -0.11cm at 204 months and a maximum of 2.65cm at 142 months of age. The comparison with the 1974 references showed a mean difference of 2.75cm (95%CI 2.63-2.87), with a minimum of 0.34cm at 36 months and a maximum of 4.55 cm at 216 months of age. There is an increase of 3.93 cm in final height for boys and 4.55 cm in girls in the last 40 years. The results are summarized in the table.

**Conclusions:** There is a need to implement the new synthetic growth references, to account for the secular trend and the differences in pubertal growth spurt that occurred in the last 40 years.

# PRIMARY EVALUATION OF GENETIC AND SYNDROMIC CAUSES OF SHORT STATURE AMONG CHILDREN WITH GROWTH HORMONE DEFICIENCY AND THOSE BORN SMALL FOR GESTATIONAL AGE

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**Objectives:** Among growth hormone-treated children with short stature, individuals with growth hormone deficiency (GHD) and those born small for gestational age (SGA) are heterogeneous regarding the etiology, clinical features and treatment response. They include a number of genetic syndromes causing short stature. The aim of this study is to determine the proportion of patients with GHD and SGA from our institutional register of children on growth hormone treatment, who have defined genetic cause of their short stature made by routine clinical evaluation prior the comprehensive genetic study.

**Methods:** From our register, 432 patients with GHD (271 boys) and 178 SGA (99 boys) were enrolled to the study (49 patients after oncological treatment were excluded). Seeking for already defined genetic cause and a strong clinical suspicion of their short stature based on the clinical documentation was performed.

**Results:** In GHD group, familial short stature (FSS) was present in 47/432 patients, 81/432 had pituitary gland abnormality on the MRI scan including 13 patients with septo-optic dysplasia, and additional 57 patients with GHD were born SGA. Among SGA group, FSS was present in 25/178 patients. Of all 610 patients, in 88 a specific genetic syndrome was strongly suspected and in 38 finally confirmed by genetic testing (in 19 with GHD and in 19 born SGA, respectively). The most prevalent diagnosis in GHD was Noonan syndrome (mutations of *PTPN11*, *SOS1*, *RAF1* in 16 patients). Among SGA children, Silver-Russel syndrome was detected in 12 patients. Other genetic causes included mutations in *ACAN* (2), *PROP1* (2), *OTX2* (2) or Charcot–Marie–Tooth disease (2), CHARGE syndrome (2), DiGeorge syndrome (3), neurofibromatosis (2) and other 12 patients with mutations in various genes.

**Conclusions:** Altogether 14.4% children with GHD and SGA have a strong clinical suspicion of a single-gene condition and 6.4% were genetically diagnosed so far. Except of Silver-Russel syndrome found only in SGA, the other genetic diagnosis were present in both investigated groups. The clinical sorting of the groups can help with the strategy for search of genetic cause of short stature before using whole exome or targeted next generation sequencing.

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P2-833

#### **FERTILITY AND SIDE-EFFECTS OF 422 GERMAN GIRLS AND BOYS UNDERGOING GROWTH REDUCTION THERAPY**

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**Objectives:** The treatment of tall children to reduce final height with high-dose sexual steroids is established since the 1950s. Long term safety is not clarified. This study was conducted to study if growth reduction therapy affects fertility and other side effects in later life.

**Methods:** Patients were contacted by letter. They were asked personal questions regarding their overall experience with the therapy. The impact of the age at the beginning of the therapy and the duration of the therapy on fertility related questions was evaluated through logistic regression.

**Results:** 72,5% of the female patients (N=262) and 84,4% of the male patients (N=160) are satisfied with the overall outcome of the therapy. Female patients suffered from weight gain (67,6%), at least one miscarriage (17,9%) for which myoma was the most frequent cause (16%). 13,7% were subfertile. 14,5% had to undergo fertility treatment. Only 6,5% stayed infertile. The age at the beginning of the therapy had a significant impact on the definitive fertility. The older the girl is at the beginning of the therapy, the lower is the risk for definitive infertility (OR=0.537). Further, the duration of the therapy had a significant impact on subfertility. The longer the duration of the therapy, the lower was the risk for temporary infertility (OR=0.945). A considerable amount of female patients has, however, reported that the sudden beginning of puberty and the gain of weight was a big burden for them. Male patients mostly suffered from acne (50%). Only 3,8 % were infertile.

**Conclusions:** High-dose estrogen-treated tall women are at risk of subfertility in later life whereas in high-dose testosterone-treated boys no affect was seen. Side effects during therapy and long term effects should be clarified in detail: physical development, need for psychological support and possible subfertility.

P2-834

#### **FIRST YEAR GH RESPONSE AS PREDICTOR OF A POOR FINAL HEIGHT IN CHILDREN WITH IDIOPATHIC GROWTH HORMONE DEFICIENCY (IGHD)**

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**Objectives:** Various methods exist to detect a poor response to growth hormone therapy (GHT) after 1 year, but it is not established how well these methods predict poor final height outcome.

**Methods:** Patients with IGHD who had reached NAH (n=1103) were selected from Pfizer International Growth Database (KIGS) to evaluate the 3 first-year criteria of poor response: delta Ht SDS < 0.5, loR < -1.0 SD, or predicted NAH < -2.0 SDS after 1y of GHT (growth prediction model (GPM) with peak GH response, Ranke 2013) to predict three criteria of a poor final height outcome: deltaHt-SDS <1.0, Height-MPH >1.3 SD or NAH SDS < -2.0 SDS

**Results:** The 3 methods to detect a poor response after 1y GHT each best predicted a different criterion for poor final height outcome. First year delta Ht SDS best predicted NAH delta Ht SDS, but had a suboptimal specificity at the 0.5 SD

cut-off value. IoR was the best parameter to predict a NAH 1.3 SD below the target height, albeit with poor sensitivity. However, the model that calculates NAH after 1y GHT had a sensitivity of 51% and a specificity of 96% to predict a NAH below -2.0 SDS and still detected nearly 50% of the patients using different cut-offs with high specificity (>95%).

**Conclusions:** The sensitivity and specificity of the first two methods at their usual cut-off were suboptimal, whereas the predicted NAH using the GPM had the highest specificity and sensitivity at different cut-off levels

NAH Test after 1 y	Delta Ht SDS <1.0			Height-MPH >1.3 SD			NAH SDS < -2.0 SD		
	cut off	sens	spec	cut off	sens	spec	cut off	sens	spec
1y deltaHt SDS	<0.30	16	97	<0.31	5	97	<0.28	7	97
	<0.37	27	95	<0.25	9	95	<0.32	9	95
	<0.5	47	86	<0.5	23	83	<0.5	26	84
IoR prediction	<-2.1	8	97	<-2.1	10	97	<-2.1	6	97
	<-1.8	11	95	<-1.8	18	95	<-1.8	10	95
	<-1.0	34	86	<-1.0	38	87	<-1.0	28	86
Predicted NAH (SDS)	<-2.6	10	97	<-2.6	10	97	<-2.2	46	97
	<-2.4	10	95	<-2.4	10	95	<-2.0	55	95
	<-2.0	26	90	<-2.0	16	88	<-2.0	51	96

P2-835

**INFLUENCE OF GH THERAPY ON VASPIN CONCENTRATION AND CORRELATIONS OF VASPIN WITH SELECTED PARAMETERS OF CARBOHYDRATE AND LIPID METABOLISM IN PREPUBERTAL NON-OBESE CHILDREN WITH GROWTH HORMONE DEFICIENCY**

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**Objectives:** High serum vaspin serum was found to be associated with obesity and insulin resistance. It has been suggested that insulin resistance may itself be the result of GH deficiency. GH therapy is also known to deteriorate insulin sensitivity. The aim of the study was to estimate the correlation of vaspin concentration and carbohydrate and lipid metabolism in non-obese prepubertal children with isolated GHD before (GHD untreated group) and 6 months of GH therapy (GHD after 6 m group).

**Methods:** The 32 (22 boys, 10 girls) non-obese, short children with GHD (mean height 117.9 cm, -2.77 SD, mean BMI -0.75 SD), mean age 8.87 years. Control group (CG) consisted of 18 (11 boys, 9 girls) age matched healthy children (mean height 125.8 cm, -0.93 SD, mean BMI -0.28 SD). Serum fasting vaspin was measured in all children. In GHD untreated and GHD after 6 m oral glucose tolerance test and lipid profile were done. AUC insulinemia, AUC glycemia and TG/HDL index were calculated.

**Results:** After 6 m of GH vaspin concentration increased significantly (0.14 ng/mL vs. 0.11 ng/mL, p<0.05). Comparing vaspin between the GHD group after 6 m of GH with CG significantly higher vaspin in the GHD group was noted (0,14 ng/mL vs. 0,08 ng/mL, p<0,05). Fasting insulin was

significantly higher in GHD after 6 m comparing to GHD untreated (7,6 v 6,6 μU/mL, p<0,05). In the GHD untreated group there was significant positive correlation of vaspin and AUC glycemia and AUC insulinemia. There was positive correlation of vaspin increase and AUC insulinemia increase (r=0.42; p<0.05). Increase of vaspin concentration correlated negatively with basal TG level before GH and positively with TG/HDL before GH (r=-0.44; p<0.05 and r=0.48; p<0.01) and HDL cholesterol before GH (r=0.41; p<0.05). Increase of vaspin correlated positively with increase of TG (r=0.40; p<0.05) and with increase of the TG/HDL (r=0.40; p<0.01) whereas negatively with increase of HDL cholesterol (r=-0.44, p<0.05).

**Conclusions:** GH therapy caused significant increase of vaspin levels when compared to control group. Increase of vaspin observed after 6 months of GH therapy may result from the adaptive mechanism that responds to increased insulin

P2-836

**COMPARISON OF INSULIN TOLERANCE TEST TO ARGININE TEST FOR THE DIAGNOSIS OF GROWTH HORMONE DEFICIENCY.**

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**Objectives:** Growth hormone (GH) stimulation testing is necessary for the diagnosis of growth hormone deficiency (GHD) and the approval of GH therapy. Insulin tolerance test (ITT) has been considered the gold standard for evaluating GHD, due to its’ increased specificity. However, it carries a risk of rare but severe adverse effects secondary to hypoglycaemia, such as seizures and is therefore avoided in many centres. The aim was to compare ITT to Arginine test as a first line test for GH deficiency evaluation in children presenting with short stature.**Methods:** All patients with possible GHD seen in the Endocrine Department of Birmingham Children’s Hospital between 2015 and 2016 were tested for GH secretion assessment. Patients with Turner syndrome, brain tumours or other conditions, that wouldn’t require a second test, and those who had an end-of treatment test were excluded. Patients who had a peak GH result of less than 6.7μg/l, underwent a second test. During 2015 all patients had ITT as a first test with 0.1 Units/kg of insulin, unless otherwise indicated, and if that was positive for GHD a 2ndtest followed (usually Arginine or glucagon). During 2016 Arginine test was used as a first line test, along with short synacthen test, and was followed by an ITT or Glucagon test as the second test. Children > 10 years with no signs of puberty had to be primed with stilboestrol (1mg BD

for 2 days). **Results:** 27 children (14 girls) needed two tests (15 had ITT first, 12 had Arginine test first). Mean age at first test was 9.84y. 66% of the children who had an ITT first had a false positive result for GHD, while only 8.3% of those who had Arginine as a first test had a false positive result ( $P = 0.0597$ ; due to small numbers). There was no correlation between lack of priming and false positive results. **Conclusions:** Even though ITT is considered the gold standard for the diagnosis of GHD, there is a high incidence of false positive results. Therefore, Arginine should be considered as a first line test, as it is a relatively safe test, easily applicable in most centers and could reduce the amount of unnecessary repeat stimulation tests. However, larger studies are needed to confirm these results.

P2-837

#### USER DRIVEN DEVELOPMENT OF A NEW DEVICE FOR WEEKLY GROWTH HORMONE ADMINISTRATION IN PEDIATRIC PATIENTS

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**Objectives:** Current treatment of growth hormone disorders involves daily injections of human growth hormone (GH) over many years. Patients are typically diagnosed and initiated on treatment in childhood; adherence is critically important to treatment outcomes. Therefore, devices for GH administration must be simple to use and well accepted. Factors limiting adherence were addressed by developing an easy-to-use electronic autoinjector for once-weekly TransCon hGH, currently in Phase 3 development.

**Methods:** Device development was driven by user feedback. 73 subjects, caregivers, health care professionals (HCP), and other potential users provided input in 5 formative usability studies conducted in the U.S., Germany, and Denmark.

**Results:** Initially, a preference study investigated three device concept models with e.g. different cartridge loading steps to guide the basic product concept design. Four subsequent studies simulated actual use of auto-injector prototypes with increasing functionality eventually similar to the complete final product system. Half of the patient and caregiver participants were trained on how to use the auto-injector by the moderator who walked them through the device components and the handling steps in the Quick Reference Guide (QRG). The other half of the patient and caregiver participants, as well as all HCP participants, did not receive any training but were given time to look over the QRG and Instructions for Use to learn the device. Upon completion of the training or learning, all participants completed one or two full use sequences including mounting needle, inserting cartridge, automatic reconstitution of the lyophilized formulation, auto-injection into an injection pad, and removal of empty cartridge. The entire preparation process, from

mounting the needle to completing an injection, is designed to take less than 5 minutes.

**Conclusions:** A series of usability studies guided the development of a device for weekly GH administration that is easy to use, well accepted and eliminates the need for daily injections, cold storage, primings, air shots, dose settings, and double injections. Furthermore, the device applies Bluetooth® technology to facilitate integration with computerized health care solutions.

P2-838

#### APPROVAL OF GROWTH HORMONE TREATMENT IN CHILDREN <18 YEARS OF AGE

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**Objectives:** The study objective was investigation of patient characteristics influencing growth hormone (GH) approval in prior authorization (PA) process.

**Methods:** A retrospective study was done in GH naïve patients seen in an outpatient endocrine clinic from 1/2015 – 12/2015. Data collected included demographics, growth data, ICD 9 code, and insurance information. Five diagnosis categories were created to facilitate data analysis: Growth hormone deficiency, Genetic etiologies, Idiopathic short stature (ISS), Chronic renal insufficiency, and Other. GH coverage denial was categorized as either Administrative (errors/misinterpretation of information in PA) or Non-administrative (not meeting PA criteria, exclusion of specific diagnosis for coverage, or exclusion of any GH coverage). Chi-square test of independence was used in assessing differences in patient characteristics between those approved versus denied GH coverage.

**Results:** 181 patients were identified. Mean age was 10.3 years, and mean height z-score was -2.64. The majority were Caucasian (63%) and male (62%). 56% had private insurance. Denial of GH coverage was received in 16% (29) of cases (Fig 1). A denial was more likely ( $P < 0.001$ ) with private insurance. No statistically significant difference was seen between diagnosis category and denial (Table 1) or between denial status and any of the remaining patient characteristics. Most denials were non-administrative (24). Administrative denials (5) appealed were easily overturned. An appeal was attempted in 42% (10 of 24) of non-administrative denials with only 3 appeals resulting in overturn and coverage of GH by insurance.

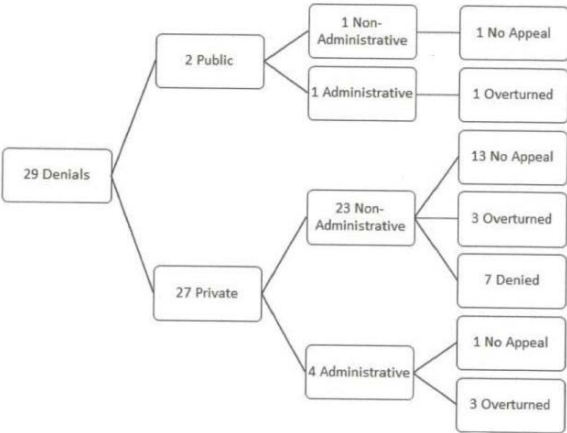
Failure to meet specific PA criteria (15) was the main denial reason used with specific diagnosis exclusion (7), mainly ISS, being the second most common reason. No statistically significant difference was seen between denial reasons.

**Conclusions:** While most patients did receive coverage for GH therapy, the likelihood of receiving insurance covered GH therapy was low in those denied. Denials by private insurance perhaps reflect efforts to more stringently manage utilization.



Pediatric endocrinologists should be familiar with criteria used in the PA process. A discussion with families regarding the prospect of a GH coverage denial should also occur.

Figure 1



P2-839

RADIOLOGICAL FEATURES PREDICTIVE OF SHOX DEFICIENCY

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**Objectives:** SHOX deficiency is a frequent cause of short stature. Heterozygous SHOX mutations are detected in 2-15% of individuals with formerly idiopathic short stature and 50-90% of individuals with Leri-Weill dyscondrosteosis. Aim of this retrospective study is to review the radiological findings of short stature patients searching for further specific features of SHOX haploinsufficiency.

**Methods:** 296 patients followed for short stature were selected with height < 2 SDS for Tanner charts, and/or sitting height/height ratio >2.5 SDS for Friedricks chart and/or height < 2 SDS for target height. Hypopituitarism, chronic diseases, Turner Syndrome in females and other known genetic disorders were considered exclusion criteria. MLPA was used to search for known SHOX deletions or duplications, PCR direct sequencing for point known mutations. To define bone age (TW2-RUS) and evaluate the carpal angle (n.v. >130°), the ulnar deviation from baseline, the distal radial lucency, the radius bowing, the 4th-5<sup>th</sup> metacarpals length, the ulnar tilt, the Madelung's wrist deformity, a burly and bowing forearm and the TI score (triangularisation score), 230 left hands and forearms X-Ray were studied.

**Results:** A SHOX gene alteration was detected in 52/296 patients (17.6%); the left hands and forearms X-Rays from 45 patients SHOX-D+ (19.6%) were compared with 185 of SHOX-D- (80.4%) (Table reported). The distal radial lucency and a

burly/bowing radius were the most predictive radiological features in patients <10 years old.

**Conclusions:** SHOX gene alteration, accordingly to the Rappold score, is associated with distal radial lucency, ulnar tilt, metacarpal pyramidalization of the distal carpal row and short 4<sup>th</sup> metacarpal. Our study suggests a possible predictive role also for the bowing of radius and the burly/bowing forearm. A detailed radiological score could therefore be useful to increase SHOX mutation detection rate in short stature.

Radiological features	SHOX-D-	SHOX-D+	P value
Carpal angle	130.3 (8.4)	128.2 (9.9)	0.17
Ulnar deviation from baseline (mm)	2.6 (1.5)	2.7 (1.6)	0.7
Distal radial lucency	34.8 %	62.2 %	0.001
Bowing of radius	28.6 %	62.2 %	0.001
Short 4th metacarpal	12.1 %	25.0 %	0.03
Short 5th metacarpal	2.7 %	2.3 %	0.7
Ulnar tilt	0.5 %	20.0 %	0.000
Madelung's wrist deformity	8.2 %	90.0 %	0.3
Burly forearm	45.8 %	80.0 %	0.005
Burly and bowing forearm	41.7 %	75.0 %	0.007
TI score	6.8 (2.3)	9.5 (4.2)	0.002

P2-840

COMPARISON OF LIPID AND GLUCOSE METABOLISM BETWEEN SHORT PREPUBERTAL CHILDREN AND HEALTHY CHILDREN OF NORMAL HEIGHT

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**Objectives:** The aim of this study is to describe the lipid and glucose metabolism of prepubertal short children with GH peaks between 7-14 µg/L and compare it with healthy children of normal height and weight. We have previously reported differences in fasting insulin and HOMA-IR between these groups, were the short children with the lowest GH peaks had significantly lower fasting insulin and signs of increased insulin sensitivity compared with the controls. In this study, we further examined the different groups' lipid and glucose metabolism using microdialysis analysis and stable isotope examinations.

**Methods:** Thirty-five pre-pubertal short children (<-2.5 SDS) aged between 7-10 years, with peak levels of GH between 7-14 µg/L in an arginine insulin tolerance test and twelve age- and sex-matched children of normal height were enrolled in the study. All microdialysis and stable isotope examinations were performed in fasting state. Microdialysate samples for glucose and glycerol analysis was collected from the abdominal subcutaneous fat in 1-hour fractions. Stable isotope examination was performed using [6,6-<sup>2</sup>H<sub>2</sub>]-glucose and [1,1,2,3,3-<sup>2</sup>H<sub>5</sub>]-glycerol tracers with blood samples collected 7 times with 10 min intervals. Glucose and glycerol production rates were subsequently calculated from the isotope ratios during the period of steady state.

**Results:** No significant differences between the short children and the controls were seen regarding the microdialysis analyses of glucose (5.33 vs 5.55 mmol/L,  $p=0.43$ ) or glycerol (152.7 vs 131.9  $\mu\text{mol/L}$ ,  $p=0.26$ ). Neither the stable isotope examinations of rates of glucose production (5.20 vs 4.94 mg/kg/min,  $p=0.40$ ) or glycerol production rate (5.2 vs 4.4  $\mu\text{mol/kg/min}$ ,  $p=0.42$ ) could detect any differences between the groups. Further subgroups analysis, dividing the short children in those with GH peak levels above or below 10  $\mu\text{g/L}$ , also failed to show any differences regarding these metabolic parameters.

**Conclusions:** We could not detect any significant differences between the group of short children with GH peak levels between 7-14  $\mu\text{g/L}$  and the control group regarding the fasting levels of glucose or glycerol in their abdominal subcutaneous fat tissue or their rates of glucose or glycerol production.

P2-841

#### DO NO HARM: COGNITIVE AND BEHAVIORAL CHANGES IN SHORT CHILDREN FOLLOWING GROWTH HORMONE TREATMENT

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**Objectives:** Treating children with growth hormone (GH) typically results in improved adult height. Whether they gain psychological and/or cognitive benefits remain critical yet unresolved questions. We sought to determine if differences in cognitive & behavioral functioning exist in children with GH deficiency (GHD) or idiopathic short stature (ISS) prior to and following GH treatment.

**Methods:** Subjects had heights  $\leq 3^{\text{rd}}$  % and were classified as GHD (peak GH  $<5$  ng/mL) or ISS (peak GH  $\geq 5$  ng/mL). All had baseline neuropsychological & parental behavioral ratings. All GHD participants received GH; participants with ISS were started on GH based on independent decisions made by the family & endocrinologist. This resulted in 3 groups: GHD treated with GH (GHD-T), ISS treated with GH (ISS-T) & ISS NOT treated with GH (ISS-NT). Follow-up testing was conducted roughly 1 year after baseline testing. Between-group comparisons were conducted using ANOVA or chi-squared tests for baseline & using repeated measures ANOVA for longitudinal comparisons.

**Results:** 38 subjects (25 boys) had baseline data; 30 subjects (21 boys) also completed follow-up testing. At baseline, GHD subjects scored significantly lower on tests of visuoconstructional ability & processing speed but did

significantly better on a response inhibition test. Behavioral ratings revealed no differences at baseline & were in the normal range for all groups. At follow-up, group-by-time interactions revealed: 1. ISS-NT group improved on 2 cognitive tasks; 2. GHD-T & ISS-T groups showed stable to somewhat declining cognitive performance; 3. GHD-T and ISS-T had significant worsening on measures of withdrawal ( $P=0.022$ ) & behavioral symptoms ( $P=0.016$ ) relative to the ISS-NT group. Mean Behavior Symptoms Index scores of GH-treated children went from the normal range to the clinically "at-risk" range.

**Conclusions:** The mild baseline cognitive abnormalities are of unclear clinical significance & did not improve with GH. The novel inclusion of an untreated control group allowed discovery of potentially concerning behavioral findings in GH treated children. Unrealistic & unachieved expectations for growth in the 1<sup>st</sup> year or "medicalizing" otherwise healthy children may result in increased concern about "not measuring up". Caution & further study are needed.

P2-842

#### GH INFLUENCES PLASMA FASTING PREPTIN CONCENTRATION IN PATIENTS WITH TURNER SYNDROME

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**Objectives:** Increased adiposity and insulin resistance are frequently observed nowadays. Many hormones are involved in the pathogenesis of the condition but therapeutic options we can offer to the patients are still scant. Each newly discovered peptide give us hope. Preptin is a newly discovered metabolic hormone involved in energy homeostasis. This homeostasis is frequently disturbed in patient with Turner Syndrome (TS). Patient with TS are unique model for studies of an effect of the treatment with supraphysiological doses of recombinant growth hormone (rGH).

We studied preptin dependance and response in a group of patients with TS treated with supraphysiological doses of rGH.

**Methods:** The study group consisted of 36 TS patients aged 3.2–16.07 yrs (mean 8.2 yrs) diagnosed by karyotyping. The rGH was applied in a dose 0.05 mg/kg/day. Prior to and following the treatment anthropometrical data were recorded as well as biochemical parameters were measured: preptin, OGTT, insulin, lipids, IGF-1, and IGFBP-3.

**Results:** The applying of rGH in patient with TS caused significant increase in preptin level (mean  $\pm$  SDS;  $67.1 \pm 47.6$  versus  $89.5 \pm 57.6$ ). Surprisingly preptin did not correlated with anthropometrical parameters.

The increase of IGF-1 concentration at the end of observation was also significant (from  $119.4 \pm 62.46$  to  $413.37 \pm 204.38$  ng/ml, mean  $\pm$  SDS,  $p = 0.000$ ). The GH treatment influenced insulin resistance revealed by increased HOMA

values (median  $0.64 \pm 0.45$  before and  $0.92 \pm 0.97$  after,  $p=0.02$ ). The correlation between preptin and IGF-1 and IGF-1 SDS levels was not significant neither before nor on the rGH treatment ( $r=0.08$  and  $r=0.04$  respectively). Preptin correlated negatively with HbA1c ( $r=-0.28$ ), and positively with glucose at 30' of OGTT ( $r=0.22$ ), and insulin at 90' of OGTT ( $r=0.24$ ) before rGH treatment but not on rGH therapy. Before GH applying preptin correlated with LDL cholesterol ( $r=0.26$ ), whereas on rGH therapy stronger correlation between preptin and total cholesterol ( $r=0.43$ ), as well as preptin and LDL cholesterol ( $r=0.39$ ) were observed.

**Conclusions:** Results of the study showed an increase in preptin level following rGH application. This effect is not mediated by IGF-1. The rGH treatment changes preptin influence on glucose and lipid metabolism.

P2-843

#### A NOVEL HETEROZYGOUS VARIANT OF NPR2 GENE IN KOREAN PATIENTS WITH IDIOPATHIC SHORT STATURE

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**Objectives:** C-type natriuretic peptide and its receptor, natriuretic peptide receptor B (NPR2 gene), is critical for endochondral ossification in growth plate. Biallelic NPR2 mutations are known as acromesomelic dysplasia, type Maroteaux which is characterized by severe short stature. A monoallelic NPR2 mutation has been suggested to mildly impair long bone growth. The purpose of this study was to identify NPR2 mutation in Korean patients with idiopathic short stature (ISS).

**Methods:** One hundred twelve patients (54 male) with ISS from Hallym Medical Center and Korea Medical Center were enrolled. The inclusion criteria were as follows: height < 3 percentile (z-score  $-1.88$ ) and stimulated growth hormone levels > 7.0 ng/mL or normal growth velocity (> 4 cm/year for prepubertal children). The exclusion criteria were as follows: born small for gestational age; syndrome or endocrine disorders which can affect to growth. NPR2 gene was sequenced and the identified variant was filtered with reference to the dbSNP database. To identify the potential effects of sequence variants on protein function, the variant sequences were assessed using PolyPhen-2.

**Results:** The mean $\pm$ SD with range of age and height z-score were  $8.1\pm3.2$  ( $2.8\sim16.0$ ) years and  $-2.35\pm0.42$  ( $-3.97\sim-1.88$ ), respectively. Of the 112 patients, 3 different heterozygous variants in NPR2 were identified in 3 patients. The known SNPs, R787W (c.2359C>T, rs114147262, benign) and R921Q (c.2762G>A, rs770276670, pathogenic), were identified in case 1 and 2, respectively. A novel variant in exon 8, R495C (c.1483C>T), was found in case 3 which was suggested to be probably damaging with a score of 0.999 in silico analysis. The case 3 was a 9.5 year-old boy whose height z-score was  $-1.98$  with a growth velocity of 5.4 cm/year. The stimulated growth hormone level was 23.6 ng/mL and his bone age was 1.5 years delayed. The height z-scores of his parents were  $-0.59$

(father) and  $0.64$  (mother). He was treated with recombinant growth hormone and growth velocity during the first 3 years after treatment was 8.0 cm/year.

**Conclusions:** The heterozygous mutations were found in 1.8% of ISS patients. One novel variant which is predicted to be probably damaging must be undergone in vitro functional study to confirm that if this could be pathogenic.

P2-844

#### LONG-TERM EFFICACY AND SAFETY OF TWO DOSES OF NORDITROPIN® (HUMAN GROWTH HORMONE, SOMATROPIN) IN SHORT STATURE DUE TO NOONAN SYNDROME: A RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL IN JAPANESE PATIENTS

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**Objectives:** This randomized, double-blind, parallel-group, multicenter trial (NCT01927861) evaluated the growth-promoting effect and safety of Norditropin® (NN-220, somatropin) in Japanese children with short stature due to Noonan syndrome.

**Methods:** Fifty-one prepubertal children aged 3–<11 years (boys) and 3–<10 years (girls) clinically diagnosed with Noonan syndrome according to van der Burgt criteria were randomized 1:1 to receive Norditropin® 0.033 mg/kg/day ( $n=25$ ; mean age 6.57 [SD: 2.42] years; 11 females) or 0.066 mg/kg/day ( $n=26$ ; mean age 6.06 [2.25] years; 8 females) for 104 weeks. Change in height standard deviation score (HSDS) from baseline to 104 weeks' treatment was analyzed based on an ANCOVA model with treatment as a fixed effect and baseline HSDS as a covariate.

**Results:** Baseline HSDS was comparable between groups (0.033 mg/kg/day:  $-3.24$  [SD 0.76]; 0.066 mg/kg/day:  $-3.25$  [0.71]) and was considerably below the reference range for Japanese children. The estimated change in HSDS after 104 weeks' treatment was statistically significantly greater in the 0.066 mg/kg/day group ( $1.47$  [95% CI: 1.29, 1.64]) vs. the 0.033 mg/kg/day group ( $0.84$  [95% CI: 0.66, 1.02]); estimated mean difference 0.63 (95% CI: 0.38, 0.88),  $p<0.0001$ . Rates and patterns of adverse events (AEs) were similar between groups. The majority were mild and reported as unlikely to be related to Norditropin®. There were no withdrawals due to AEs and no differences in serious AEs between groups. Insulin-like growth factor-I SDS increases from baseline were greater with 0.066 mg/kg/day ( $-1.71$  to  $0.63$ ) vs. 0.033 mg/kg/day ( $-1.71$  to  $-0.64$ ). From baseline to 104 weeks, HbA<sub>1c</sub> increased slightly (0.033 mg/kg/day:  $+0.14\%$ ; 0.066 mg/kg/day:  $+0.13\%$ ), glucose profiles in the oral glucose tolerance test (OGTT) were almost unchanged, and insulin profiles in the OGTT increased in both groups.

There were no clinically significant abnormal ECG evaluations or transthoracic echocardiography findings.

**Conclusions:** In Japanese children with short stature due to Noonan syndrome, treatment over 104 weeks with Norditropin® 0.033 mg/kg/day and 0.066 mg/kg/day improved HSDS in both groups and demonstrated a favorable safety profile.

P2-845

#### **NOVEL HETEROZYGOUS VARIANT IN LYSINE DEMETHYLASE 3B, KDM3B C.2827C>T (P.ARG943TRP), ASSOCIATED WITH IDIOPATHIC SHORT STATURE**

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**Objectives:** We sought to identify the genetic etiology of short stature in a 4 year old female who presented with a height of -3.5 SD. Her parents were both of normal height. In addition to short stature, the patient's symptoms included mild sensorineural hearing loss, language delay, and mild intellectually disability. She had a normal endocrine evaluation including normal IGF-1, IGFBP-3, and stimulated growth hormone levels. A karyotype and microarray were normal.

**Methods:** We performed whole exome sequencing (WES) in the patient and her parents. The candidate variant in KDM3B was regenerated in a plasmid via site-directed mutagenesis. The plasmid was then transfected into HEK293 cells and H3K9 methylation levels were assessed via immunoblotting.

**Results:** WES showed a de novo heterozygous missense variant in Lysine Demethylase 3B (KDM3B), p.R943W. KDM3B specifically removes mono- and di-methyl groups from 9<sup>th</sup> lysine on the third histone (H3K9). Western blotting showed that the variant does not affect protein expression. However, the mutant variant significantly decreased the demethylation of mono- and tri-methylated H3K9 when compared with wild-type KDM3B.

**Conclusions:** We identified a de novo missense variant in the histone lysine demethylase KDM3B as a possible cause for short stature and intellectual disability in a single patient. Additional studies are needed to identify other patients with potentially pathogenic variants in KDM3B.

P2-846

#### **GROWTH HORMONE DEFICIENCY IN MYCN GENE DELETION(FEINGOLD SYNDROME -1)-RARE FINDING IN A RARE DISEASE**

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**Objectives:** A 3 year old, Indian origin, male child presented to the Pediatric endocrine clinic with chief complaint of severe failure to thrive. Child was first born, product of non-consanguineous marriage, born at 36 weeks with severe proportionate growth restriction. There was no other positive family history of (h/o) similar cases in family or h/o long term illness or medications in child.

**Methods:** Clinical examination showed anthropometry with weight at -3SDS, Height at -4SDS and Head circumference at -5 SDS. Mild to moderate development delay (predominant speech) was noted. General examination revealed brachcephaly, small dysplastic milk teeth, short palpebral fissures, micrognathia, severe clinodactyly and brachymesophalangy bilateral (b/l) 5th finger, b/l simian creases, tapered fingers-2nd to 4th, fingers hyperlaxity, normal feet and genitals. Rest of the systemic exam was normal.

**Results:** Labs showed iron deficiency anemia, mild high SGOT, with normal renal functions and negative celiac screen. Growth hormone stimulation test (post clonidine) showed a peak of GH at 120 minutes at 2ng/ml only. Rest of the hormonal evaluation and anterior pituitary functions were normal. Bone age was significantly delayed, MRI Brain and Pituitary was normal. Patient was started on GH therapy at 0.025 mg/kg/day and multi-disciplinarian management initiated. Meanwhile the genetic analysis (CGH -array) results showed 10.5 Mb deletion from gene LOC339788 to KCNS3 overlapping the MYCN gene deletion responsible for Feingold syndrome -1.

**Conclusions:** This was a case of proportionate severe short stature who was found to have Feingold syndrome 1 (missing one copy of MYCN gene). The Feingold syndrome is a very rare, predominantly autosomal dominant syndrome characterised by microcephaly, facial dysmorphism, gastrointestinal atresias and mild to moderate learning disabilities. This syndrome will be reviewed with respect to usual and unusual findings in this case in particular detection of severe GH deficiency, de-novo mutation, genetic counselling, multi-disciplinarian management and possibilities of other associations to be looked for in future in view of other gene deletions. And perhaps the initial encouraging response to GH therapy entails a detailed work up for GH deficiency in similar cases with MYCN gene deletion.

P2-847

#### **A BOY WITH SEVERE SHORT STATURE AND AUTOIMMUNE DISEASES DUE TO A NOVEL HOMOZYGOUS MISSENSE MUTATION IN STAT5B GENE**

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**Objectives:** STAT5b deficiency is a rare autosomal recessive disorder associated with profound postnatal growth failure, severe IGF-1 deficiency and clinical manifestations of immune dysregulation, including eczema, chronic pulmonary disease, etc. However, the full spectrum of this disorder has not been determined. We present the auxological, clinical and laboratory signs of a 15-year-old boy with severe short stature due to a homozygous STAT5b mutation.

**Methods:** The boy is the first child of consanguineous family. He is born full-term from a second uneventful pregnancy, with normal birth weight and length. There is no family history of growth failure and his younger sister is of normal stature. Poor weight gain and growth failure were noted after 2 years of age. He was treated for iron-deficiency anaemia. At 4 years of age Levothyroxine was commenced due to autoimmune thyroiditis and hypothyroidism. In the following years he developed atopic dermatitis, alopecia, IgA and vitamin D deficiencies, with cold intolerance and persistent skin itching treated with topical medications. At the age of 12 his height was far below the 3<sup>rd</sup> percentile with no pubertal signs; IGF-1 level was 62.5 ng/ml (r.r. 143-693). Two GH stimulation tests were performed with peak GH levels < 7.5 ng/ml. Treatment with rhGH was initiated.

**Results:** For 2 years the boy gained only 5 cm and rhGH therapy was stopped. At the age of 14 years the patient was referred to Newcastle University, UK. Cyclosporine was initiated with regular follow-up of its serum levels. For 1.5 years of treatment the boy's height increased with 8 cm; there was significant improvement in the skin, alopecia and weight gain, and puberty began. Due to the combination of GH-treatment refractory short stature, autoimmune hypothyroidism, severe atopic dermatitis, alopecia and T-cell lymphopenia, a defect in the GH signaling pathway was suspected. Molecular studies revealed a novel homozygous missense mutation p.L151P of STAT5b gene. Functional studies are underway.

**Conclusions:** STAT5b gene mutations should be suspected whenever severely short statured patients express signs of autoimmune disease. Earlier diagnosis might improve clinical outcome.

P2-848

**NOVEL VARIANT C.97C>T OF THE GROWTH HORMONE RELEASING HORMONE RECEPTOR GENE CAUSES ISOLATED GROWTH HORMONE DEFICIENCY TYPE IB**

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**Objectives:** Isolated growth hormone deficiency (IGHD), type Ib is an autosomal recessive genetic condition, caused by mutation to either GH1 gene or to GH releasing hormone (GHRH)/GHRH receptor gene. Affected subjects present with symptoms of GHD characterised by low but detectable levels of GH, delayed skeletal maturation, short stature and a positive responsiveness to rhGH therapy. Laron syndrome is an autosomal recessive genetic form of dwarfism caused by mutations in the receptor (GHR) gene, accompanied with severe short stature, obesity, augmented levels of GH and low levels of insulin-like-growth-factor I (IGF-I). Affected patients are responding to exogenous rhIGF-I administration.

**Methods:** We describe a 14-month old girl who presented with severe postnatal growth failure and phenotype of Laron syndrome. Provocation tests and IGF-I generation test were performed in order to exclude GH deficiency or insensitivity, respectively. Whole exome sequencing (WES) of patient and of no consanguineous parents was performed.

**Results:** Extremely low GH values, low basal IGF-I levels and no increase of IGF-I levels in IGF-I generation test were documented (Table1). Patient's WES revealed a novel homozygous variant in the GHRHR gene, c.97C>T, which creates a premature stop codon. The variant was detected in the mother in a heterozygous state, not found in the father, suggesting a large deletion in the paternal allele. No mutation was found in the GHR gene. Since pathogenic variants of the GHRHR gene are associated with IGHD type IB, rhGH (0.28mgr/kg/week) administration was applied, improving growth velocity and head circumference.

Table1

Time (min)	GH (ng/ml)			IGF-I (ng/ml)	
	Clonidine	Glucagon	Arginine	IGF-I Generation Test	
0	0.441	1.65	1.35	Day	
30	1.37	0.96	2.98	0	8.9
60	3.45	2.3	3.63	1st	11.3
90	1.1	4.77	1.18	2nd	13.4
120	0.595	2.03	1.1	3rd	13.6
150	-	0.84	1.27	4 <sup>th</sup>	11.7
180	-	0.44	-	-	-

**Conclusions:** This is the first time that the variant c.97C>T of the GHRHR gene is reported in an IGHD patient. Although Laron syndrome was not genetically confirmed the absence of response to IGF generation test has to be elucidated.

P2-849

**SHORT STATURE WITHOUT HYPERTRICHOSIS CUBITI: ATYPICAL PHENOTYPE OF WIEDEMANN-STEINER SYNDROME WITH A NOVEL NONSENSE KMT2A (MLL) MUTATION**

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**Objectives:** Wiedemann-Steiner syndrome (WDSTS) is a rare autosomal dominant disorder characterized by hypertrichosis cubiti, short stature, distinctive facial features and learning

disabilities. Here, we report a boy with phenotypic overlap with WDSTS, however lacking hypertrichosis cubiti.

**Methods:** Data were collected from patient's medical records at Mayo Clinic.

**Results:** At 7 y of age, this Caucasian-African American boy presented with proportional short stature (height Z-score -4.3), failure to gain weight (weight Z-score -4.7), dysphagia during infancy, constipation, right-sided sensorineural hearing loss, hyperopia, learning disabilities, behavioral difficulties and recurrent croup and otitis media. At 2 months, height Z-score was -2.9 and weight Z-score was -2.3. Physical features included proportionate microcephaly, long eyelashes, normal slanting but narrow palpebral fissures, hypertelorism, broad nasal bridge, long philtrum, thin upper lip, patchy hypertrichosis of back, mild fifth finger clinodactyly and shallow sacral dimple. Bone age was within 2SD of the mean. His IGF-1 concentration was persistently low for tanner stage despite improvement in nutritional status. Growth velocity was 4.8 cm/y over 18 months of follow-up. Head MRI revealed a small pituitary gland. A novel heterozygous nonsense c.1027G>T (p.E343X) pathogenic variant in the *KMT2A* gene (chromosome 11, exon 3) [Lysine (K)-specific methyltransferase 2A] was detected on whole-exome sequencing and confirmed with Sanger sequencing. His biological parents were not available to confirm whether it was inherited or a *de novo* alteration. Parents declined growth hormone treatment.

**Conclusions:** Substantial phenotypic variations exist within WDSTS. Less than 30 patients with confirmed *KMT2A* mutations have been described. Hypertrichosis of the back, as seen in present case, has been reported as frequently (73%) as hypertrichosis cubiti (67%). Postnatal growth retardation was noted in 100% of cases. Limited evidence supports efficacy of growth hormone therapy. Findings in our patient that may expand the phenotype associated with *KMT2A* mutations include sensorineural hearing loss, hyperopia and refractory constipation.

P2-850

#### RECURRENT UNEXPLAINED HYPOGLYCAEMIA IN CHILDREN IN RESOURCE LIMITED SETTINGS; COULD THIS BE GROWTH HORMONE DEFICIENCY?

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**Objectives:** Data on hypoglycaemia as a feature of growth hormone deficiency in children over 1 year from resource limited settings is very scarce. The objectives of this study is to describe the two cases of recurrent hypoglycaemic attacks on toddlers who had failure to thrive and short stature who the underlying cause was growth hormone deficiency

**Methods:** The first case is a 3 years old boy who presented to his local clinic with history of recurrent hypoglycaemic episodes and focal seizures since 1 year of age. Some of the hypoglycaemic episodes have been associated with

prolonged fasting. However, most of the hypoglycaemic attacks occurred without any underlying cause. He had uneventful perinatal history and he developed stagnated growth in both the weight and height since 1 year of age. The second case is a 2 years old boy who presented to his local clinic with history of recurrent episodes of floppiness and teeth clenching secondary to hypoglycaemia since infancy. He had uneventful birth history and failure to thrive since 1 year of life. Both cases were admitted to the hospital for controlled fasting test and further investigations.

**Results:** The 2 cases described above had severe underweight and stunting (both weight and height for age were less than -3 z-scores). They sustained the blood glucose within the normal range throughout the controlled fasting test. The investigation profile performed at the end of the controlled fasting state revealed very low Insulin-like Growth Factor 1 (levels <25 ng/mL for both cases) and very low Growth Hormone levels. The Cortisol, C-Peptide, Insulin and Glucose were all within the normal limits. They had delayed bone age and the MRI brain scan revealed the presence of anterior pituitary hypoplasia in both cases. The diagnosis of growth hormone deficiency was made and they were started on somatropin therapy with the resolution of the symptoms as well as attainment of improved growth over a period of time

**Conclusions:** Recurrent hypoglycaemia, failure to thrive and short stature in toddlers warrants extensive investigations. If adequate nutrition has been provided without any resolution of the signs and symptoms, clinicians should consider the possibility of Growth Hormone Deficiency (GHD)

P2-851

#### GROWTH HORMONE AND TRIPTORELIN ACETATE TREATMENT IN EARLY DIAGNOSED SILVER-RUSSELL SYNDROME

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**Objectives:** Introduction

Silver-Russell syndrome is a genetic disorder in which intrauterine and postnatal growth retardation, relative macrocephaly, triangular face, body asymmetry. The hypomethylation of the imprinted control region, which is localized in the chromosome region 11p15 to 35-65% of the cases, is responsible. Here we present a Silver-Russell syndrome followed by growth hormone deficiency and precocious puberty.

**Methods:** Case

Three years old girl was admitted to hospital because of short stature. On physical examination there were triangular face, bilateral clinodactyly for 5th finger and bilateral lower and upper limb asymmetry. She was term baby and there was intrauterine growth retardation. Silver-Russell syndrome pre-diagnosis was made. Growth hormone treatment for growth hormone deficiency since 4 years old and triptorelin acetate

treatment for early puberty since 7 years were given. Body weight: 37 kg< (50-75p), height: 133 cm (10-25p) at the age of 10 years old. Hypomethylation was detected in the H19 region for diagnosis of Silver-Russel syndrome in genetic study.

**Results:** n/a

**Conclusions:** Result

In Silver-Russel syndrome, we wanted to emphasize that growth hormone therapy at an early age. We also found that precocious puberty may be associated with this syndrome.

P2-852

#### AN UNUSUAL CASE OF KBG SYNDROME WITH ADVANCED BONE AGE AND TALL STATURE

*Yuezhen Lin, MD, Baylor College of Medicine, Houston, TX, United States*

**Objectives:** To present a case of KBG syndrome with unusual presentation - advanced bone age and tall stature.

**Methods:** Retrospective chart review and literature search were conducted for this case report

**Results:** Case: Patient was a 8-year-old boy with autism spectrum disorder that was diagnosed at the age of 2 years. Genetic workup revealed a missense ANKRD11 gene mutation (c.6065C>T (p.P2002L)). Combined with behavioral phenotype, and some physical features (macrodonia and ridging of his teeth), KBG syndrome was diagnosed at age 8. The referral to endocrine was prompted by the finding of advanced bone age and tall stature.

Workup and clinical course: Bone age was +4.1 SD advanced (11 years 6 months at chronological age of 8 years). Endocrine evaluation revealed history of growth acceleration over past 1-2 years and tanner stage 2 for his genital exam. Central precocious puberty was confirmed by GnRH stimulation test with peak LH of 7.9 mIU/ml. His brain MRI was normal. The patient was started on GnRH agonist (supprelin implant). His bone maturation has slowed down since treatment, and most recent bone age was +3.3 SD. His height has been tracking 90-95th percentile without further acceleration.

**Conclusions:** KBG syndrome is a rare autosomal disorder characterized by distinctive craniofacial and skeletal features, short stature and developmental delay. It is caused by haploinsufficiency of the ANKRD11 gene. Patients with KBG syndrome typically present with short stature with delayed bone age. We describe the first case of KBG syndrome with tall stature and advanced bone age secondary to precocious puberty. Meticulous evaluation of physical and skeletal findings is important in patients with KBG syndrome. Further research is warranted to determine the classic and variant presentations of this condition, with follow-up data providing valuable insights into its natural history and long-term prognosis.

P2-853

#### MUTATION IN CUL7 GENE IN 3-M SYNDROME LEAD TO GH AND GROWTH FACTORS RESISTENCE

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**Objectives:** 3M syndrome-1(3M1) is an autosomal recessive primordial growth disorder characterized by severe pre and post-natal growth restriction, caused by homozygous or compound heterozygous mutations in the CUL7 gene on chromosome 6p21.1. The product of this gene play a critical role in maintaining microtubule integrity with defects leading to aberrant cell division. Dysmorphic features, skeletal abnormalities and normal intelligence characterize this syndrome. This condition probably underdiagnosed, has been reported in approximately 200 cases in the literature with a clinical variability currently discussed.

**Methods:** Massive sequencing and Sanger of CUL7 and OBSL1 genes.

**Results:** We report a 14 year-old boy who was referred with short stature at the age of 2.3 years. He was born SGA, BW 2.22g -2.34 SD, lenght 42cm -4.16 SD. He was product of non-consanguineous healthy parents with two healthy younger sibilings. Phenotypically he showed a triangular face with sharp chin, prominent mouth and lips, large head circumference, prominent forehead, short broad neck and thorax, hyperlordosis, short digits, prominent heel with normal intelligence. The height was 70.8 cm (-4.9SD). During chilhood the presence of celiac disease was demostrates. GH-IGF1 axis reveals peak GH level on arginine stimulation test of 42 ng/dl, with basal IGF1 levels of 17.4 ng/ml (-2.85SD)and IGFBP3: 2472 ng/ml. IGF-1 post generation test of 84 ng/ml (-0.47SD) and IGFBP3: 3024 ng/ml. Gluten-free diet and growth hormone treatment did not show substantial benefits in growth. The genomic analysis confirmed homozygous mutation in exon 23 of the CLU7 gene, variant c.4391A>C (p.His1464Pro)

**Conclusions:** The findings reported in this patient demonstrate this genetic defects can be identified in children with the presence of the short stature and features of GH -IGF1 insensitivity. The variant has previously been described in the HGMD and NCBI databases in three Italian families (Huber 2009) and not having been reported in Argentine patients. This condition contributes to demonstrate the inability of CUL7 to recruit ROC1, since it acts as one ubiquitin-ligase and is know to interact with p53 cyclin D-1 and the growth factor of the IRS-1 signaling molecule, could explain the resistance to GH-IGF.



EVALUATION OF 7 PATIENTS FROM 3 FAMILIES WITH ISOLATED GROWTH HORMONE DEFICIENCY DUE TO TWO DIFFERENT GHRHR GENE FUNCTION LOSS MUTATIONS

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**Objectives:** Mutations in the GHRHR gene constitute 10% of cases of autosomal recessive familial isolated growth hormone deficiency. Here, we report seven cases of three families with 2 mutations in GHRH function loss (2 families, Turkish; 1 family, Syria) and the cases will be discussed in the clinical and laboratory findings.

**Methods: Cases:** Seven cases with GHRHR mutation were identified as 1 female and 6 male.

**Results:** The earliest diagnosis was 9 years and 4 months, and the latest diagnosis was 15 years and 11 months. The mean heightSDS at diagnosis were between -3.6 and -8.6. The three patient's heightSDS from Syria, which detected a different GHRHR mutation, were much more pathologic. Pubertal stages of a girl patient and a boy patient who applied at 15 years of age were stage 3, whereas other cases were seen to be applied to prepubertal. The bone age at the time of diagnosis delayed ranged from 2 to 6 years, according to chronological age. Basal and stimulated growth hormone levels, IGF-1 and IGFBP3 levels of patients are very low. It was seen that the pituitary size was smaller in the pituitary imaging. Growth hormone deficiency was isolated in all patients. It was seen that 2 patients who were treated at the age of 15 years and 8 months and 14 years and 3 months and had given for growth hormone treatment for 2.5 years reached 154.9 and 156.5 cm final height, respectively. The patient's target heights were 171 cm and 162 cm. The patient applied to the growth hormone treatment irregularly at the age of 9 years and 4 months reached 143.8 cm final height. The final height in this case was attributed to the irregular use of growth hormone. The patient 1 was 7 cm growth velocity in 2 years before treatment and 22.7 cm in 2 years in treatment. In three Syrians siblings, growth velocity before treatment were 1.1 / 1.4 / 0.5 cm at 6 months, and 11.4 / 11 / 9.7 cm at 9 months of growth hormone therapy (Table 1).

**Conclusions:** GH deficiency due to GHRHR gene mutation is rare. Genetic studies should be performed in the presence of low IGF-1 levels, inadequate response to BH stimulation tests,

and hypophyseal hypoplasia, especially in cases where family history is positive.

	First Family Turkish Family	Second Family Turkish Family	Third Family Syrian Family
Consanguinity	Second degree	Third degree	Third degree
GHRHR mutation in father	Heterozygote c.161-1G>A	Heterozygote c.161-1G>A	Not available
GHRHR mutation in mother	Heterozygote c.161-1G>A	Heterozygote p.Phe169Leu	Heterozygote Ala153Asp (c.458C>A)
Father's height	162.7 cm	163 cm	174 cm
Mother's height	165 cm	149 cm	162 cm
Target Height/ SDS	171 cm / +0.34 SDS	162 cm / +1.61 SDS	161.5 cm / +0.2 SDS (F) 174.5 cm / +0.2 SDS (M)
	Patient 1	Patient 2	Patient 3
GHRHR Mutation	Homozygous c.161-1G>A	Homozygous c.161-1G>A	Compound Heterozygote c.161-1G>A p.Phe169Leu
Age of diagnosis (year)	11 years 11 months	15 years 8 months	14 years 3 months
Height SDS at diagnosis	124.5 cm / -3.8	139.5 cm / -4.5	130 cm / -3.7
Weight SDS at diagnosis	28.5 kg / -2.08	33.9 kg / -3.7	41 kg / -1.96
	Patient 4	Patient 5	Patient 6
GHRHR Mutation	Compound Heterozygote c.161-1G>A p.Phe169Leu	Homozygous Ala153Asp (c.458C>A)	Homozygous Ala153Asp (c.458C>A)
Age of diagnosis (year)	9 years 4 months	15 years 11 months	13 years 11 months
Height SDS at diagnosis	-3.6	124.5cm/-8.6	118cm/-4.9
Weight SDS at diagnosis	23 kg / -1.48	26.25 kg/-6.6	21.45 kg/-5.03

RELATIONSHIP BETWEEN THE LEVEL OF TRACE ELEMENTS AND GROWTH IN SCHOOL CHILDREN GROUP OF 6 TO 12 AGES WITH GOITRE

Ilknur Demir, MD; Zerrin Orbak, MD; Cahit Karakelleoglu, MD, Ataturk University, Erzurum, Turkey

**Objectives:** Iodine deficiency is considered one of the world's most important public health issues. Trace elements affect many biological functions such as physical growth, psychomotor development and immunity. The aim of the study was to determine level of trace elements and whether it is related to the growth in children with goitre.

**Methods:** The study was performed in children of ages 6 to 12 years. Goitre staging was performed according to the WHO criteria.

**Results:** A total of 86 cases, 55 with goitre and 31 as control group, were included in the study. When parameters were compared in cases with and without iodine deficiency, TSH and FT3 levels were determined significantly higher in cases with iodine deficiency. TT3, FT4 and TT4 values were in normal ranges and there were no significant differences between the two groups. In cases with iodine deficiency, selenium (Se) level was detected as low, zinc (Zn) level was high but there was no significant difference between manganese (Mn), iron (Fe) and copper (Cu) levels. When parameters were compared in cases with and without goitre, no difference was detected in TT3, TT4 and FT4 values while TSH and FT3 values were significantly higher in cases with goitre. Serum selenium level was detected lower in cases with goitre but no statistically significant differences were detected in the levels of other trace elements between the two groups.

It was also observed that height standard deviation score (height SDS) and body weight standard deviation score (weight SDS) of cases with goitre were negatively affected in cases with advanced stage of goitre. Statistically significant positive correlation was found between height SDS and serum Zn, Se, Cu, Fe and ferritin. Zn was found to be the most influential trace element for height SDS. A negative correlation was found between height SDS, weight SDS and

Mn. A positive statistically significant correlation was found between weight SDS and Se, Zn, Fe and Cu levels, Se was observed to be the most influential trace element for weight SDS.

**Conclusions:** Trace elements have an important role for height and weight gain. Importance of nutrition, trace element intake and iodized salt usage should be explained to families.

P2-856

#### **IGRO A NEW MEDICAL SOFTWARE TO IMPROVE GH TREATMENT IN CHILDREN WITH GH DEFICIENCY: A STUDY BASED ON ITS DAILY USE IN CLINICAL PRACTICE**

*Daniela Simoncini, MD; Letizia A Fumagalli, MD; Alex Moretti, MD, University of Insubria, Varese, Italy; Manuela Deiana, MD; Roberta Cardani, MD; Roberta Biasoli, MD, ASST Settelaghi, Varese, Italy; Alessandro Salvatoni, MD, University of Insubria, Varese, Italy*

**Objectives:** Aim of this study was to assess the reliability and the usefulness of a web-hosted software based on a growth prediction model (iGRO) as tool of treatment modulation and compliance evaluation in GH deficient children treated with human recombinant GH.

**Methods:** Target height, birth weight, height, weight, pubertal stage, maximum GH response, bone age and GH dose of 32 children (23 boys) aged 9.34(5.9) years with GH deficiency, were recorded on iGRO before and during GH treatment. We perform the statistical evaluation through single and multiple regression analysis. The data are reported as median (IQR).

**Results:** First year height velocity was positively correlated to body weight ( $p < 0.05$ ), GH dose ( $p < 0.02$ ) and growth response in the second ( $p < 0.01$ ) and in the third year ( $p$ -value  $< 0.01$ ) of therapy. Thanks to the software, height velocity prediction (HVP) during the years of therapy, and the index of responsiveness (IoR) were obtained only in 16 pre-pubertal patients. In the other 16 patients HVP and IoR was not available because they start puberty during the first year of treatment. Growth response matched the predicted in most of the patients ( $p < 0.002$ ). Only two children had a IoR outside the normal range ( $-1.28; +1.28$ ). In the first case a IoR of  $+1.88$  suggested a patient high responder to GH, in the second a IoR of  $-1.61$  was suspicious of non-compliance.

**Conclusions:** Since there is a high individual variability in the response to GH treatment, clinicians need to use prediction models in daily clinical practice. The experience conducted in our clinic shows that iGRO is a simple, useful, easy available device that allows to correctly start, monitor and improve GH treatment with a better outcome on final height.

P2-857

#### **THE ADHERENCE TO GROWTH HORMONE THERAPY IN CHILDREN WITH GROWTH HORMONE DEFICIENCY**

*Ayca Torel Ergur, MD; Sevinc Odabasi Gunes, MD; Onur Bahceci, MD, Kirikkale University Faculty of Medicine, Kirikkale, Turkey*

**Objectives:** Growth hormone therapy (GHT) has been used effectively in children diagnosed with growth hormone deficiency (GHD). Adherence to GHT may effect growth velocity and to reach the optimal adult height. Purpose of this study is to evaluate the adherence of patients to GHT in first, second and third year of the treatment.

**Methods:** Twenty-seven children who were diagnosed GHD in between January 2013 and January 2017 were involved in the study. Dosage of GHT was adjusted according to etiology of GHD and patients were called for follow-up visits for every 3 months in order to evaluate anthropometric measurements and laboratory test for fasting blood glucose, fasting insulin, thyroid functions, total blood count, IGF1, IGFBP3. Besides, in every visit dosage applied by the patient/parents and adherence to therapy was controlled via evaluating the data of the electronic GHT device. Children missing  $\leq 2$  injections per month (92% of injections given) were considered adherent to treatment. At the end of every year, GHT was discontinued for 6 weeks and insulin tolerance test was done in order to evaluate GHD.

**Results:** 17 girls and 10 boys, whose age was  $10.50 \pm 2.54$  years and bone age was  $8.02 \pm 2.4$  were involved in the study. Diagnoses of the patients were as follows: 9 total GHD, 15 partial GHD, 2 syndromic short stature (Turner syndrome, cleidocranial dysostosis), 1 neuro-secretory dysfunction. 11 patients were prepubertal and 16 were pubertal. **Adherence to therapy was as follows: in the first 6 months (27 patients)  $94.84 \pm 5.66\%$ , 1<sup>st</sup> year (14 patients)  $95.75 \pm 4.45\%$ , 2<sup>nd</sup> year (5 patient)  $96.09 \pm 4.72\%$ .** Height SDS of the patients were as follows:  $-2.94 \pm 0.63$  at the beginning,  $-2.6 \pm 0.59$  at the end of 6 months,  $-2.58 \pm 0.74$  at the end of 1<sup>st</sup> year,  $-2.73 \pm 0.71$  at the end of 2<sup>nd</sup> year. Growth velocity of the cases was  $4.23 \pm 1.81$  cm/6months,  $8.97 \pm 2.07$  cm/first year,  $7.3 \pm 1.54$  cm/second year.

**Conclusions:** Adherence to GHT in our cases was high compared to the adherence rates reported in the literature. Also, adherence rates were higher in long-term patients compared to first year patients. We think the high adherence rates in our cases were due to close follow-up and monitoring adherence to GHT through device.

## POSTER SESSION 2

Friday, September 15, 2017, 11:30am-12:30pm

### P2 - Neuroendocrinology including hypothalamic pituitary

P2-1000 – P2-1014

P2-1000

#### ENDOCRINE OUTCOMES AND FOLLOW-UP IN PEDIATRIC MEDULLOBLASTOMA

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**Objectives:** Endocrine dysfunction is the main sequela in the long-term care of patients with brain tumors. To assess endocrine sequelae in patients treated for medulloblastoma and the impact of craniospinal radiotherapy (CRT).

**Methods:** Patients (0-21 years) with confirmed medulloblastoma between 2004 and 2014 in a pediatric reference hospital were included. Received treatments, endocrine disorders and outcomes were retrospectively evaluated until February 2017.

**Results:** A total of 56 patients were included (39 males, 17 females). Median age at diagnosis: 5.2 years (range: 0.6-16.2). A total of 44 patients received CRT at a mean age 5.9 years (range: 2.2-15.4); mean delivered dose was  $31.3 \pm 9.5$  Gy. All patients were controlled by pediatric endocrinologists with a median follow-up of 2.5 y (range: 0.2-12). Thyroid hormone deficiency was the most frequent disorder (40%) after a mean of 3 y (range: 1.2-6.1) from CRT, followed by GH deficit (25%) after 3.2 y (range: 0.1-7), and hypocortisolism (20%) after a mean of 2.3 y (range: 0.05-6.7). Hypogonadism developed in 9% of patients. Obesity was present in 14%. Five years after CRT, the cumulative incidence of a hormone deficiency was 63% (CI95%:44-82). The correlation between total CRT dose and the number of hormone deficiencies was  $r=0.391$  ( $p=0.033$ ).

Regarding GH deficiency, 9 patients received rhGH treatment at a median age of 12.1 y (range: 7.9-13.7). The mean time to start treatment was 2.9 y (range: 1.6-5.4) after completing oncological treatment. Six patients have already finished treatment with a mean duration of 2.4 y (range: 0.8-6.8). The mean difference between target height and final height was  $-1.63 \pm 0.68$  SDS. None of the patients receiving rhGH developed complications or tumor relapse. Five-year overall survival was 58% (CI95%:43-73).

#### Conclusions:

1. Patients with medulloblastoma have a high risk of developing pituitary hormone deficiencies, mainly secondary to radiotherapy and increasing with time.

2. Endocrine surveillance and close follow-up are essential to reduce morbidities.

P2-1001

#### ROTH'S HYPOTHALAMIC LESION SCORE: A USEFUL TOOL TO PREDICT OBESITY IN CRANIOPHARYNGIOMA?

Marie Philippart, medical student; Geraldine Gilbert, MD; Francis Zech, MD; Renaud Menten, MD, Université Catholique de Louvain, Brussels, Belgium; Veronique Beauloye, PhD, Cliniques Universitaires Saint-Luc/University Catholique of Louvain, Brussels, Belgium, Brussels, Belgium

**Objectives:** Excessive weight gain frequently occurs in patients treated for a craniopharyngioma (CP). Surgical damage to the hypothalamus has been shown to be associated to a higher BMI increase after surgery. Recently, Roth et al. have developed a hypothalamic lesion score (HLS) to quantify hypothalamic damage following surgery and have correlated this with the development of obesity.

**Objective:** to determine the value of this novel scoring system in the prediction of obesity in our postsurgical CP patients.

**Methods:** Post-surgery digital brain magnetic resonance imaging (MRI) and clinical outcomes were studied retrospectively in 14 (7 females) patients who had surgery for CP. Subjects' BMI-z-score were assessed at the time of surgery (mean age  $\pm$  SEM:  $10.82 \pm 1.62$  years) and at last visit (mean age  $\pm$  SEM:  $28.45 \pm 3.85$  years). Obesity and overweight were defined according to the IOTF criteria. The HLS score was calculated according to Roth et al. For patients having a tumour recurrence (5/14), the HLS score was calculated on the MRI performed after the latest surgery. Additionally, 7 patients underwent transcranial irradiation (of which one received protontherapy) because of incomplete resection of the tumour or tumour recurrence.

**Results:** Mean BMI-z-score  $\pm$  SEM at the time of surgery was  $0.58 \pm 0.31$  and at last visit  $2.08 \pm 0.44$ . At last follow-up, 50% were obese and 29 % overweight. HLS score was positively correlated with last visit BMI-z-score ( $r=0.401 \pm 0.243$ ;  $p=0.099$ ) but this do not reach statistical significance. HLS score  $>5$  was associated with a greater risk of obesity.

**Conclusions:** HLS score could be a useful tool to assess the outcomes of CP patients and to improve their management but needs to be further studied in larger cohort.

P2-1002

#### MELATONIN: SECRETORY PATTERNS IN DIFFERENT NEUROMETABOLIC DISORDERS

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**Objectives:** In addition to its well-known action in the synchronization of biologic rhythms, melatonin acts as a neuroendocrine transducer of information collected from the environment and the metabolic status. Therefore, we

decided to evaluate melatonin secretion in different endocrine and metabolic disorders.

**Methods:** We studied 74 male children and adolescents: 8 with untreated GH deficiency (GHDnt): 12.0 yr (4.0-16.1); 16 with treated GH deficiency (GHDt): 11.3 yr (4.0-15.7); 6 with Prader-Willi syndrome (PWS): 13.1 yr (6.1-15.1), 24 obese (Ob): 9.9 yr (4.0-14.7) and 20 controls (C): 9.1 yr (6.0-15.6). Measurements of 6-sulfatoxymelatonin (6-SM) were performed in diurnal and nocturnal urine samples (radioimmunoassay, Stockgrand Ltd, Guildford, UK). The nighttime-daytime delta value ( $\Delta$  6-SM) was calculated.

**Results:** Table (Md and range)

\* $p < 0.01$  vs C; \*\* $p < 0.05$  vs C; \*\*\* $p < 0.001$  vs C

**Conclusions:** Patients with GHD showed lower excretion of 6-SM than controls, mainly during nighttime, flattening the circadian rhythm. 6-SM levels increased with GH treatment, not attaining statistical significance.

Patients with PWS showed high and significant 6-SM excretion, particularly during daytime and a tendency towards higher levels during nighttime ( $p = 0.09$  vs C). Obese patients showed melatonin hypersecretion, maintaining the circadian rhythm.

The dissimilarity in melatonin secretion in the various conditions evaluated might reflect changes in the cross-talk between the central nervous system, the endogenous metabolic status and the environment.

Group	GHDnt	GHDt	PWS	Ob	C
Diurnal 6-SM ( $\mu$ g)	0.19 (0.04 - 0.35)	0.28 (0.04 - 3.50)	3.30 *** (0.98 - 6.93)	0.32 (0.01 - 6.31)	0.25 (0.01 - 3.57)
Nocturnal 6-SM ( $\mu$ g)	0.41 * (0.12 - 0.92)	0.62 * (0.09 - 4.40)	6.77 (1.27 - 28.56)	6.87 * (0.75 - 31.46)	2.54 (0.23 - 13.67)
Total 6-SM ( $\mu$ g)	0.71 * (0.23 - 1.27)	0.85 * (0.30 - 5.90)	10.73 ** (2.25 - 33.04)	7.51 * (0.77 - 31.57)	3.37 (0.32 - 17.24)
$\Delta$ 6-SM ( $\mu$ g)	0.25 ** (-0.10 - 4.20)	0.07 *** (-1.10 - 4.20)	3.99 (-0.61 - 24.08)	5.72 * (0.74 - 31.35)	1.85 (0.00 - 10.10)

P2-1003

#### CLINICAL AND LABORATORY CHARACTERISTICS OF HYPERPROLACTINEMIC CHILDREN AND ADOLESCENTS: NATIONAL SURVEY

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**Objectives:** Various causes may lead to hyperprolactinemia in adolescence and the most common is pituitary adenoma. An increase in prolactin (Prl) level due to drugs can be seen. The etiology cannot be elucidated in some patients. We aimed to study the characteristics on admission, diagnosis, treatment, and follow-up of hyperprolactinemic cases in a large multicenter study.

**Methods:** We reviewed 233 hyperprolactinemic patients below 18 years of age who were followed at 31 centers. Microadenoma was defined as a pituitary tumor of less than 1 cm diameter whereas macroadenoma was defined as a tumor above 1 cm diameter. Drug-induced hyperprolactinemia was diagnosed if the patient had a history of using drugs. If there were no mass in pituitary MRI or no drug exposure, it was called idiopathic hyperprolactinemia. Complaints of the patients and their treatment (medication and/or surgery) responses were evaluated in detail.

**Results:** The mean age of the patients with hyperprolactinemia was 14.4 years and 86.9% of them were female. In terms of etiology; pituitary microadenoma was observed in 32.6%, macroadenoma in 27%, idiopathic hyperprolactinemia in 22.7%, drug-induced hyperprolactinemia in 6.4%, and other causes of hyperprolactinemia in 11.3% were defined. Common complaints in females ( $n = 206$ ) were sorted as menstrual irregularities, headache, galactorrhea, primary or secondary amenorrhea, and weight gain; whereas headache, gynecomastia, short stature, and blurred vision were common in males ( $n = 27$ ). Mean prolactin levels were  $138.2 \pm 127.8$  ng/ml,  $675.2 \pm 956.5$  ng/ml,  $83.4 \pm 51.2$  ng/ml,  $101.6 \pm 41.7$  ng/ml, and  $84.2 \pm 40$  ng/ml for microadenoma, macroadenoma, idiopathic hyperprolactinemia, drug-induced, and other causes of hyperprolactinemia, respectively. Of 172 patients with hyperprolactinemia, 77.3

was treated with cabergoline and 13.4% with bromocryptine. The remaining 9.3% was switched from bromocryptine to cabergoline because of treatment failure.

**Conclusions:** We present the largest cohort of children and adolescents with hyperprolactinemia in the literature so far. Hyperprolactinemia is more common in females. Macroprolactinemia must be ruled out especially in patients with idiopathic hyperprolactinemia. Cabergoline is very effective and practical to use in the adolescents due to its biweekly dosing.

P2-1004

#### **ENDOCRINE DYSFUNCTION IN PEDIATRIC PATIENTS WITH RATHKE'S CLEFT CYSTS: AN IMPACT ON GROWTH AND PUBERTAL DEVELOPMENT.**

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**Objectives:** Rathke's cleft cysts (RCCs) are nonneoplastic epithelial lesions of sellar or suprasellar regions. RCCs are usually asymptomatic; however, patients with RCCs seldom present with headaches, visual disturbances and endocrine dysfunctions. Surgical management is recommended in patients for with headaches or visual disturbances, whereas endocrine dysfunctions were usually treated conservatively. In pediatric population, RCCs are less often than adults. Symptomatic RCCs are rare and endocrine dysfunctions, especially an impact of growth and pubertal development, remain unclear. We aimed to investigate endocrine dysfunctions, radiographic findings, clinical course and efficacy of treatment in pediatric patients with RCCs.

**Methods:** We included 10 pediatric patients with RCCs associated with endocrine dysfunctions. Clinical information abstracted from the medical record including sex, age, height and weight, sexual maturity rating, signs and symptoms, endocrine dysfunctions, bone ages, radiographic findings of the cyst, treatment modalities, recurrence, and follow-up and treatment period.

**Results:** Of these 10 patients, four were male and six were female, the mean age at diagnosis was 7.6 years, and mean follow-up period was 44 months. Growth disturbances (short stature or growth retardation) were the most common sign, followed by precocious puberty, and headache. Six of 10 patients showed higher signal intensity on T1-weighted images than cerebrospinal fluid. Most of cysts were located between anterior and posterior lobes, one had suprasellar extension. One patient underwent surgery, and had relief of headache and visual disturbance, but endocrine dysfunctions were not improved. Four patients with growth hormone deficiency were treated with recombinant growth hormone

and showed an improvement in height. Four patients with central precocious puberty, two of them were treated with GnRH analog and showed suppressed pubertal development.

**Conclusions:** We observed that growth disturbances and precocious puberty are common signs and symptoms in pediatric patients with symptomatic RCCs and these diseases are treatable conservatively.

P2-1005

#### **MRI IN CHILDREN WITH ISOLATED GROWTH HORMONE DEFICIENCY: DO WE NEED CONTRAST?**

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**Objectives:** Children with growth hormone deficiency (GHD) often have a MRI of the brain as part of the diagnostic evaluation. Emerging evidence shows that repeated administration of Gadolinium-based contrast agents may lead to signal changes within the brain due to gadolinium deposition. The purpose of this study is to evaluate the yield of contrast versus non-contrast MRI in newly diagnosed isolated GHD patients.

**Methods:** An IRB approved, retrospective chart review of subjects aged 0-21 years who received MRI between 1/2005 and 12/2015 as part of the diagnostic evaluation of isolated GHD was conducted. Included subjects were all diagnosed with GHD prior to neuro-imaging. Subjects were excluded if they had biochemical diagnosis of multiple pituitary hormone deficiencies or known brain tumor prior to the MRI. MRIs with and without contrast were compared for the detection of structural pituitary malformations, other structural brain malformations, or neoplasm.

**Results:** Among 804 GH deficient subjects (74.1% male; mean age 10.2 years, SD 3.3 years) with brain MRIs, 196 subjects (24.4%) had baseline imaging with gadolinium, and 608 subjects (75.6%) had non-contrast MRI. Overall, 119 (14.8%) were found to have a clinically significant anatomic abnormality on imaging. Detection of any relevant anatomic abnormalities was more frequent with contrast MRI (31.1%) than non-contrast MRI (9.5%) ( $p < 0.001$ ). With respect to specific abnormalities, pituitary stalk abnormalities and pituitary hypoplasia were detected more commonly in subjects who had contrast studies than non-contrast (stalk abnormalities: 8.2% vs 1.3%,  $p < 0.001$ ; hypoplasia: 15% vs 2.9%,  $p < 0.001$ ). Pituitary adenomas were detected on 3 contrast studies (1.5%) and no non-contrast studies.

**Conclusions:** In the low risk setting of recently diagnosed isolated GHD, use of gadolinium adds to the diagnostic yield of brain MRI prior to initiation of GH treatment. Although we picked up stalk abnormalities and pituitary hypoplasia, these often do not alter management decisions. Since the clinical significance of central nervous system gadolinium deposition is not currently known, these findings suggest that utilization of gadolinium in this population can occasionally alter management.

# **QUALITY OF LIFE, GROWTH, AND HYPOTHALAMIC LESIONS IN CHILDHOOD-ONSET CRANIOPHARYNGIOMA – RESULTS OF THE MULTINATIONAL PROSPECTIVE TRIAL KRANIOPHARYNGEOM 2007**

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**Objectives:** Quality of life (QoL) after childhood-onset craniopharyngioma (CP) is frequently impaired by tumour and/or treatment-related factors such as endocrine deficits and hypothalamic involvement (HI).

**Methods:** In the context of KRANIOPHARYNGEOM 2007, we prospectively analyzed parental and self-assessment of CP patient QoL at 3 mo, 1 and 3 yrs after CP diagnosis related to growth hormone (GH) substitution and HI. Forty-seven of 194 CP patients recruited 2007 - 2015 fulfilled the inclusion criteria: 1.) histological CP diagnosis, 2.) age at diagnosis 6-18 yrs; 3.) availability of QoL data one and three yrs after diagnosis. QoL was assessed using the Pediatric Quality of Life (PEDQOL) questionnaire.

**Results:** Parents estimated QoL of their children worse than patients did themselves for the PEDQOL domains emotional stability (3 mo,  $p<0.05$ ; one yr,  $p<0.001$ ) and social function / friends (one yr,  $p<0.01$ ; 3 yrs,  $p<0.05$ ). HI was associated with lower self-assessed QoL 3 mo after diagnosis (body image,  $p<0.01$ ; social function/friends,  $p<0.01$ ). The negative impact of HI on QoL was greater for parental assessed QoL at all time points. GH substitution had no relevant effect on short-term weight and height development. CP patients, GH-treated at 3 yrs follow-up, presented at baseline (1 yr after diagnosis, before GH substitution) with reduced self-assessed QoL for the PEDQOL domains autonomy ( $p<0.05$ ), cognition ( $p<0.01$ ), physical function ( $p<0.05$ ), and social function/friends ( $p<0.01$ ), when compared with GH non-treated CP patients. QoL stabilized during 1-3 yrs of follow-up in GH treated patients, whereas non GH-treated patients experienced decreases in QoL for the PEDQOL domains physical function and social function/frinds.

**Conclusions:** Parents assess QoL in CP survivors worse than their children. As HI is a major risk factor for reduced QoL, treatment strategies in CP should aim at prevention of (further) hypothalamic damage. GH substitution should be considered as an effective option to ameliorate imminent impairments of QoL after CP.

# **A RARE CASE OF INSULINOMA IN AN ADOLESCENT WITH RECURRENT EPISODES OF ALTERED MENTAL STATUS**

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**Objectives:** To review the presentation of an adolescent diagnosed with an insulinoma and discuss its management.

**Background:** Insulinoma is a rare pancreatic neuroendocrine tumor with an estimated incidence of less than 1 per 250,000 person-years in the general population. The majority of patients are diagnosed in the fifth decade of life. Because these tumors are extremely rare in children and adolescents, diagnosing an insulinoma can be challenging in the pediatric age group.

**Methods:** A case report.

## **Results: Case Presentation:**

A 15-year-old adolescent boy presented with intermittent episodes of headaches, dizziness and confusion. His outpatient evaluation included CT brain, which was normal, multiple drug screens, which were negative, and documentation of hypoglycemia on a chemistry panel, but otherwise inconclusive results. Initially, he was diagnosed as having complex migraines. Interestingly, he did experience symptomatic relief with NSAIDs, but in retrospect, he recognized that these were taken with orange juice or soda. Due to recurrent episodes, he was admitted to a tertiary children's hospital four months after the initial evaluation. A critical sample was obtained that showed a blood glucose of 42 mg/dl, an elevated insulin level (14.1 mIU/L), and proinsulin level (108.9 pmol/L). A glucagon challenge confirmed hyperinsulinism. Serum ketones and free fatty acids were low at the time of hypoglycemia. A magnetic resonance imaging (MRI) of the abdomen confirmed the presence of a mass in the neck of the pancreas. He underwent surgical resection via enucleation of the tumor, resulting in complete resolution of his symptoms. Pathology confirmed the diagnosis of insulinoma. Genetic testing for MEN-1 syndrome was negative.

**Conclusions:** In adolescents presenting with altered mental status, clinicians should be vigilant in their evaluation for organic disease such as insulinomas. Rapid diagnosis and prompt management of hyperinsulinemic hypoglycemia is essential to avoid hypoglycemic brain injury, especially in the pediatric population.

# **UNUSUAL GROWTH HORMONE EXCESS IN A BOY WITH NEUROFIBROMATOSIS TYPE 1 AND PRECOCIOUS PUBERTY**

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**Objectives:** Neurofibromatosis type 1 (NF1) is a rare disorder characterized by the growth of tumors affecting predominantly skin, bone and central nervous system, which can cause endocrine disorders. Short stature, macrocephaly and central precocious puberty (CPP) have been specifically described in this condition. GH excess with NF1 is extremely rare with unknown mechanism. Only few cases have been reported with the presence of optic pathway gliomas (OPG). We report a case of NF1 with CPP and GH excess.

**Methods:** Case Report

**Results:** 4-year-old boy with known history of NF1 was referred to Endocrine clinic for evaluation of enlarged testes. Parents denied any pubic hair or axillary hair development. He was not on any medications. He had normal birth history with normal developmental milestones. His exam was pertinent for normal BP and head circumference, ht>99% and wt>99%. His growth velocity (GV) was 14cm/yr. His skin exam showed >20 café-au-lait spots (>5mm) over his trunk and extremities and axillary freckling. There was no gynecomastia. His testicular volume was 8-10ml bilaterally with no pubic hair. Endocrine workup revealed high LH (1.79mIU/ml), testosterone (49.1ng/dl), prolactin (42.5ng/ml) and IGF-1 (437ng/ml). FSH, DHEAS, ACTH, cortisol, TFTs, CMP and urine specific gravity were normal. MRI brain was consistent with NF1 and OPG with normal pituitary gland. Bone age was normal. OGTT revealed unsuppressed GH levels (0, 30, 60, 90, 120 min, GH 9.9, 1.8, 3.7, 5.3, and 3.1ng/ml, respectively). He was diagnosed with CPP and GH excess. He was started on leuprolide acetate 7.5 mg IM monthly and bromocriptine 1.25mg PO daily. At follow up visits, GV decreased to 12 cm/year and testosterone decreased to <2.5ng/dl. However, LH (2.76mIU/ml) and IGF-1 (418ng/ml) remained elevated. We, therefore, increased bromocriptine to 2.5mg with a plan to gradually increase to achieve normal IGF-1. Due to normal vision, radiotherapy and chemotherapy were not recommended for OPG.

**Conclusions:** NF1 patients who have CPP causing tall stature should have IGF-1 measured due to the possibility of the coexistence of CPP and GH excess as seen in this patient. GH excess in NF1 is rare and the mechanism is unclear. Therefore, the treatment is challenging.

P2-1009

#### **FRACTIONATED URIC ACID EXCRETION IN THE DIFFERENTIATION OF CEREBRAL SALT WASTING SYNDROME AND INAPPROPRIATE ANTIDIURETIC HORMONE SYNDROME**

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**Objectives:** Cerebral salt wasting syndrome and inappropriate antidiuretic hormone syndrome are two common endocrinological reason of hyponatremia. The differential diagnosis of this two syndrome can be challenging. Additionally they can be presented in the same patient concomitantly. Clinical features, urine volume

measurement, plasma and urine sodium and uric acid levels can be helpful in the differential diagnosis but not always. Fractional excretion of uric acid (FEUrate) can be an additional parameter in order to differentiate these two similar conditions as in the presented cases.

**Methods:**

**Results:** Case1:

Hyponatremia (Na:127 mmol/L) in a 13 years old child hospitalized due to diffuse axonal damage occurred after a traffic accident. The laboratory evaluation of the patient revealed a high sodium excretion (132mmol/L). Urine output was 1008 and the urine output was 3.1cc/kg/hour. FEUrate was %14.9 at the time of hyponatremia and was %11.2 at the time of normal serum sodium levels. The serum sodium levels reached normal values with oral and parenteral sodium and mineralocorticoid replacement. The diagnosis was cerebral salt wasting syndrome

Case 2:

Hyponatremia (Na:129mmol/L) was observed in a four year old boy, 4 days after the operation of arachnoid cyst. Urine Na levels were high as 90mmol/L. ProBNP levels were 230pg/ml and urine output was normal. Because of the high levels of BNP CSW was considered in the diagnosis and oral sodium replacement therapy was given. Sodium requirement of the patient decreased by the time and the therapy was stopped. After a period hyponatremia reoccurred and urine sodium levels were 59 and the proBNP levels were in normal range.

The diagnosis was checked and uric acid level was 3.7mg/dl; FEU rate was 13% when Na 127mmol/L, and 7.9% when Na was 132mmol/L. The patient is diagnosed with SIADH after FEU rate improvement.

**Conclusions:** Cerebral salt wasting and SIADH are two endocrinologic conditions that are clinically similar and can be confused on basis of laboratory analysis. It is claimed that uric acid levels could be of help to differentiate these two conditions but the fact is that uric acid levels could be low in both. Use of FEU rate could be helpful in these cases.

P2-1010

#### **BILATERAL INFERIOR PETROSAL SINUS SAMPLING: DIAGNOSTIC DIFFICULTIES IN PEDIATRIC CUSHING PATIENTS**

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**Objectives:** Bilateral Inferior Petrosal Sinus Sampling (BIPSS) is the gold standard procedure to differentiate between Cushing Disease (CD) and Ectopic ACTH Syndrome (EAS), with a false negative rate of 1-10%, mainly because of technical difficulties. To reduce false negatives, previous investigators used prolactin as a marker of successful catheterization, and



they "normalized" peak ACTH IPS/P ratio (Central/Peripheral) in case of unsuccessful catheterization. The aim is to describe the use of prolactin during BIPSS in 2 pediatric patients with Cushing Syndrome (CS)

**Methods:** ACTH and prolactin were determined at Right IPS (RIPS), left IPS (LIPS) and femoral vein (P) at time 0 and 3, 5 and 10 minutes after 10 mcg of desmopressin. The following indexes were calculated: ACTH RIPS/P; LIPS/P at each time PRL IPS/P at time 0. Basal ACTH IPS/P > 2 or peak ACTH IPS/P > 3 was indicative of CD (positive test), while values below were indicative of EAS (negative test). A ratio PRL IPS/P above 1,8 (ipsilateral to the peak ACTH IPS/P ratio) was indicative of successful catheterization. If PRL IPS/P ratio < 1,8 (suggesting unsuccessful catheterization) we "normalized" peak ACTH IPS/P by dividing it by the basal ipsilateral PRL IPS/P ratio; values > 0,8 suggested CD, whereas those < 0,6 implied EAS.

**Results:** Both patients are boys (10-13 years old), with CS (UFC p1: 295 mcg/24hs, p2: 3500 mcg/24hs, ACTH p1 65; p2 150 pg/ml, negative dexamethasone test and indeterminate MRI). They underwent BIPSS: Patient 1: basal ACTH IPS/P ratio 1,08 and peak ACTH 1 (negative); basal PRL IPS/P ratio 1 (unsuccessful catheterization) and normalized peak ACTH 1 (> 0,8 consistent with CD). Patient 2: basal ACTH ratio 1,33 and peak 2,13 (negative); basal PRL IPS/P ratio 1,53 (unsuccessful catheterization) and normalized peak ACTH 1,39 (> 0,8 consistent with CD). Both patients were surgically treated and CD was confirmed by biopsy. They remained asymptomatic.

**Conclusions:** In our patients PRL determination and normalization of ACTH improved diagnostic accuracy. Patients had negative BIPSS but positive after correction. We suggest using PRL during BIPSS as catheterization of IPSS is troublesome in pediatric patients and a lower catheter positioning (as jugular bulb) may be sufficient

P2-1011

#### UNIQUE HOMOZYGOUS SNRPN POINT MUTATION AS POTENTIAL A NEW CAUSE OF PRADER-WILLI (LIKE) SYNDROME

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**Objectives:** **Introduction** Prader-Willi syndrome (PWS) is a rare condition characterized by hypothalamic dysfunction (leading to hyperphagia, abnormal temperature regulation, abnormal pain registration and pituitary hormone deficiencies) and cognitive impairment. PWS is generally believed to be caused by loss of expression of an entire cluster of paternally expressed genes within the PWS region on chromosome 15, due to deletion, uniparental disomy or imprinting center defects. We describe a unique patient with the complete spectrum of PWS features, in whom these regular genetic causes were ruled out. Additional genetic testing revealed a homozygous point mutation

in *SNRPN* (one of the genes located in the PWS region) which was located in a large homozygous region. This patient is unique, because point mutations in a single gene have never been described before in a patient with PWS.

**Methods:** We performed additional genetic tests: automated sequencing (as part of obesity diagnostics), a methylation test (to exclude regular causes of PWS), Multiplex Ligation-dependent Probe Amplification (MLPA) analysis (MLPA kit: ME028-B2, to exclude copy number variations) and a SNP array (to exclude homozygosity).

**Results:** In the 46-year-old index patient, genetic diagnosis of PWS was initially rejected after regular genetic tests for PWS showed normal results. Since the patient had nearly all phenotypic features corresponding to PWS, we performed additional genetic testing which revealed a homozygous mutation in *SNRPN*, located in a large homozygous region on chromosome 15. The parents of the patient turned out to be first-degree relatives.

**Conclusions:** Until now, it was generally accepted that Prader-Willi syndrome could only be caused by functional loss of an entire cluster of genes within the PWS region on chromosome 15q11.2-q13. The unique finding of a homozygous point mutation in a single gene of this region (*SNRPN*) in a patient with virtually all features of PWS, means a revolutionary change in our knowledge of the pathophysiology of the syndrome.

P2-1012

#### NEUROFIBROMATOSIS-1 PRESENTING WITH GIGANTISM AND PRECOCIOUS PUBERTY

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**Objectives:** GH excess in children is rare and most commonly associated with a pituitary adenoma. There is only limited data in the pediatric literature of gigantism associated with neurofibromatosis.

**Methods:** **Clinical case:** A 3-year old boy presented with hyperphagia and excessive growth for 1 year prior to evaluation. Birth history was unremarkable; developmental history was significant for delayed expressive language and gross motor milestones; the patient walked at the age of 18 months, and has continued coordination difficulties with jumping and climbing. Review of systems revealed frequent night sweats, dry skin with almost constantly sweaty hands, and significantly increased appetite. Physical exam showed head circumference, height and weight all above the 99<sup>th</sup> percentile for his age, L congenital ptosis, large ears, broad and doughy hands, L 4<sup>th</sup> toe and R 2<sup>nd</sup> toe clinodactyly, 7 café-au-lait spots at R chest area with most of them measuring < 0.5 cm in diameter, enlarged scrotum bilaterally with testicular volume 5 cc bilaterally and Tanner stage 1 pubic hair.

**Results:** Initial laboratory testing showed markedly elevated IGF1 683 ng/ml (reference range 49-289ng/ml), random GH of 9.9 ng/mL (normal <3) and elevated high sensitivity LH by ICMA at 1.4 mIU/mL (pubertal range defined as  $\geq 0.3$ ) and FSH 1.5U/L and 2.0U/L respectively. Oral glucose tolerance test was performed revealing a baseline GH at 4.99ng/ml (reference range 0-3.0ng/ml) rising to 8.81ng/ml 120minutes after 40g of oral glucose. Sedated brain MRI showed a R optic glioma with a hypothalamic tumor and diffuse gliomatosis. The patient was started on a combined chemotherapy regimen of carboplatin and vincristine. Furthermore, the patient was started on octreotide and leuprolide analogue to suppress the GH excess and early puberty.

**Conclusions:** Conclusion: We describe a case of a pediatric patient presenting with excessive growth and precocious puberty found to have an optic glioma and hypothalamic tumor in the setting of neurofibromatosis type 1. The mechanism by which the optic glioma causes GH excess is thought to be due to loss of the inhibitory effect of somatostatin on GH secretion.

P2-1013

#### **RAPID DIFFERENTIAL DIAGNOSIS OF POLYURIA-POLYDIPSIA SYNDROME IN CHILDREN: THE COPEPTIN APPROACH. A CASE REPORT.**

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**Objectives:** Diabetes insipidus is characterized by hypoosmotic polyuria related to deficiency of Arginin Vasopressin (AVP) secretion (Central Diabetes Insipidus, CDI) or renal insensitivity to AVP (Nephrogenic Diabetes Insipidus, NDI).

The water deprivation test with assessment of AVP activity is currently the gold standard for differential diagnosis in patients presenting primary polydipsia, CDI and NDI. Nevertheless, it can be dangerous without proper surveillance and its interpretation may be challenging, especially for partial diabetes insipidus.

Other markers have been suggested. Direct quantification of circulating AVP is not sufficient for precise diagnosis: it is an unstable hormone, large volume of plasma is needed, radioimmunoassay analysis is complex and long.

AVP comes from the prohormone preprovasopressin with concomitant release of copeptin (C-terminal moiety) in an equimolar ratio. Plasmatic copeptin is much more stable in vitro and its measurement is easy and rapid (< 4h). Past studies have shown greater sensitivity and specificity of copeptin versus AVP to discriminate etiologies of polyuria-polydipsia syndrome in adults, but its value has not been demonstrated in infants yet.

**Methods:** Observation

We report the case of a 7 month-old infant who presented poor weight gain and polyuria-polydipsia syndrome. The

laboratory tests pointed out severe hypernatremia (170 mmol/L), blood hyperosmolarity (330 mOsm/L) with inappropriate urinary hypoosmolarity (168 mOsm/L).

**Results:** Plasmatic copeptin measurement was found in a very high level, 303 pmol/L (1-14 pmol/L). DdAVP administration did not improve the polyuria, confirming the final diagnosis of NDI. Hyperhydration with hypoosmolar diet normalized within a week hydration status and circulating levels of copeptin.

**Conclusions:** Copeptin, a stable peptide reflecting AVP secretion, could be a safer and faster biomarker for etiological diagnosis of polyuria-polydipsia syndrome in children. A single baseline copeptin measurement may be enough to discriminate nephrogenic diabetes insipidus from other etiologies, central diabetes insipidus and primary polydipsia, without water deprivation test. Further investigation is needed in order to establish pediatric normal range.

P2-1014

#### **A PATIENT WITH APLASTIC ANEMIA WITH ISOLATED HYPOGONADOTROPIC HYPOGONADISM CAUSED BY TRANSFUSION-ASSOCIATED IRON OVERLOAD**

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**Objectives:** Background: Patients with aplastic anemia depends on frequent regular blood transfusions because of chronic anemia. It is known that transfusion-associated iron overload causes hypopituitarism, but there have been no reported the childhood onset hypogonadotropic hypogonadism in Japan.

**Methods:** Case: A 15-year-old girl has been diagnosed aplastic anemia at 5-year-old. She was performed bone marrow transplantation when 6-year-old. Then she was transplanted peripheral blood stem cell at 8, 11, and 13-year-old. One hundred and eighty four units of red blood cell transfusions had been performed by last transplantation of peripheral blood stem cell. At 13-year-old age, she developed diabetes due to iron deposition to pancreas and she was treated insulin therapy. She had not menstruated ever since. Finally, she was diagnosed with hypogonadotropic hypogonadism based on the results of LHRH stimulating test and pituitary MRI, which showed decreased signal intensity on T2-weighted images.

**Results:** Discussion: The prevalence of iron overload in patients with childhood onset aplastic anemia reported about 5%. And it is known that a half of the adulthood onset aplastic anemia patients with iron overload have been diagnosed hypogonadotropic hypogonadism. The patients with childhood onset aplastic anemia having a long period of the blood transfusion can cause hypogonadotropic hypogonadism with the iron overload.

**Conclusions:** Conclusion: We should be careful for hypogonadotropic hypogonadism with transfusion-associated iron overload in patients with childhood onset aplastic anemia.

## POSTER SESSION 2

Friday, September 15, 2017, 11:30am-12:30pm

### P2 - Obesity, lipids, and co-morbidities

P2-1100 – P2-1146

P2-1100

#### THE RELATION OF SERUM GALECTIN-1 LEVEL WITH CLINICAL AND METABOLIC PARAMETERS IN OBESE CHILDREN

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**Objectives:** Galectin-1, a recently discovered peptide, is released from many tissues, especially adipose tissue. The function of this peptide is poorly understood. Experimental obese animal studies have shown that galectin-1 levels increase with obesity. Moreover, an anti-inflammatory effect was observed after administration of galectin-1. To evaluate the relation of serum galectin-1 level with clinical and laboratory parameters in childhood obesity.

**Methods:** The study included obese children with a body mass index  $>95^{\text{th}}$  percentile and healthy children who were similar regarding age and gender. Clinical (body mass index, waist circumferences, percentage of body fat, systolic blood pressure, diastolic blood pressure) and biochemical (glucose, insulin, lipids, galectin-1, hsCRP and leptin levels) parameters were measured.

**Results:** Forty-three obese (mean age:  $12.1 \pm 3.1$  years) and 30 healthy children (mean age:  $11.8 \pm 2.2$  years) were enrolled. Significant differences were found between obese and healthy children in terms of BMI, BMI-SDS, WC, fat mass, PBF, HOMA-IR, serum insulin, TG, TC, LDL-C, HDL-C, galectin-1, hsCRP, and leptin levels ( $p < 0.05$ ), whereas no significant difference was observed in serum glucose levels between both the groups ( $p < 0.05$ ). With regard to the existence of insulin resistance in obese children, no significant differences were observed for TC, HDL-C, LDL-C, galectin-1, hsCRP, and leptin levels ( $p > 0.05$ ). In the obese group, galectin-1 was negatively correlated with fasting glucose ( $r = -0.346$ ,  $p = 0.020$ ), and positively correlated with fat mass ( $r = 0.326$ ,  $p = 0.026$ ).

**Conclusions:** In conclusion, this study demonstrated that obese children had significantly higher galectin-1 levels in proportion with fat mass in obese cases. Finally, this study provides evidence regarding the role of galectin-1 in glucose metabolism.

P2-1101

#### CHARACTERIZATION OF POLARIZED MONOCYTE PHENOTYPES IN CIRCULATION OF OBESE AND DRUG NAÏVE TYPE II DIABETES: MODULATION BY METFORMIN

Mohammed Al Dubayee, MD, King Abdullah Specialist Children's Hospital, Riyadh, Saudi Arabia; Awad Alshahrani, MD; Hind Alayed, MBBS; Rana Almansour, MBBS; Nora Alqaoud, BS/BA, King Saud bin Abdulaziz University for Health Sciences (KSAU-HS, Riyadh, Saudi Arabia; Rahaf Alnamlah, MBBS, King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), Riyadh, Saudi Arabia; Dana Obeid, MBBS; Ahmad Aljada, PhD, King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), Riyadh, Saudi Arabia

**Background:** Macrophages are differentiated cells of the mononuclear phagocytic system. Multiple studies have demonstrated the ability of macrophages to polarize into different phenotypes in response to different micro-environmental stimuli. Macrophages can exhibit distinct phenotypes and functions in response to stimuli and can polarize into one of three distinct phenotypes, a pro-inflammatory (M1), an anti-inflammatory pro-tissue (M2) and metabolically-activated (MMe) macrophage phenotypes. Since obesity and type II diabetes have been associated with low chronic inflammatory states, we examined macrophage phenotypes in lean, obese, drug naïve type II diabetics and diabetic patients on Metformin.

**Methods:** Thirty normal healthy adult volunteers of normal weight, 30 obese subjects, 20 obese newly diagnosed diabetics and 30 obese diabetics on Metformin were recruited for the study. Fasting blood samples were collected and mononuclear cells (MNCs) were isolated from whole blood. Macrophage polarization markers (M1: CD86, IL-6, TNF $\alpha$ , iNOS, CD36, CD11c, and CD169, and M2: CD206, and CD163) were measured by RT-qPCR. Gene expression fold change was calculated using the  $2^{-\Delta\Delta Ct}$  method for RT-qPCR. **CD11b**, **CD14** and CD68 were used as a marker for pan macrophages.

**Results:** Obesity and diabetes are associated with macrophage differentiation as indicated by an increased CD68 marker. mRNA expression of CD11b, CD11c, CD169 and CD163 were significantly reduced in obesity and diabetes and Metformin reversed this inhibition. CD206 was not significantly inhibited except in obese diabetics on Metformin. There were no significant changes in CD14 and CD86 in obese and obese diabetics on Metformin. On the other hand, M1-like phenotype was observed in obesity and diabetes as demonstrated by increased mRNA expression of IL-6, iNOS, TNF $\alpha$ , and CD36.

**Conclusions:** These data support the notion that metabolically activated MMe phenotype in obesity and type II diabetes are associated with increased levels of CD68, IL-6, iNOS, TNF $\alpha$ , and CD36 and decreased levels of CD11b, CD11c, CD169, CD206 and CD163. Metformin treatment inhibited MMe phenotype.

### PHYSICAL LITERACY IN A MULTIDISCIPLINARY CLINIC

Adrian Araya, MD; Kristin Dayton, MD; Angelina Bernier, MD; Rebecca Mercado, MS/MA; Lindsay Thompson, MD, University of Florida, Gainesville, FL, United States

**Objectives:** Physical literacy equips children with knowledge, skills and values to participate with confidence and competence in physical activity. Without physical literacy, children withdraw from physical activity and sports, and physical inactivity is a major cause of childhood obesity. The Physical Literacy Assessment for Youth (PLAY) is a survey used in Canada, shown to correlate with physical activity. This tool evaluates both child and parental perceptions of a child's physical literacy with domains specific to motivation, confidence, physical competence, knowledge and understanding.

We aimed to assess baseline physical literacy in an outpatient multidisciplinary clinic and to evaluate children's and parents' perceptions of the child's physical literacy with attention to deficient domains and discrepancies between parent and child perceptions.

**Methods:** Participants at a multidisciplinary pediatric clinic completed the PLAY survey at the "Fun & Fit Center" which provides onsite information about physical activity, nutrition and sleep for families. Patients are referred if overweight, obese, or have low rates of physical activity. Patients may also self-select to participate in the activities or information. The PLAY survey was adapted to reflect Florida geography and climate and was offered by iPad. Child and parent surveys were linked via a confidential code created by the parent.

**Results:** The survey was trialed successfully (8/29/16-3/9/17), with 43 parents and 48 children completing the evaluation. Only 30% were consistently active all year long, with 60% citing sufficient activity only in the summer. 64% of children worry about trying a new activity, and 43% describe their bodies as preventing their participation. 27% of parents described their children's overall fitness as low, yet 51% rated their child's physical literacy as low (less than 50%).

**Conclusions:** Implementation of a physical literacy assessment is feasible in the clinical setting and can help identify deficient skills and activity levels in children. Parents are aware of these deficiencies. This easily implemented survey can help design interventions to increase physical literacy, and in turn increase physical activity

### DEPRESSIVE SYMPTOMS ARE RELATED TO MENSTRUAL STATUS IN ADOLESCENT GIRLS ACROSS THE WEIGHT SPECTRUM

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Boston, MA, United States; Meghan Slattery, DNP; Franziska Plessow, PhD, Massachusetts General Hospital, Boston, MA, United States; Kendra R Becker, PhD, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States; Miriam A Bredella, MD, Massachusetts General Hospital, Boston, MA, United States; Kamryn T Eddy, PhD, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States; Elizabeth A Lawson, MD, Massachusetts General Hospital, Boston, MA, United States; Madhusmita Misra, MD, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

**Objectives:** Extremes of weight are associated with mood alterations. However, data relating mood to menstrual status in adolescence, a period characterized by a spike in mood disorders, are limited. We compared self-reported depressive symptoms in girls aged 10-21 years across the weight spectrum in relation to their menstrual status.

**Methods:** We included 42 girls with anorexia nervosa (AN), 26 healthy normal-weight controls (C) and 25 girls with severe obesity (OB) and between the ages of 10-21 years. Beck Depression Inventory II (BDI-II) or the Child Depression Inventory (CDI) was administered based on age. All raw scores were converted to T-scores. Menstrual cycles were defined as regular if subjects reported more than 9 cycles in the past year.

**Results:** The groups did not differ for age (mean age 17.8±0.3 years); average BMI was 17.1±0.2, 21.4±0.5 and 44.1±1.5 for AN, C and OB respectively. OB had more girls of Hispanic ethnicity (AN, C, OB: 5%, 8% and 40%, p=.0004) and fewer of the Caucasian race (AN, C, OB: 86%, 85%, and 44%, p<.0001). Depressive symptom T-scores were higher in AN (58.6±1.5) and OB (52.9±2.0) compared to C (43.3±1.3) (p ≤ .0007 for both). Differences between groups persisted even after controlling for age, race and ethnicity. BMI and BMI-Z scores exhibited a U shaped relationship with depressive symptom T-scores, with a significant quadratic polynomial fit (p<0.05). Girls with irregular menstrual cycles had significantly higher depressive symptom T-scores (57.2±1.7) compared to girls with regular cycles (49.0±1.7) even after controlling for BMI-Z scores (p<.01). Depressive symptom T-scores correlated inversely with total periods in the previous 6 months, and this association persisted after controlling for BMI-Z scores (p<0.04).

**Conclusions:** In adolescent girls, depressive symptom T-scores exhibit a U shaped relationship with BMI, and extremes of weight are associated with greater depressive symptoms. Further, menstrual status of adolescents is associated with depressive symptoms independent of weight, indicating a possible role of gonadal hormone alterations in mediating depression. This relationship needs to be explored in future interventional studies.

# RESTING ENERGY EXPENDITURE (REE) AND THE DIFFERENCES IN APPENDICULAR LEAN MASS AND TRUNK LEAN MASS AMONGST AFRICAN AMERICAN AND CAUCASIAN AMERICAN CHILDREN

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**Objectives:** Prior studies have reported that African American (AA) children and adults have lower resting energy expenditure (REE), adjusted for total lean body mass (LBM), fat mass (FM), and bone mass, than Caucasian American (CA) children and adults. The lower REE of AA has been proposed as a factor promoting undue weight gain in the AA population. Because appendicular lean mass (ALM) is also reported to be greater in AA than CA for any given body weight, and ALM has low energy expenditure (EE) at rest, we tested the hypothesis that accounting for trunk lean mass (TLM, primarily composed of high EE organs) and ALM separately would explain the race-associated difference in REE.

**Methods:** We studied a convenience sample of 594 non-obese and obese AA (n=281) and CA (n=313) children, mean age  $11 \pm 2.6$ y [SD]. REE was measured using indirect calorimetry either at the National Institutes of Health or at Pennington Research Center. DXA (Hologic 2000 or 4500) was used to assess body composition. ANCOVAs were performed to examine the differences in REE for AA and CA, accounting for sex, age, height, pubertal stage, sub-total FM, total bone mass, head volume, DXA machine, and either for total LBM or for both TLM and ALM.

**Results:** AA children had greater ALM ( $20.3 \pm 0.2$ kg [SE] vs  $18.6 \pm 0.2$ kg [SE] respectively,  $p < 0.001$ ) and lower TLM than CA children ( $19.4 \pm 0.2$ kg [SE] vs  $20.3 \pm 0.2$ kg [SE] respectively,  $p = 0.001$ ) after accounting for age, sex, puberty, height, DXA machine, and FM. REE adjusted for these covariates and total LBM was  $79.7 \pm 16$ kcal/day [SE] lower in AA than CA ( $p < 0.001$ ). However, after accounting for ALM and TLM separately, the discrepancy in REE between the groups was no longer significant ( $-35.7 \pm 18.9$ kcal/day [SE] in AA;  $p = 0.06$ ). ALM was not significantly associated with REE in this model ( $p = 0.22$ ), although TLM was ( $p < 0.001$ ).

**Conclusions:** The majority of the disparity in REE between AA and CA children can be accounted for by racial differences in TLM (presumably representing high EE organs) and ALM, known to have low resting EE. Elucidating the remaining 36 kcal non-significant difference in REE between AA and CA may require organ-tissue volume and metabolic rate measurements.

# CLUSTERED CARDIOMETABOLIC RISK FROM ADOLESCENCE TO EMERGING ADULTHOOD IN CHILEAN INFANCY COHORT: THE ROLE OF INSULIN RESISTANCE

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**Objectives:** Insulin resistance (IR) is the most common metabolic alteration related to obesity and represents an important link between obesity and cardiovascular disease, type 2 diabetes, hypertension and dyslipidemia. We compared the cardiometabolic profile in emerging adulthood of youths with and without IR at 16y and explored the association of IR with the odds of having cardiometabolic risk at 22y, independent of obesity.

**Methods:** Observational prospective study in 328 22 year-olds (51% males) from an infancy cohort in Chile. Waist circumference (WC), fat mass (FM%;DEXA), blood arterial pressure (BAP), triglycerides (TG), HDL, glucose and insulin were measured at 16y and 22y. BMIz, HOMA-IR, Metabolic Syndrome z score (zMetS) (Gurka), SPICE and TG/HDL were estimated. MetS was diagnosed using the AHA/NHLBI/IDF criteria whereas IR was diagnosed using HOMA-IR  $\geq 2.6$ . After controlling for obesity status, multivariate logistic regressions tested the associations of IR at 16y with the odds of MetS and its components at 22y, and ANCOVA examined the association of IR with selected cardiometabolic markers

**Results:** There was a significant association ( $P < 0.01$ ) of IR at 16y with anthropometric and cardiometabolic marker at 22y. Adolescents with IR had significantly higher values of BMIz, WC, FM%, BAP, TG, TG/HDL, zMetS, insulin and HOMA-IR. Also, they had lower values of HDL and SPICE compared to non-IR adolescents. After controlling obesity at 16y, we found that obese with and without IR had higher risk of MetS and all its components at 22y compared to non-obese, non-IR participants (reference group). Non-obese participants with IR had significantly increased risk of MetS, IR and abdominal obesity at 22y compared to the reference group. The odds of MetS and IR were lower in this group, compared to obese participants with and without IR. Compared to the reference group, obese participants with and without IR had significantly increased values in all cardiometabolic markers at 22y. IR non-obese participants had no difference compared to the reference group.

**Conclusions:** In emerging adulthood, obesity in adolescence increases the cardiometabolic risk associated with IR. **Funding:** NHLBI-HL088530, CONICYT-PAI79140003.

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Table 1 Anthropometric and cardiometabolic profile in emerging adulthood (22y) by presence of insulin resistance at 16y.

	IR 16y (+) (n=52)		IR 16y (-) (n=275)		Difference <sup>c</sup>
	Mean	SD	Mean	SD	
Age (y)	16.8	0.3	16.8	0.3	0.0
BMI	30.3	6.9	25.9	5.2	4.4 <sup>***</sup>
Total Fat Mass (%)	39.3	8.4	35.2	9.5	4.1 <sup>***</sup>
Waist circumference (cm)	91.0	15.0	80.8	11.1	10.2 <sup>***</sup>
Systolic BP (mm Hg)	116.6	11.6	110.6	11.4	6.0 <sup>***</sup>
Diastolic BP (mm Hg)	72.4	8.2	68.9	7.7	3.4 <sup>***</sup>
Glycaemia (mg/dl)	94.5	11.0	89.5	9.1	5.0 <sup>***</sup>
Insulin (uU/dl)	19.4	12.1	13.4	9.8	6.0 <sup>***</sup>
HOMA-IR	4.6	3.0	2.9	1.7	0.8 <sup>***</sup>
SPISE Index	5.5	2.1	6.8	2.1	-1.3 <sup>***</sup>
Triglycerides (mg/dl)	115.9	62.2	96.8	62.1	19.1 <sup>*</sup>
HDL (mg/dl)	44.3	13.3	44.6	13.1	-0.3
TG/HDL Index	3.1	2.4	2.5	2.0	0.7 <sup>*</sup>
Metabolic Syndrome (z score)	-0.07	0.9	-0.45	0.7	0.38 <sup>***</sup>

<sup>a</sup> Student's t test for independent samples. Statistical significance: <sup>\*</sup>p<0.05, <sup>\*\*</sup>p<0.01, <sup>\*\*\*</sup>p<0.001

reduced insulin-stimulated NO production and bioavailability, endothelial ER stress and increased NF-kB activation.

P2-1107

## PULSE WAVE VELOCITY IN CHILDREN WITH DOWN SYNDROME—ADDRESSING SYNDROMIC SHORT STATURE

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**Objectives:** Pulse wave velocity (PWV), an index of aortic stiffness and independent predictor of adult cardiovascular events, is increased in youth with prediabetes. Age-adjusted (age-PWV-Z) and height-adjusted (Ht-PWV-Z) PWV reference data enable comparisons for youth, but the extent to which these adjustments are generalizable to children with syndromic or pathologic short stature is not known.

**Methods:** PWV (SphygmoCor v8.2) was performed as part of a study of cardiometabolic risk (CMR) in youth with Down Syndrome (DS) and control youth of comparable age-, sex-, BMI%-, race-, and ethnicity. Age-PWV-Z and Ht-PWV-Z were generated and compared between and within these groups. Predictors of PWV were assessed in youth with DS and the control group.

**Results:** As expected, DS (n=127, 58M/69F) and controls (n=79, 34M/45F) were comparable in age (14.9±3.4y vs 15.1±3y, p=0.63) and BMIZ (1.2±1 vs 1.2±1, p=0.99) but not height-Z (-2.2±1.1 vs 0.2±0.9, p=0.0001) or sitting height (122.4 cm vs 129.5 cm, p=0.0001); mean arterial pressure (MAP) was higher in DS (80±9) vs controls (76±6), p=0.01. The difference in raw PWV in DS (5.0±0.7 m/s) vs control (5.2±0.8 m/s) approached significance, p=0.06. While age-PWV-Z was not different between the groups (-0.17±1.1 vs 0.07±1.1, p=0.1), Ht-PWV-Z was higher in DS (0.43±1.21) vs controls (0.06±1.12), p=0.03, and Ht-PWV-Z was higher than age-PWV-Z in DS (p=0.001). In adjusted models, PWV was positively associated with age (p=0.001), BMIZ (p=0.003), and MAP (p=0.001) but not height (p=0.47) in controls, (R<sup>2</sup>=0.41). In contrast, while BMIZ (p=0.008) and MAP (p=0.06) were positively associated with PWV their explanatory value was limited in DS models (R<sup>2</sup>=0.08), and neither age nor height (nor sitting height) were associated with PWV in DS. In combined models adjusted for age, MAP, and BMIZ, DS was associated with lower PWV (beta=-0.24, p=0.015, R<sup>2</sup>=0.2).

**Conclusions:** In children with syndromic short stature, Ht-adjusted PWV may overestimate aortic stiffness, and the extent to which PWV captures CMR in DS remains to be resolved. The limitations of adjusting for anthropometric

P2-1106

## PLASMA FROM PREPUBERTAL OBESE CHILDREN IMPAIRS ENDOTHELIAL NITRIC OXIDE BIOAVAILABILITY: LINKING INSULIN RESISTANCE, INFLAMMATION AND ER STRESS.

Francesco Chiarelli, MD; Natalia Di Pietro, PhD; Assunta Pandolfi, PhD; Angelika Mohn, MD, University "G. d'Annunzio", CHIETI, Italy

**Objectives:** Childhood obesity is commonly associated with early signs of endothelial dysfunction, characterized by impairment of vascular Nitric Oxide (NO) availability, insulin resistance and inflammation. Recently all these features have been associated with endoplasmic reticulum (ER) stress; however, its role in the mechanism/s leading to vascular dysfunction in childhood obesity is still unclear. Thus, we tested the hypothesis that insulin-stimulated NO production and availability are impaired and related to Endoplasmic Reticulum (ER) in Human Umbilical Vein Endothelial Cells (HUVECs) cultured with plasma obtained from severely obese (OB) and normal-weight (CTRL) prepubertal children.

**Methods:** Plasma were obtained from OB- (N=28, age: 8.8 ± 2.2; BMI z-score: 2.15 ± 0.39) and CTRL-children (N=28, age: 8.8 ± 1.7; BMI z-score: 0.17 ± 0.96). Fasting insulin and glycemic levels were measured. HUVECs were serum starved for 16 hrs and cultured with 10% CTRL- or OB-plasma for 3hrs or 24 hrs, in some experiments Insulin, ODQ (heme-site inhibitor of soluble guanylyl cyclase competitive with NO) and PBA or TUDCA (known ER stress inhibitors) were also used. Then we evaluated: ER stress markers (GRP78, PERK, eIF2alpha, ATF6, IRE1, XBP1s), inflammatory markers (IkBalpha and NF-kB) and Akt/eNOS activation (phospho-Ser<sup>473</sup> Akt and phospho-Ser<sup>1177</sup> eNOS) by flow cytometry; eNOS activity by conversion of L-[3H]-arginine into L-[3H]-citrulline; intracellular cGMP levels by EIA.

**Results:** OB-plasma significantly impaired HUVECs insulin-stimulated NO production and bioavailability compared to CTRL-plasma. In parallel, endothelial stimulation with OB-plasma significantly increased GRP78 levels and activated PERK, eIF2alpha, ATF6 and IkBalpha. Moreover, OB-plasma increased endothelial NF-kB activation and its nuclear translocation. Notably, all these effects proved to be significantly restored by using PBA and TUDCA.

**Conclusions:** Our study demonstrate for the first time that plasma from obese children is able to induce in vitro endothelial insulin resistance, which is characterized by

differences requires assessment in children with other forms of syndromic and pathologic short stature.

P2-1108

#### **MATERNAL AND INFANT EXPOSURE TO NON-NUTRITIVE SWEETENERS: EFFECTS ON GUT AND BREAST MILK MICROBIOME**

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**Objectives:** Epidemiologic data support an association of non-nutritional sweeteners (NNS), surprisingly similar to sugar, with obesity, metabolic syndrome, diabetes, and cardiovascular disease. Even indirect exposure to NNS, in utero and during lactation, has been reported to be associated with greater weight gain as documented by higher infant body mass index (BMI) at one year of age. In rodent studies, the gut microbiome has been identified as a crucial link between NNS exposure and metabolic abnormalities. We speculate that NNS ingestion in humans can lead to comparable metabolic derangements as seen in rodents, and that the gut microbiome plays a crucial role.

**Methods:** We plan 1) to determine NNS concentrations (acesulfame potassium, sucralose, saccharin) in biospecimens collected from women who undergo elective C-sections (including maternal plasma, urine, amniotic fluid, and CSF) and their infants (placental tissue, cord blood and urine) and 2) to determine changes in the microbiome of maternal/infant gut and breast milk during a 12-month follow up (at 8 time points that coincide with routine well-baby visits). We will recruit 30 women-infant dyads before elective C-section and 30 dyads before normal vaginal delivery. Microbiome analyses will be controlled for type of delivery to ensure that any differences seen are not due to the mode of delivery. NNS concentrations will be determined with liquid chromatography-mass spectrometry and microbiome with 16S rRNA gene PCR and Illumina MiSeq sequencing.

**Results:** This study will be open for recruitment within 2 months and results will be reported as available at the time of presentation.

**Conclusions:** We speculate that NNS consumption plays a causal role in the widespread development of obesity and its complications, plausibly through critical changes in the gut microbiome. In nursing mothers, NNS ingestion has a triple target: maternal and infant intestinal flora and breast milk microbiome. Our hypothesis is based on epidemiologic data in humans and experimental evidence from in vitro and animal studies. Our study is a prospective case control, nonrandomized, pilot study that will shed light on the effects of NNS on microbiome changes in mother and infant dyads for 12 months post-partum.

P2-1109

#### **OBESITY AND COMPLEMENT GENE COPY NUMBER VARIATION PREDICTS ENDOTHELIAL FUNCTION**

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**Objectives:** Obesity is associated with increased cardiovascular risk. Complement components C3 and C4 play an important role in regulating inflammation which plays a role in the development of cardiovascular disease. C3 and C4 are related to cardiovascular risk in adults but these relationships have not been studied in adolescents.

**Methods:** Endothelial function was measured using post-occlusion, shear stress-induced, endothelial mediated vasodilation (Venous occlusion plethysmography/reactive hyperemia (RH)). After completion of endothelial function testing we obtained a blood sample for evaluation of complement levels in 19 healthy adolescents (age 15.7+/-1.9, BMI 22.8+/-5.6). Augmentation index (AI) (arterial tonometry) was used to assess arterial stiffness. Protein levels for complement C3 and C4 from EDTA-plasma were determined by single radial immunodiffusion. Copy-number (CN) variations for total C4, long (C4L) and short (C4s) forms were measured by southern blot analyses of genomic DNA samples digested by Pmel, Taql, PshAI/PvuII and resolved by gel electrophoresis.

**Results:** BMI positively correlated with C3 concentration ( $r=0.67$ ,  $p=0.002$ ) as did BMIPC ( $r=0.61$ ,  $p=0.005$ ). RH compared to C4L showed that the more copies of C4L the worse the endothelial function ( $r=0.50$ ,  $p=0.038$ ) and RH improved with higher C4s CN ( $r=-0.47$ ,  $p=0.057$ ). As levels of C3 and C4 increased systolic blood pressure increased ( $r=0.50$ ,  $p=0.03$ ). The AI positively correlated with total C3 ( $r=0.42$ ,  $p=0.07$ ). AI also positively correlated with total C4 levels ( $r=0.49$ ,  $p=0.03$ ) showing that as complement levels increase arterial stiffness increases.

**Conclusions:** These results clearly demonstrate that the complement system plays an important role in conjunction with obesity to regulate cardiovascular risk in adolescents. Decreased C4s CN may be useful in identifying adolescents at high risk.

P2-1110

#### **DEVELOPING A NOVEL SCREENING STRATEGY IN OVERWEIGHT AND OBESE CHILDREN AT RISK FOR NON-ALCOHOLIC FATTY LIVER DISEASE**

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**Objectives:** Non-alcoholic fatty liver disease (NAFLD) is associated with elevated risk for metabolic syndrome, type 2 diabetes, cardiovascular disease and cirrhosis. Available diagnostic tools (plasma aminotransferases and liver



ultrasound) have low sensitivity. This study is novel in that it aims to screen a broad population of at-risk youth with a combination of imaging tools and biomarkers previously used only in children with known liver disease. We hypothesize that NAFLD is common in overweight and obese pediatric patients and associated with a characteristic metabolic and imaging signature that will allow for effective screening.

**Methods:** Patients were recruited from general pediatric and subspecialty clinics. They underwent liver  $^1\text{H}$  magnetic resonance spectroscopy, liver Fibroscan, and fasting lab studies. Plasma biomarkers included in the analysis are hemoglobin A1c, lipid panel, AST and ALT levels.

**Results:** To date, 8 patients were recruited. Two patients (i.e., 25%) had an intrahepatic triglyceride content  $>5.5\%$ , consistent with a diagnosis of NAFLD. Both patients also had a diagnosis of prediabetes either by A1c or fasting plasma glucose. Two additional patients with A1c in the prediabetes range had hepatic steatosis  $4.8\%$ , close to the cutoff of  $5.5\%$ . Three out of the 4 patients with IHTG content  $\geq 4.8\%$  had reduced plasma HDL-C. However, none showed significant LDL-C or triglyceride elevation. One patient already showed a positive Fibroscan suggesting presence of moderate fibrosis. While only 2 patients had elevations in plasma ALT over the ULN, plasma ALT was still strongly correlated with IHTG content ( $r=0.89$ ,  $p<0.001$ ).

**Conclusions:** NAFLD is common in overweight pediatric patients and is associated with a worse metabolic profile. An intrahepatic triglyceride accumulation below the  $5.5\%$  threshold is still associated with important metabolic abnormalities (low plasma HDL-C, prediabetes). This suggests that a different cut-off may be needed for pediatric populations.

Forty patients will be included in this study. Additional studies include MR-elastography and genetic polymorphisms, advanced lipid testing, adipocytokines and homeostatic model of insulin resistance. Based upon these results, a diagnostic algorithm will be proposed for evaluating overweight youth for NAFLD.

P2-1111

#### THE SEVERITY OF THE METABOLIC SYNDROME (METS) IN CHILDHOOD IS ASSOCIATED WITH FUTURE METS SEVERITY, INSULIN RESISTANCE, AND OXIDATIVE STRESS AS YOUNG ADULTS: THE BOGALUSA HEART STUDY

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**Objectives:** The metabolic syndrome (MetS) is a cluster of cardiovascular disease (CVD) risk factors associated with insulin resistance and oxidative stress. We previously used confirmatory factor analysis to develop a continuous MetS severity Z-score, using cross-sectional data from adolescents age 12-19 years participating in NHANES. This MetS severity Z-score is based on an individual's measurements for the 5 MetS components (BMI Z-score, systolic BP, triglycerides, HDL, and fasting glucose), with differential weighting for

these components by sex- and racial/ethnic group. A separate score was derived for adults. Our goal currently was to assess longitudinal associations of childhood MetS severity with future fasting insulin (as a marker of insulin resistance) and uric acid (as a marker of oxidative stress), as a test of the durability of MetS severity and associated risk factors over time.

**Methods:** We evaluated Bogalusa Heart Study data from 285 white and black participants age 4-19 yrs, assessing correlations between baseline MetS severity at mean age  $13.3\pm 2.9$  yrs and subsequent risk factors as young adults at median age  $25.3\pm 4.4$ , as well as the associations between young-adult MetS severity and fasting insulin and uric acid.

**Results:** Childhood MetS severity Z-scores overall were significantly associated with later MetS severity score (Pearson's  $R=0.522$ ,  $p<0.001$ ), fasting insulin (Pearson's  $r=0.338$ ,  $p<0.001$ ), and uric acid (Pearson's  $r=0.283$ ,  $p<0.001$ ). When assessed on a sex- and race/ethnicity-specific basis (see Table), childhood MetS severity was significantly correlated with future insulin in all groups (all  $p<0.05$ ). Childhood MetS severity was correlated with future uric acid, with the exception of among white males (Pearson's  $r=0.145$ ,  $p=0.24$ ). As expected, these correlations were stronger when assessed using cross-sectional data in young adults (all  $p<0.001$ ).

**Conclusions:** Our sex- and race/ethnicity-specific MetS severity Z-score exhibited durability over 12.5 yrs from childhood to young-adulthood, including correlations with markers of future insulin resistance and oxidative stress. Future research will be focused on determining thresholds of risk for future disease based on degree of childhood MetS severity.

P2-1112

#### CHARACTERIZATION OF METABOLIC CHANGE IN PEDIATRIC NON-ALCOHOLIC LIVER DISEASE (NAFLD): A PRELIMINARY STUDY

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**Objectives:** Non-alcoholic liver disease (NAFLD) is the most common cause of chronic liver disease in children in the United States. NAFLD encompasses a wide spectrum from nonalcoholic fatty liver with steatosis to non-alcoholic steatohepatitis (NASH) which can progress to cirrhosis. There is a need for noninvasive biomarkers to predict risk for NAFLD and progression to NASH. Pathogenesis of NAFLD is unclear but inflammation and formation of toxic metabolites such as advanced glycation end products (AGEs) may be important. Our aim was to measure and compare skin AGEs, CRP and other metabolites in obese children with and without NAFLD.

**Methods:** We identified 22 obese children 4-18 years of age with NAFLD based on sonographic evidence of fatty liver. We measured skin auto-fluorescence (AF) to estimate tissue AGEs noninvasively in these children using the SCOUT DS Veralight machine and compared it with 27 obese children without

NAFLD. In addition, alanine transaminase levels, aspartate transaminase levels, total and direct bilirubin, total protein, albumin, hemoglobin, CRP, 25 OH vitamin D and hemoglobin A1c levels were measured.

**Results:** There was no statistical difference in age, sex and race between the NAFLD and obese groups. Nine children with NAFLD had skin AFs measured. ALT and AST, total and direct bilirubin were significantly higher in NAFLD patients. Total and direct bilirubin increased with age only in the NAFLD group. Otherwise, there was no significant difference between skin AFs, total protein, GGT, albumin, hemoglobin, CRP, 25 OH vitamin D and hemoglobin A1c levels between the two groups.

**Conclusions:** In this small preliminary study, we found that total and direct bilirubin increases with chronologic age in patients with NAFLD compared to unaffected obese children. Increase in bilirubin may be an important marker/factor in the clinical progression and severity of the disease. Further study will be needed to better understand its relevance.

**Table 1.** Difference in characteristics between NALFD and obese controls

	Age in Years	BMI	ALT	AST	T bilirubin*	D bilirubin
NAFLD (N=22)	13.1 ± 4	32.8 ± 4	123.09 ± 121	59.8 ± 56	0.54 ± 0.43	0.14 ± 0.26
Obese (N=27)	13.6 ± 2	32.2 ± 4	22.9 ± 8	15.7 ± 6	0.35 ± 0.17	0.06 ± 0.07

\*Statistically significant - p value < 0.05

P2-1113

**ASSOCIATION OF WAIST TO HEIGHT RATIO AND HYPERURICEMIA IN FILIPINO ADOLESCENTS**

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**Objectives:** This study aimed to determine the association of Waist- to-height ratio (WhtR) and hyperuricemia in Filipino adolescents. To determine the clinical profile, prevalence of hyperuricemia andn its association with other clinical measurements of overweight and/or obesity.

**Methods:** A total of 186 Filipino adolescents seen at the Out-patient Department of a tertiary hospital and Pediatric Endocrinology Clinics of Metro Manila were included in the study. Their weight, height, waist circumference, hip circumference, blood pressure and serum uric acid levels were measured. Hyperuricemia was defined as above the cut-off value given by the laboratory. Waist- to- height ratio of >= 0.5 was used to denote central obesity.

**Results:** Of the 186 participants, 94 had WhtR of >= 0.5 (mean age: 13.84 +/- 2.62, 48 females, 46 males, mean BMI: 27.03 +/- 4.17) while 92 had WhtR of < 0.5 (mean age: 14.22 +/- 2.33, 49 females, 42 males, mean BMI: 19.94 +/- 2.82). The overall prevalence of hyperuricemia was 37% (65% in those with WhtR of >= 0.5 vs 8% with WhtR of <0.5). Snoring (66%), acanthosis nigricans (56%), daytime sleepiness (44%) and polyphagia (28%) were the most common signs and symptoms seen in adolescents with central obesity. The most common co-morbidities noted in this group were: hyperuricemia (64%), hypovitaminosis D (62%), non- alcoholic fatty liver disease (43%), and dyslipidemia (37%). WhtR of >= 0.5 showed a higher likelihood of developing hyperuricemia (OR 22.44; p<0.001). As to BMI, the chance of

developing hyperuricemia was 5.9 times and 24.5 times higher if with BMI z-score of 1SD to 2SD respectively (95% CI). The odds of hyperuricemia was also higher if waist circumference is >90th centile (OR 15.9; 95% CI). No statistical significance was seen between waist- to-hip ratio and hyperuricemia. Higher prevalence of hyperuricemia was seen as WhtR increased.

**Conclusions:** The overall prevalence of hyperuricemia in Filipino adolescents in this study was 37%. WhtR of >= 0.5 is significantly associated with hyperuricemia. BMI z-score of >2SD showed the highest odds of hyperuricemia followed by WhtR and waist circumference (OR 24.52, OR 22.44 and OR 15.90 respectively).

Association of Waist- to- height ratio and Hyperuricemia in Filipino Adolescents

Tables  
Table 1. Demographic characteristics of participants

Parameters	N= 186 (%)	WhtR= ≥ 0.5 N= 94 (%)	WhtR= <0.5 N= 92 (%)	p-value
Age group (yr)				
Mean ± SD	14.63 ± 2.49	13.84 ± 2.62	14.22 ± 2.33	
16-12 (n= 55)	55 (30%)	32 (34%)	23 (25%)	0.15
13-15 (n= 75)	75 (40%)	32 (34%)	43 (47%)	
16- <19 (n= 56)	56 (30%)	30 (32%)	26 (28%)	
Sex				
Female (n=37)	97 (52%)	48 (51%)	49 (54%)	0.76
Male (n=88)	88 (47%)	46 (49%)	42 (46%)	
BMI (kg/m <sup>2</sup> )				
Mean ± SD	23.47 ± 5.64	27.03±4.17	19.94±2.82	
Normal (z score < 1SD to 1SD)	94 (51%)	15 (16%)	79 (86%)	< 0.001
Overweight (z score >1SD to <2SD)	41 (22%)	28 (30%)	13 (14%)	
Obese (z score >2SD)	51 (27%)	51 (54%)	0 (0%)	
Signs and symptoms				
Polyuria	19 (10%)	15 (16%)	4 (4%)	0.01
Polydipsia	24 (13%)	18 (19%)	6 (7%)	0.01
Polyphagia	32 (17%)	26 (28%)	6 (7%)	< 0.001
Easy fatigability	17 (9%)	17 (18%)	0 (0%)	< 0.001
Snoring	66 (46%)	62 ( 66%)	24 (26%)	< 0.001
Daytime sleepiness	43 (23%)	41 (44%)	2 (2%)	< 0.001
Acanthosis nigricans	58 (31%)	53 ( 56%)	5 (5%)	< 0.001
Irregular menses	8 (4%)	7 (7%)	1 (1%)	0.06
Hirsutism	8 (4%)	8 (9%)	0 (0%)	0.001
Joint pains (hip, knees)	8 (4%)	8 (9%)	0 (0%)	0.001
Depression	8 (4%)	7 (7)	1 (1%)	0.001
Co- morbidities				
Hypertension (%)	8 (4%)	8 (9%)	0 (0%)	0.05
Dyslipidemia (%)	39 (21%)	35 (37%)	4 (4%)	< 0.001
Diabetes (%)	3 (2%)	3 (3%)	0 (0%)	0.24
Hyperuricemia (%)	68 (37%)	61 (65%)	7 (8%)	< 0.001
Non alcoholic fatty liver disease (%)	46 (25%)	40 (43%)	6 (7%)	< 0.001
Metabolic syndrome (%)	13 (7%)	13 (14%)	0 (0%)	< 0.001
Insulin resistance	35 (19%)	35 (35%)	0 (0%)	< 0.001
Hypovitaminosis D	0 (0%)	58 (62%)	0 (0%)	< 0.001
Lifestyle				
No physical activity for health (%)	105 (56%)	57 (61%)	48 (52%)	0.391

P2-1114

**INTERFERON ACTIVATED GENE IFI202B LINKS TUMOR SUPPRESSOR GENE AIM2 TO OBESITY**

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**Objectives:** Absent in Melanoma (Aim) 2 is a tumor suppressor gene, and one of the inflammasomal proteins from HIN-200 domain family. Aim 2 is a cytosolic sensor for double-stranded DNA, with recognized roles in inflammation and infection. Our objective in this study is to investigate the role of Aim2 in glucose and lipid metabolism *in vivo*.

**Methods:** Wild type (WT) and Aim2 knockout (Aim2<sup>-/-</sup>) mice were housed under 12-hour light–dark cycle with access to food and water *ad libitum*. Body weight and food intake were recorded once a week from 8-week to 12-months of age. Body composition, fasting glucose, glucose and insulin tolerant tests (GTT and ITT) were performed at indicated ages. Immune cell infiltration in WAT was analyzed by flow cytometry. Adipogenesis was assessed using stromal vascular cells isolated from white adipose tissue (WAT).

**Results:** Aim2<sup>-/-</sup> mice demonstrated higher body weight compared to the WT mice from 8-week to 12-months of age (n=8 each) without significant change in food intake. Fat mass was significantly higher in Aim2<sup>-/-</sup> mice from age of 13-week onwards. Aim2<sup>-/-</sup> mice show higher fasting glucose levels (78±2.9 vs. 109±4.9 mg/dL, p<0.0001) and impaired GTT and ITT (p<0.01) at 5 months of age. Increased CD4+ and CD8+ lymphocytes infiltration and macrophages were found in the WAT in Aim2<sup>-/-</sup> mice. The increase in macrophages in WAT was demonstrated before the onset of obesity. Significant increase in expression of Ifi202b, a member of the interferon stimulated protein and pro-adipogenic gene was noted in liver and WAT by RNA Seq and real time PCR from 2 months of age. Consistent with the increase in adipogenic ifi202b, stromal vascular cells isolated from WAT demonstrated higher adipocyte differentiation potential in Aim2<sup>-/-</sup> mice.

**Conclusions:** In conclusion, Aim2 deletion in the mouse induces spontaneous obesity and impaired glucose homeostasis that is mediated through ectopic overexpression of ifi202b, an interferon stimulated protein, on inflammation and adipogenesis.

P2-1115

#### THE EFFECT OF ENVIRONMENTAL FACTORS IN CHILDCARE FACILITIES ON THE ASSOCIATION BETWEEN INFANTILE OBESITY AND LIFESTYLE; A MULTIVARIATE MULTILEVEL ANALYSIS.

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**Objectives:** Infant lifestyle as well as maternal factors are associated with the onset of infantile obesity. However, it is unknown whether environmental factors in childcare facilities have an impact on the association between infantile obesity and lifestyle. The aim of this study was to examine the effect of environmental factors in childcare facilities on the association between infantile obesity and lifestyle. We stratified individual factors and environmental factors related to the childcare facility and analyzed these relationship by using a multilevel analysis.

**Methods:** Subjects included total 2898 infants, aged 4 to 6 years old, from 28 kindergartens and 28 nursery schools in Kitakyushu City, Japan. Of 118 obese infants (4.1%) in total were obese; 71 (2.4%) were mild, 38 (1.3%) were moderate and 9 (0.3%) were severe obesity. A stratified multilevel analysis was conducted with two strata: factors related to individual lifestyle habits as the individual level and environmental factors related to the infantile facility (presence or absence of a playground, exercise time, extracurricular activities, nap, refill school lunch, physical measurements, provision of snacks, outdoor or indoor play space) as the environmental level. Two-level multilevel regression analysis was conducted with the presence or absence of obesity as a dependent variable and the items of the individual level and the environmental level as independent variables.

**Results:** The prevalence of obesity was significantly associated with the mastication, nutritional methods in infancy, usual play activity, screen-time on weekdays, maternal body mass index, and maternal weight increase during pregnancy in individual level. On the other hand, the prevalence of obesity was only significantly associated with the provision of snacks by using multilevel analysis within the individual level and environmental level.

**Conclusions:** The present results showed that the acquirement of lifestyle to eat snacks regularly in childcare facilities may prevent infantile obesity, suggesting that establishing and maintaining environmental factors in childcare facilities may play important roles for prevention of obesity from infancy.

P2-1116

#### ASSOCIATIONS AMONG DIETARY PRACTICES, DEMOGRAPHICS, AND BODY COMPOSITION IN A PEDIATRIC WEIGHT MANAGEMENT CLINIC

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**Objectives:** We examined the associations of caregiver-reported and self-reported dietary practices, demographics, and body composition in youth seeking treatment for obesity.

**Methods:** Caregivers of 469 pediatric patients at a multidisciplinary weight management clinic completed questionnaires assessing the child's dietary practices during the preceding 7 days. Adolescents completed self-reported questionnaires of the same questions. Baseline anthropometrics and body composition by bioelectrical impedance analysis (InBody 770) were obtained. Nominal p-values are reported (p<0.005 significant after Bonferroni multiple comparison correction).

**Results:** Subject characteristics: age 12.3±3.6y, 63% female, 70% African American, BMI 40.1±8.7 kg/m<sup>2</sup>, BMI-Z 2.67±0.45, waist-Z 3.40±2.18, percent body fat 48.9±5.9%. Caregiver and self-reported responses of adolescents were moderately well correlated (rho 0.24-0.58; p's<0.001); hereafter, caregiver responses described. After adjusting for sex, race, and BMI-Z, the associations between age and soda intake, fast food intake, and meal skipping were significantly positive (p's<0.005) and nominally positive for sweets (p=0.02) and fried food (p=0.005). After adjusting for age, race, and BMI-Z, boys had nominally higher sports drink intake than girls (p=0.02). After adjusting for age, sex, and BMI-Z, African-American subjects had significantly higher juice intake (p<0.001), and nominally higher sports drink, fried food, and fast food intake (p's≤0.03). After adjusting for age, sex, and race, nominal positive associations were observed between juice consumption and BMI-Z (p=0.01), and for sports drinks consumption with percent body fat (p=0.04) and waist-Z (p=0.005).

**Conclusions:** In our racially diverse cohort, differences in dietary practices appear to be associated with child's age, sex, and race. Juice and sport drink consumption may be associated with more severe central adiposity. However, neither causality nor direction of effect can be inferred from this cross-sectional study. The longitudinal impact of reducing beverages with natural or added sugar on body composition in this cohort is currently under analysis to determine if targeting these dietary practices will be beneficial for metabolic health.

P2-1117

#### PREDICTORS OF THE METABOLICALLY OBESE NORMAL WEIGHT PHENOTYPE IN YOUTH

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**Objectives:** Although metabolically obese normal weight (MONW) adults are at increased risk of type 2 diabetes and cardiovascular disease (CVD), little is known regarding MONW children. The aim of this project was to determine the predictors of the MONW phenotype among previously healthy normal weight children as they enter puberty.

**Methods:** The QUALITY cohort comprises Caucasian youth (n= 630) with at least one obese biological parent recruited at 8-10 years of age and followed up 2 years later. Of these, healthy normal weight children were identified at baseline and were classified as MONW at 10-12 years of age if they had normal weight and at least one of: triglycerides > 1.24 mmol/L, fasting glucose > 6.1 mmol/L, HDL-cholesterol < 1.03 mmol/L, blood pressure (BP) > 90<sup>th</sup> percentile for age and sex and height, or waist circumference > 90<sup>th</sup> percentile for age and sex. Height, weight and waist circumference were measured using standardized protocols, and adiposity using DXA at both baseline and follow up. At 8-10 years, moderate

to vigorous physical activity was assessed using accelerometry, screen time was self-reported, and diet was assessed using 3 non-consecutive 24-hr recalls. Parental questionnaires provided information on family history of CVD and related disorders. Multivariable logistic regression models were used to identify predictors of MONW at 10-12 years of age. All models were adjusted for age, sex, and nurse assessed Tanner stage.

**Results:** Of the 193 children who were normal weight and metabolically healthy at age 8-10 years, 45 (23%) became MONW two years later. Baseline waist circumference (OR=1.20; 95% CI= 1.05; 1.36) and weight gain (in BMI z-score) over the 2-year period, adjusting for baseline BMI z-score (OR=4.15; 95% CI =1.74; 9.86) predicted the MONW status. Lifestyle habits and family history of CVD/ related disorders did not predict the development of the MONW status following adjustment for potential confounders.

**Conclusions:** Normal weight pre-pubertal children with higher waist circumference, and those with greater weight gain as they enter puberty are at increased risk of developing metabolic risk factors, despite remaining normal weight.

P2-1118

#### HYPOTHALAMIC OBESITY: 4 YEARS OF THE INTERNATIONAL REGISTRY OF HYPOTHALAMIC OBESITY DISORDERS

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**Objectives:** Hypothalamic obesity (HyOb) causes rapid weight gain due to brain injury or malformation resulting in early metabolic co-morbidities. Despite pragmatic efforts, effective treatment strategies have not been elucidated due in part to the rarity of disease. We aimed to design a registry to characterize HyOb subjects and compare treatment effects.

**Methods:** The International Registry of Hypothalamic Obesity Disorders (IRHOD) ([www.irhod.org](http://www.irhod.org)), was created to provide information about HyOb and function as a registry entry portal. Demographic, etiological, treatment, and biomorphic data were collected from registrants. Participants were stratified by BMI classification with those <20 years classified using BMI percentile for age and gender, and adults >20 years classified using standard BMI categories.

**Results:** Eighty-seven participants were included for analysis with median age of 27 years (range 3-71 years), 97% with obesity at maximal weight and 3% (n=3) with overweight status. Etiologies included brain tumor (86%), congenital brain malformation (5%, n=4), traumatic brain injury (3%, n=3), and genetic associated obesity (2%, n=2). Ninety percent of participants received therapy for obesity: nutritional counseling (82%), pharmacotherapy (59%), bariatric surgery (8%, n=7), and vagal nerve stimulator (n=1). Forty participants (46%) reported follow-up BMI after

treatment. Effects were as follows: Surgery (n=6, median BMI change  $-8.2\text{kg/m}^2$ , median time 2.6 years), pharmacotherapy (n=21, median BMI change  $-2.3\text{kg/m}^2$ , median time 0.8 years), nutritional counseling (n=11, median BMI change  $-3.4\text{kg/m}^2$ , median time 1.2 years). Most participants remained in the obesity classification (80%), with lower rates in overweight (18%) and normal BMI (2%, n=1) categories. Severe obesity persisted with 55% of participants.

**Conclusions:** The IRHOD registry identified a cohort with self-reported HyOb treated with several different approaches. Surgical therapy was most effective at weight reduction. Nutritional counseling alone improved BMI modestly and was similar to pharmacotherapy. Severe obesity persisted in 55% of follow up participants. This well-described cohort of HyOb participants is available to other investigators for future study.

P2-1119

#### **TWO-YEAR FOLLOW-UP OF 70 OBESE CHILDREN AND ADOLESCENTS AFTER A MULTIDISCIPLINARY THERAPEUTIC EDUCATION PROGRAMME**

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**Objectives:** Multidisciplinary family care programme including therapeutic education is a key point in pediatric obesity management. However long-term outcome is a main challenge as lost of follow-up is very frequent.

**Objectives:**

- To evaluate the weight loss 2 years after a family therapeutic education programme (TAKAPHER) implemented in a pediatric endocrinologist unit aiming to organize a personalized follow-up such as participation to a therapeutic education programme during 1 year or regular consultations with the general practitioner combined with consultation with a pediatric endocrinologist of the hospital twice a year.
- To identify limiting factors of success and family expectations.

**Methods:** A retrospective study was conducted in 151 children and adolescents who participated to the TAKAPHER programme in 2013 using medical files information and a phone standardized survey.

**Results:** 70 patients were reached and included. Mean duration of follow-up was 2.8 years, 73% of patients had significantly reduced their BMI (relative delta z-score BMI  $< -0.10$ ). The mean SD score BMI in 2013 was 4.08 SD vs 2.85 SD at follow-up ( $p < 0.0001$ ) with a relative delta z-score BMI at  $-0.28 \pm 0.32$ . Fifty-six percent had changed their eating habits, 44% had increased their physical activity and only 12% had reduced screen time. Principal barriers of lifestyle changes identified by families were lack in dietetic follow-up (34%), lack of motivation (46%) and inappropriate parental education style (32%). Eighty seven percent of the patients were regularly followed by a health professional. Weight loss

was not significantly different regarding the type of follow-up proposed.

**Conclusions:** These results are very encouraging as 50% of the children responded to the survey and most of them continued follow-up. A comprehensive and personalized follow-up, adapted to each patient and family, facilitates lifestyle modifications. The general practitioners in links with pediatric endocrinologists play an essential role in the structured and long-term follow-up.

P2-1120

#### **ASSOCIATION OF FERRITIN AND THE PALMITOLEATE/PALMITATE DESATURATION INDEX AMONG OBESE AND LEAN YOUTHS**

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**Objectives:** Obesity is associated with low iron availability, likely due to both insufficient dietary iron intake and trapping of iron in macrophages and enterocytes through an interleukin-6 (IL-6) dependent pathway. Inadequate iron availability may in turn play a role in inflammation, resulting in a perpetual cycle of further iron deficiency and inflammation. Stearoyl-CoA desaturase enzyme 1 (SCD1) is an iron-dependent enzyme that produces monounsaturated fatty acids from saturated fatty acids, thereby decreasing inflammation. In animal studies, low iron availability decreases SCD1 activity.

The objectives of this study are to compare iron status and SCD1 activity between obese and lean youths; and to determine the association between iron status and SCD1 activity.

**Methods:** 19 obese (BMI z-score  $> 2.0$ ) and 28 lean (BMI z-score  $-2.0 - 1.0$ ) subjects were recruited (mean age 14 years, range 9-17 years) in a cross-sectional study. Fasting serum was collected and used to measure markers of liver iron stores (ferritin), iron availability to the bone marrow [soluble transferrin receptor (sTfR)], estimated SCD1 activity, and IL-6. Iron deficiency was defined as sTfR level  $> 8.3\text{ mg/L}$ . SCD1 activity was estimated by calculating the product-to-precursor ratios (palmitoleate/palmitate and oleate/stearate) from the serum fatty acid profile as analyzed by gas chromatography/mass spectrometry. T-test was used to compare iron status, inflammation, and the SCD1 ratios between the obese and lean groups. Linear regression was used to test for the relationship between iron status and fatty acid ratios.

**Results:** Based on sTfR, 10% of obese subjects were iron-deficient (0% of lean). Mean sTfR, ferritin and IL-6 were significantly higher in obese vs. lean subjects (all  $p < 0.05$ ). The palmitoleate/palmitate ratio was also significantly higher in obese subjects ( $p = 0.03$ ). Ferritin, but not sTfR or IL-6, was

positively associated with the palmitoleate/palmitate ratio ( $p=0.02$ ) in the whole cohort.

**Conclusions:** Iron deficiency was identified among obese but not lean youths. Ferritin, reflecting liver iron stores, may promote liver SCD1 activity as an adaptive mechanism to decrease inflammation. Therefore, iron may have a role in micronutrient modulation of inflammation in obesity.

P2-1121

**EVALUATION OF GLYCATED HAEMOGLOBIN AS A DIAGNOSTIC MARKER FOR ABNORMAL GLUCOSE HOMEOSTASIS IN OBESE CHILDREN & ADOLESCENTS.**

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**Objectives:** Incidence of obesity is on the rise in children & adolescents in UK. Significant proportion of obese children with type 2 diabetes mellitus remain asymptomatic unlike type 1 diabetes mellitus.

**Aim:** To estimate the prevalence of type 2 diabetes and abnormal glucose homeostasis in obese children & assess the role of HbA1C as a diagnostic marker for diabetes and abnormal glucose homeostasis.

**Methods:** Retrospective study of 156 overweight & obese children (BMI Z SCORES > 1.33) aged 3-19 years., who underwent standard oral glucose tolerance testing with administration of 1.75g/kg (up to maximum of 75g) of oral glucose at a tertiary paediatric hospital in the UK. Information regarding ethnicity, anthropometry, comorbidities and various other risk factors associated with diabetes were recorded on a predefined proforma. Venous blood sample was drawn at the start of the test for fasting glucose, insulin and HbA1C, this was followed by a 120 min venous blood sample for glucose measurement

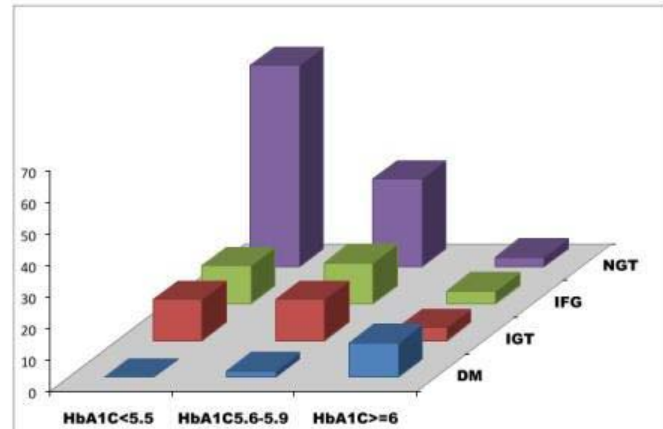
**Results:** Of the total children, 8.3% (10 female, 3 male) had type 2 diabetes (8 Asians, 5 non Asians), 95(61%) had a normal glucose tolerance, 18(12%) impaired fasting glucose, 19(12%) impaired glucose tolerance & 11(7%) had both impaired fasting glucose & impaired glucose tolerance. ROC curve analysis demonstrated that HbA1c of  $\geq 6\%$  was excellent screening tool for diagnosis of DM but performed moderately for prediabetes.

**Conclusions:** Despite HbA1c being an overall less sensitive diagnostic tool compared to OGTT, due to the ease of testing, a wider application can lead to higher detection of diabetes in asymptomatic obese children.

PLEASE SEE TABLES IN NEXT COLUMN

Distribution of glucose tolerance results within HbA1C categories.

OGTT (N=156)	HbA1C %		
	<5.5	5.5-5.9	$\geq 6$
	N(%)	N(%)	N(%)
NGT(95)	64(68)	28(30)	3(2)
IGT(30)	13(43)	13(43)	4(14)
IFG(29)	12(41)	13(45)	4(14)
DM(13)	0(0)	2(15)	11 (85)



P2-1122

**ADIPOSIITY IMPACT IN CHILDHOOD VITAMIN D LEVELS**

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**Objectives:** Evidences have shown that hypovitaminosis D in children and adolescents is related to fat mass and obesity. For this reason the objectives of the present study were to characterize vitamin D status in children and adolescents and

to identify factors associated with its variability as might be the adiposity.

**Methods:** To determine vitamin D status the circulating levels of 25-hydroxy-vitamin D 25(OH)D were quantified by LIAISON method and analyzed in correlation to gender, pubertal period, age and Body Mass Index (BMI) in 471 children and adolescents (2 to 18 years age). BMI was used as an adiposity indicator and the study sample was classified as obese/overweight and normal-weight by using standard definition from Cole et al (331 were obese/overweight and 140 were normal-weight).

**Results:** As result, low prevalence of optimal vitamin D status (25(OH)D levels  $\geq 30$  ng/ml) was observed in children and adolescents (32.9%). Higher 25(OH)D deficiency (25(OH)D levels  $< 20$  ng/ml) was observed in females than in males (45.3% vs 33.8%  $P < 0.01$ ) and in pubertal children the 25(OH)D circulating levels were lower than prepubertal ( $P < 0.05$ ). Respect to adiposity, higher 25(OH)D deficiency was observed in obese/overweight children than normal-weight (43.2% vs 31.4%  $P < 0.05$ ). Moreover, a novel non-linear regression model showed that 39.6 % of 25(OH)D levels variability was explained by BMI.

**Conclusions:** In conclusion, low vitamin D status was highly prevalent among children and adolescents. Being female, adolescent and obese increase the risk of suffering low vitamin D levels. The novel non-linear regression model shows that adiposity, indicated by BMI, is an important powerful factor that impact vitamin D levels.

P2-1123

#### EVALUATION OF ANTHROPOMETRIC INDEXES, METABOLIC AND HORMONAL PROFILE BEFORE AND AFTER AT LEAST 1 YEAR OF CLINICAL AND NUTRITIONAL FOLLOW-UP OF CHILDREN WITH OVERWEIGHT AND OBESITY.

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**Objectives:** Obesity is a worldwide problem, affecting children and adolescents. Obese children already have metabolic alterations, increasing cardiovascular risks. The goal of this study was to assess if after at least one year of clinical and nutritional follow-up there were changes in the metabolic and hormonal profile of overweight and obese children.

**Methods:** Children followed at the obesity clinic from a university hospital were invited to participate. Body mass index (IMC) z-score was calculated according to WHO (2007) standards. Samples for Vitamin D, HDL cholesterol, LDL cholesterol and insulin were drawn in the morning, after fasting for 12 hours.

**Results:** Thirty one children with a mean age ( $\pm$  DP) of 8,23 years ( $\pm 1.87$ ) participated in the study. The average follow-up time was 1,5 years. The mean BMI z-score in the first visit was 3,21  $\text{kg/m}^2$  ( $\pm 1,09$ ) and after at least 1 year of follow up the mean z-score decreased to 2,9  $\text{kg/m}^2$  ( $\pm 0,89$ ) ( $p=0,008$ ).

The mean HDL-cholesterol in the first visit was 43,4 mg/dl ( $\pm 6,85$ ) and after at least 1 year of follow up it was increased to 46,9 mg/dl ( $\pm 10,94$ ) ( $p=0,025$ ). There were no statistically significant differences between serum levels of insulin, Vitamin D or LDL-cholesterol before and after follow-up.

**Conclusions:** After at least 1 year of clinical and nutritional follow up the BMI z-score decreased accompanied with a discrete, although statistically significant, increase in HDL cholesterol. The remained metabolic markers investigated remained unchanged. We conclude that despite a weight loss after at least one year of follow up the metabolic profile showed very little improvement. There is a need to better understand what needs to be done to decrease cardiovascular risks of these children.

P2-1124

#### THYROID STIMULATING HORMONE, DEGREE OF OBESITY AND METABOLIC RISK MARKERS IN A COHORT OF SWEDISH CHILDREN WITH OBESITY.

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**Objectives:** Thyroid stimulating hormone (TSH) is affected in obesity and might influence metabolic risk. It is unclear whether TSH is increased directly due to obesity or indirectly to maintain normal thyroid hormone levels. Underlying mechanisms causing elevated TSH and metabolic consequences are still unclear.

We aimed to investigate TSH status in children with obesity, whose TSH lies within the normal range, and the association of TSH with obesity level and metabolic parameters.

**Methods:** A total of 3459 children, aged 3.0-17.9 years with records of BMI SDS and thyroid hormone levels were identified in the Swedish Childhood Obesity Treatment Registry, BORIS. TSH, fT3 and fT4, BMI SDS, lipid profiles (total cholesterol, triglycerides, HDL- and LDL-cholesterol) and variables of glucose metabolism (fasting insulin, fasting glucose and HOMA) were examined.

**Results:** Children with high-normal TSH ( $> 3.0$  mU/L) (28.8%) had higher BMI SDS compared to children with low-normal TSH ( $< 3.0$  mU/L) ( $p < 0.001$ ) together with unaltered fT3 and fT4. We found associations of TSH with BMI SDS ( $\beta$ : 0.21, 95% CI: 0.14-0.28,  $p < 0.001$ ) adjusted for age and sex. TSH and thyroid hormones were associated with markers of lipid and glucose metabolism adjusted for BMI SDS, age and sex; high-normal TSH was positively associated with f-insulin, HOMA, total-cholesterol and triglycerides.

**Conclusions:** In our cohort of children with obesity, a positive association between TSH and degree of obesity was confirmed. TSH and thyroid hormones were associated with several metabolic risk markers, although further longitudinal studies are necessary to clarify whether TSH and thyroid hormones contribute to obesity co-morbidities, or whether the metabolic consequences of obesity affect thyroid hormone production and turnover.



OVERWEIGHT AS A CARDIOVASCULAR RISK FACTOR IN CHILDREN

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**Objectives:** We decide to compare lipid profile in overweight (OW) and obese (OB) children with different cut off points in order to identify early cardiovascular risk (CVR).

**Methods:** We included 159 children, 3-15 years of age, 93F/66 M. We selected 53 OW and 106 OB children according to Centers for Disease Control and Prevention criteria, matched by age, gender and sexual development. The z - score BMI, lipid profile, TG/ HDL-C index and TC/HDL-C index were evaluated. We compare the 75<sup>th</sup> versus 95<sup>th</sup> percentile of lipid profile as CVR factor according to American Academy of Pediatrics criteria. It was considered 75<sup>th</sup> percentile: TC  $\geq 170$  mg%, LDL-C  $\geq 110$ mg%, TG: 0-9 years old  $\geq 75$ mg%, 10-19 years old  $\geq 90$ mg%; HDL-C  $\leq 45$ mg%, and 95<sup>th</sup> percentile: TC  $\geq 200$  mg%, LDL-C  $\geq 130$ mg%, TG: 0-9 years old  $\geq 100$ mg%, 10-19 years old  $\geq 130$ mg%; HDL-C  $\leq 40$ mg%. Also, we considered high TG/HDL-C index  $\geq 2.32$  and TC/HDL-C index: women  $\geq 4.5$ , men  $\geq 5$ . We used t student, nonparametric equality of medians tests and Chi-square considering significant  $p < 0.05$ .

**Results:** The mean age in OW was  $10.45 \pm 2.72$  years and in OB  $10.42 \pm 2.67$ . The BMI z- score in OW was  $1.43 \pm 0.15$  and  $2.19 \pm 0.33$  in OB ( $p < 0.001$ ). The means of lipid profile show significant differences in TC and TG (0-9 years old). However, we found not significant differences as regards frequencies of CVR when comparing 95<sup>th</sup> percentile versus 75<sup>th</sup> percentile as shown in Table 1. Finally, the TG / HDL-C index identified CVR in 66% of children with OW vs 71.7% in OB ( $p=0.46$ ); and the TC/ HDL-C index identified CVR in 24.5% of children with OW vs 32% in OB, with no significant difference ( $p=0.32$ ).

**Conclusions:** Overweight children showed similar cardiovascular risk than obese children despite of the cut point of lipid profile.

Tabla 1  
Cardiovascular risk factors in overweight and obese children according to lipid profile percentile

	95th percentile			75th percentile		
	Overweight (n=53)	Obese (n=106)	p	Overweight (n=53)	Obese (n=106)	p
TC	5.66 %	16.04%	0.06	26.42	41.51	0.06
LDL - C	7.55 %	13.21 %	0.29	20.75	27.36	0.37
TG	47.17%	57.55%	0.22	77.36	80.19	0.68
HDL - C	45.28%	51.89 %	0.43	60.38	75.47	0.049

CAROTID IMT AND PLASMA LIPID LEVELS AMONG CHILDREN AND ADOLESCENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA. A SINGLE CENTER EXPERIENCE 2007-2014

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**Objectives:** Familial hypercholesterolemia (FH) is an inherited error of lipoprotein metabolism characterized by elevated cholesterol and premature atherosclerotic cardiovascular disease. Current guidelines advocate early evaluation in pediatric carriers of FH. Assessment of carotid intima media thickness (cIMT) is often used to evaluate preclinical atherosclerosis in FH. Early cIMT progression was observed in FH subjects, and statin therapy was shown to slow the progression of IMT. The objective of the study was to determine the relation between plasma cholesterol levels, age and cIMT in young patients with FH.

**Methods:** Plasma lipid profile testing and cIMT measurements were performed on a group of FH patients which consisted of children and adolescents with a clinical and biochemical diagnosis of FH , from the pediatric lipid clinic in our medical center. The control group for the cIMT measurements consisted of fifty five (33 females) healthy normocholesterolemic subjects aged 18-30 years.

**Results:** Thirty seven patients were assessed, 18 males and 19 females. The average age at assessment was  $12.1 \pm 3.2$  years for the males and  $11.6 \pm 3.5$  for the females. Fasting plasma LDL-cholesterol levels were  $210.2 \pm 62.3$  mg/dl for the females and  $198.7 \pm 45.2$  mg/dl for the males. Average cIMT values in males were  $0.5 \pm 0.05$  mm and  $0.46 \pm 0.06$  mm in females, and  $0.488 \pm 0.05$  mm in the control group. 11 males over the age of twelve years, had cIMT values above the control group.

**Conclusions:** cIMT was linearly related to age in both genders and is increased in male FH adolescents. Particular attention should be paid to this high risk group of patients.

FREQUENCY OF ADVANCED BONE AGE AND ASSOCIATED FACTORS IN PERUVIAN OBESE CHILDREN

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**Objectives:** We aimed to determine the frequency of Advance bone age (ABA) and associated factors in Peruvian obese children attending the Endocrinology Unit of a National Institute.

**Methods:** We performed a cross-sectional study, with sampling method by convenience. For descriptive analysis we assessed the normal distribution of variables, for parametric or non-parametric analysis. We defined bone age (BA) as the mean value calculated either between two endocrinologists, one endocrinologist and a radiologist, or between both of three –according to the Greulich and Pyle atlas and ABA was defined as BA > +2 SD. Anthropometric data were collected following CDC growth charts. Abdominal obesity was defined as >90 percentile of waist circumference. Biochemical tests were requested, such as basal glycemia and insulin levels, total cholesterol, LDL-and HDL-cholesterol and triglycerides. Puberal stage was measure according to Tanner and Marshal. For univariable analysis we performed linear regression and logistic regression, when BA was continuous or categorical (ABA vs non-ABA). For statistical analysis we used the STATA program version 10 (STATA Corp, College Station, TX, US), with 95% confidence interval (95%CI).

**Results:** One hundred and thirty five obese children were included, whose mean age was 110.1 months (SD=28.5), being 50.7 % male patients. We found mean bone age of 9.9 years (SD 25), and 20% of obese children with ABA. Abdominal obesity was found in 63.2%. Most patients relied to prepuberal Tanner stage (71.2%). We found high levels of total cholesterol, triglycerides, LDL-cholesterol, in 19.3%, 46.7%, 20 %, respectively; 50.4% having low HDL-cholesterol level. Univariable analysis showed association between bone age with age, weight, height, body mass index, abdominal circumference and Tanner stage. Multivariable analysis could not demonstrate a significant association between bone age or ABA with any variable.

**Conclusions:** High level of ABA was found in this study, without a statistical association with any of them in adjusted models. Although Peruvian children evaluated in this study demonstrated high levels of abnormal metabolic parameters, they seem to not relate to ABA. Further investigations in a population-level representative data could clarify this relationship.

P2-1128

#### PHENOTYPES AND OUTCOME OF VIETNAMESE PRIMARY HYPERLIPIDEMIA PATIENTS

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**Objectives:** Primary hyperlipidemia is genetic dyslipoproteinemia. Without any intervention, cardiovascular diseases and acute pancreatitis may be occurred. Detection and appropriate management of pediatric hyperlipidemia can have a significant impact upon the disease course and can prevent complications. The article aims to describe phenotypes of Vietnamese primary hyperlipidemia patients and to evaluate outcome of treatment.

**Methods:** From 2007 to 2015, 35 children were diagnosed with primary hyperlipidemia using included and excluded

criteria and were treated with diet and/or lipid-lowering drug therapy.

**Results:** Among 35 cases from 33 families, 10 patients were mixed hyperlipidemia (MHL), 14 patients were hypertriglyceridemia (HT) and 11 patients were hypercholesterolemia (HC). Mean age of diagnosis was 5.7 years (1 months-16 years). The rate of male/female was 17/18. Clinical manifestations included hepatomegaly (5 cases), xanthemas in the knees and elbows (7 cases), “creamy” blood (24 cases), acute pancreatitis (4 cases). A total of 11/35 patients had family history with hyperlipidemia and cardiovascular diseases. Serum cholesterol level of HC group was 9.6±4 mmol/L. Serum triglyceride level of HT group was 25.6±9.9 mmol/L. In MHL group, serum cholesterol level and serum triglyceride level were 12.1±4.5 mmol/L and 20.3±10.5 mmol/L, respectively. After interventions, HT group had the best result with serum triglyceride level was 10.1±4.6 mmol/L, next to MHL group with serum cholesterol level was 5.8±1.8 mmol/L, and serum triglyceride level was 9.5±5.2 mmol/L; finally, serum cholesterol level of HC group was 12.4±5.5 mmol/L. Five infants with HT had the best results of treatment: serum triglyceride level decreased from 19-57.6 to 5-10 mmol/L. Three patients suspected homozygous family hypercholesterolemia had the worsen results (unchanged blood lipid level) and cardiovascular consequences.

**Conclusions:** Primary hyperlipidemia had poor clinical manifestations and limited outcomes. Screening for primary hyperlipidemia help to prevent premature cardiovascular diseases and acute pancreatitis.

P2-1129

#### ADIPONECTIN AND FATTY ACID BINDING PROTEIN 4 SERUM LEVELS AND CHARACTERISTICS OF BODY COMPOSITION IN ADOLESCENTS WITH OBESITY AND METABOLIC SYNDROME

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**Objectives:** Adipokines - adipose tissue hormones, connect obesity and its complications. Decreased serum adiponectin and increased fatty acid binding protein 4 (FABP4) levels are independent predictors of metabolic syndrome (MS), diabetes and cardiovascular disease in adults. Visceral obesity is also associated with decreased levels of adiponectin and various metabolic disorders. Aim of our research was the measurement plasma levels of FABP4, adiponectin, visceral (VAT), subcutaneous (SAT) adipose tissue and % of body fat in adolescents with obesity depending on MS.

**Methods:** A total of 108 adolescents with simple obesity (SDS BMI +2,95 [2,8;3,3]) aged from 13 to 17 years (15,5 [14,3;16,7]) were studied. Obesity is diagnosed according to World Health Organization criteria. MS is diagnosed according to International Diabetes Federation criteria for children. Plasma FABP4 and adiponectin were measured using ELISA. VAT and SAT area were detected by single slice magnetic resonance imaging. % of body fat was estimated by bioelectrical impedance analysis.

**Results:** Serum FABP4 level was significantly higher ( $p<0,01$ ) in adolescent girls with MS compared with peers without MS (27,9 [24,9;29,3] vs 23,3 [17,2;27,4] ng/ml). Plasma FABP4 in girls positively correlated with SAT area ( $r=0,4$ ;  $p<0,05$ ) and % of body fat ( $r=0,52$ ;  $p<0,05$ ). In adolescent boys with MS revealed decreased serum adiponectin (9,3 [7,1;13,1] vs 11,3 [9,4;13,4];  $p<0,05$ ) and higher VAT area (111 [68;148] vs 70 [43;90] cm<sup>2</sup>;  $p<0,01$ ) compared with adolescents without MS. Plasma adiponectin in boys negatively correlated with VAT area ( $r=-0,56$ ;  $p<0,01$ ). Serum FABP4 level was comparable in groups regardless of MS.

**Conclusions:** In adolescent boys with obesity and MS revealed decreased serum adiponectin associated with visceral obesity. Adolescent girls with MS have higher plasma FABP4 level correlated with % of body fat and quantity of SAT.

P2-1130

#### VITAMIN D STATUS AND GLUCOSE METABOLISM IN THE OBESE CHILDREN- PRELIMINARY STUDY

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**Objectives:** Aim. To evaluate the status of vitamin D and carbohydrates metabolism in a group of obese children and adolescents evaluated during 12 months.

**Methods:** We evaluated 86 children, aged  $11,5 \pm 3,8$  years (2-17,9 y), 39,5 % girls ( $n=34$ ) and 60,5% ( $n=52$ ) boys, sex ratio F/M=1/1,5, who were diagnosed as overweight or obese. Their clinical evaluation included anthropometric indexes (weight, height, BMI, results interpreted according to WHO standards) and clinical elements relevant for insulin resistance (purple striae, acanthosis nigricans); besides the usual investigations we determined 25 OH vitamin D (25OHD) levels, blood glucose (fasting and within OGTT), HbA1c, insulinemia (basal /stimulated /OGTT- in selected cases).

**Results:** According to WHO standard criteria: 11 children (12,8%) were overweight, 38 children (44,2%) were obese and 37 children (43%) were severely obese, meaning that the majority presented with important weight excess (87,2%). Depending on the serum 25 OHD levels, we divided the lot in 3 groups: A - 60 cases (69,8%) with vitamin D deficiency ( $<20$  ng/ml), group B - 23 cases (26,7%) vitamin D insufficiency (21 - 29 ng/ml) and group C - 3 cases (3,5 %) vitamin D sufficient ( $>30$  ng/ml). Although most of the recent studies reported a negative correlation between serum 25OHD and fat mass, we found no correlation between IBM (SDS) and serum 25OHD. We found impaired glucose tolerance (IGT) in 5 cases (2 obese and 3 severely obese) - of which 3 associated insulin resistance (IR), all included in group A.

**Conclusions:** Obese children present vitamin D deficiency, which may have negative consequences on glucose

homeostasia and insulin resistance. Precocious nutritional intervention combined with physical activity, aiming for weight loss, together with an appropriate vitamin D supplementation of all obese children could be helpful to avoid the occurrence of metabolic disturbances associated to obesity.

P2-1131

#### SEX DIFFERENCES IN THE IMPACT OF THINNESS, OVERWEIGHT, OBESITY AND PARENTAL HEIGHT ON ADOLESCENT HEIGHT

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**Objectives:** The secular trend of increasing weight may lead to a decline in height gain compared to the genetic height potential. The impact of weight on height in healthy male and female adolescents compared to their genetic height was assessed.

**Methods:** Height and weight were measured in Israeli adolescent military recruits aged 16-19 years between 1967 through 2013. The study population comprised 355,229 recruits for whom parental height measurements were documented. Subjects were classified into four BMI percentile groups according to the US CDC BMI percentiles for age and sex:  $<5^{th}$  (underweight),  $5^{th}$ - $49^{th}$  (low-normal),  $50^{th}$ - $84^{th}$  (high-normal) and  $\geq 85^{th}$  (overweight-obese). Short stature was defined as height  $\leq 3^{rd}$  percentile and tall stature as height  $\geq 90^{th}$  percentile for age and sex.

**Results:** Overweight-obese females had a 73% increased risk for short stature (OR 1.73, 95%CI=1.51-1.97,  $p<0.001$ ). Conversely, underweight females had a 56% lower risk of short stature (OR 0.44, 95%CI=0.28-0.70,  $p=0.001$ ) and a two-fold increased risk for being tall (OR 2.08, 95%CI=1.86-2.32,  $p<0.001$ ). Overweight-obese males had a 23% increased risk of being short (OR 1.23, 95%CI=1.10-1.37,  $p<0.001$ ). Underweight females were on average 4.1 cm taller than their mid-parental height.

**Conclusions:** Overweight-obese males and females had an increased risk of being short compared to those with normal weight. A greater influence of body mass index (BMI) on height was observed in females. Underweight females were significantly taller compared to those with normal weight, and taller than their expected genetic height. The significantly increased height among underweight

INCREASED FATTY ACID DESATURATION ACTIVITY IS LINKED TO RAPID WEIGHT GAIN IN INFANCY BUT NOT EARLY CHILDHOOD

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**Objectives:** Examine whether stearoyl-CoA desaturase isoform-1 (SCD1) activity in cord blood predicts accelerated weight gain during the first 5 years of life. Rapid weight gain in childhood and overweight status at age 5 increase risk for future obesity and metabolic syndrome. Stearoyl-CoA desaturase isoform 1 (SCD1) desaturates saturated fatty acids (FA) stearate (18:0) and palmitate (16:0) to make monounsaturated oleate (18:1n9) and palmitoleate (16:1n7), respectively. Increased SCD1 activity (i.e. desaturation index [DI]: ratio of monounsaturated product to saturated substrate) correlates with increased body mass index (BMI), visceral and subcutaneous adiposity in humans.

**Methods:** Cord blood samples and anthropometric data analyzed from 98 mother-infant pairs meeting inclusion criteria: >35wks gestation, maternal age 18-40 yrs, ≥ 2 risk factors (infant SGA/LGA status, maternal anemia, maternal diabetes, Medicaid insurance, African American, Latina, Asian). Plasma lipids extracted by a modified Folch method with appropriate internal standards added for FA acid quantification and transmethylation efficiency. FA methyl esters analyzed by gas chromatography, and chromatograms analyzed using HP ChemStation software. Results expressed as ug FA/ul plasma. BMI z-scores from WHO growth charts. Correlations between DI and change in BMI z-score (ΔzBMI) evaluated using nonparametric Spearman’s correlation analysis.

**Results:** Mean gestational age was 39.4 (SD 1.2); 51/98 female, 68 Caucasian, 23 C-sections, 29 LGA infants, 21 with maternal diabetes. There was a strong trend toward a positive correlation between DI and weight gain: correlations were 0.16-0.19 between DI and ΔzBMI during the first year (higher DI is associated with a higher ΔzBMI, p=0.094-0.129). Between 1-3 years of age, the DI was non-predictive for changes in BMI z-score. The Table shows correlations between DI and ΔzBMI.

**Conclusions:** Given SCD1’s demonstrated role in hepatic *de novo* lipogenesis, these data suggest that higher neonatal SCD1 activity may contribute to rapid weight gain in infancy. Future studies will reveal whether SCD1 plays as important role in children as it appears to in adults.

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Age	Correlation DI vs. ΔzBMI	95% CI	p-value
< 6 months	0.19	-0.03-0.38	0.094
6-12 months	0.16	-0.05-0.36	0.129
12-24 months	-0.04	-0.26-0.18	0.711
24-36 months	0.07	-0.18-0.32	0.571
36-48 months	0.12	-0.15-0.37	0.376
48-60 months	0.16	-0.20-0.47	0.382

P2-1133

FRUCTOSE LIMITATION AS A PREVENTION STRATEGY FOR PEDIATRIC NON-ALCOHOLIC FATTY LIVER DISEASE

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**Objectives:** Non-alcoholic fatty liver disease (NAFLD) affects 38% of overweight youth. Increased fructose consumption is associated with development and progression of NAFLD, and high fructose corn syrup consumption in the US has increased by 50% over the past decade. However, whether reducing fructose intake in children lowers risk for NAFLD remains unknown.

**Purpose:** To compare the effect of a 6-month low-fructose diet versus control diet on adiposity, indicators of insulin resistance (IR), body composition, and hepatic fat.

**Methods:** Twenty obese youth meeting inclusion/exclusion criteria, age 11-17 years with BMI >95th%tile were stratified by ethnicity and randomized into low fructose or standard weight loss dietary intervention groups. Fasting labs, MRI, DXA, current dietary habits (including fructose and carbohydrate consumption), race and ethnicity, and pubertal stage are assessed at baseline. Dietary adherence is followed obtained with weekly food frequency questionnaire and 24-hr recall at beginning, middle and end of study. Study design/schedule described in Figure 1.

**Results:** Baseline data on first 10 subjects shown in Table 1. HOMA-IR and Matsuda Index indicate significant baseline insulin resistance and baseline fructose intake correlated significantly with HOMA-IR (r=0.77, p=0.01). Mean MRI hepatic fat fraction (7.1±3.3) exceeded the diagnostic threshold for hepatic steatosis (5.6%), correlated significantly with ALT (r=0.68,p=0.03) and showed a correlation trend with HOMA-IR (r=0.60, p=0.07). DXA Brozek Fat Percentage did not correlate with any metabolic measures or with MRI liver fat.

**Conclusions:** This study utilizes new imaging methods to investigate the effect of a fructose-reduction diet on hepatic fat and IR in obese children at high risk for NAFLD. Data collected over the next 6 months will add to knowledge regarding dietary therapy as a strategy for prevention and treatment of NAFLD. Final data analysis will be complete by June 2017.

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PLEASE SEE TABLES ON THE FOLLOWING PAGE



**Figure 1:** Study Design – a total of 20 subjects (12 control, 8 intervention) have completed the study as of March 2017.

	Control n=6	Low Fructose n=4
Age	14.3(1.5)	13.0(0.0)
BMI	33.0(3.1)	34.8(8.8)
Waist Circumference	107.03(11.95)	110.15(12.73)
Fasting Glucose	82.3(3.4)	85.3(1.5)
Fasting Insulin	30.5(24.2)	104(133.8)
Matsuda Index	2.28(1.66)	2.96(3.67)
HOMA-IR	6.29(5.04)	21.99(14.22)
ALT	32.8(8.2)	34.0(18.7)
Liver Pdff	7.6(3.1)	6.3(3.7)
DXA Brozek Fat Percent	33.5(4.5)	40.8(5.6)*
Fructose Intake (grams/day)	1.59(2.00)	5.05(5.54)
Carbohydrate Intake (% daily diet)	50.25(4.99)	48.50(7.33)

Table 1: Data are mean (SD). The only significant difference was higher baseline DXA Brozek Fat Percent in the Low Fructose group (\*p<0.04). Trend toward significant difference in HOMA-IR (p=0.06). Abbreviations: BMI, body mass index; HFF, hepatic proton density fat fraction; HOMA-IR, homeostatic model assessment-insulin resistance; SHBG, sex hormone binding globulin; WC, waist circumference

and 7.9% OB (BMI equal or more than 30 kg/m<sup>2</sup>); at 8 years 67.4% were normoweight, OW 23.5% and OB 9.1%. There are negative association between pregnancy vitamin D status and lipid profile at 8 years [ln(TG/cHDL) and totalCOL/cHDL (r=-0.163, p 0.01 and r=-0.143, p 0.02 respectively)]. Vitamin D status at 8 years was related with BMI category: mean vitamin D 27.03 ng/dl (SD 8.67) in normoweight, 24.52 ng/dl (7.97 SD) in OW and 23.23 ng/dl (SD 9.57) in OB.

**Conclusions:** High prevalence of hypovitaminosis D in pregnancy and at 8 years was detected. Correlation between them was found. An adverse metabolic profile and OW and OB were associated with lower circulating vitamin D levels. Global cardiovascular risk prevention must be started from pregnancy and infancy.

P2-1135

## HOME-BASED PHYSICAL ACTIVITY POSITIVELY AFFECTS CARDIOMETABOLIC RISK FACTORS IN CHILDREN WITH AND WITHOUT PRADER-WILLI SYNDROME

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**Objectives:** Physical activity, independent of diet and body fat level, improves cardiometabolic risk factors in youth with non-syndromic obesity. Prader-Willi Syndrome (PWS) is characterized by excessive adiposity, low lean mass, endocrine abnormalities, and poor spontaneous physical activity, potentially increasing the risk of developing comorbidities. The objective of this study was to determine whether cardiometabolic adaptations occurred in response to a 24-week, home-based physical activity intervention in youth with and without PWS.

**Methods:** Participants included 24 youth with PWS (age=10.3±0.5y; BMIz=1.83±0.18; body fat=46.6±1.8%) and 35 youth classified as obese for age and sex (age=9.5±0.2y; BMIz=2.25±0.07; body fat=45.2±1.1%). Active Play at Home is a home-based, parent-led physical activity program consisting of playground and active video games completed four days per week over a 24-week period. Baseline measurements included anthropometrics, body composition and physical activity. Fasting blood draws were obtained pre and post intervention and were analyzed for glucose, insulin, total cholesterol (TC), triglycerides, high-density lipoprotein (HDL), low-density lipoprotein, c-reactive protein (CRP), interferon-gamma (IFN-γ), interleukins (IL-4, IL-6, IL-8, IL-10), and tumor necrosis factor alpha (TNFα). HOMA was computed as an indicator of insulin resistance.

**Results:** At baseline, youth with PWS presented lower (p<.05) HOMA-IR, IL-10 and TNFα or a statistical trend towards lower (p<.08) glucose, insulin, CRP, and IFNγ than youth with obesity. Conversely, TC and HDL were higher in PWS than youth without PWS (p<.05). In response to the intervention,

P2-1134

## PRENATAL MATERNAL VITAMIN D STATUS AND LIPID PROFILE OF THE OFFSPRING AT 8 YEARS

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**Objectives:** To analyze association of prenatal maternal vitamin D status and ponderal status and metabolic profile at 8 years.

**Methods:** 494 pregnant mothers recruited between 2003 and 2008 from the Spanish population-based cohort study Environment and Childhood [Infancia y Medio Ambiente] Project (INMA). Research protocol was approved by the Ethics Committee. We analyzed circulating 25OH vitamin D, in pregnancy (n 243) and at 8 years (n 255) and body mass index (BMI). Lipid profile was determined at 8 years. We classified as overweight (OW) and obesity (OB) according to IOTF.

**Results:** Mean vitamin D in pregnancy was 28.15 ng/dl (11.04 SD) and at 8 years 26.1 (8.70 DS). 4.6% mothers were underweight (BMI less than 18.5 kg/m<sup>2</sup>), 68.8% normoweight (BMI 18.5-24.9 kg/m<sup>2</sup>), 18.7% had OW (BMI 25-29.9 kg/m<sup>2</sup>)



youth with nonsyndromic obesity demonstrated a decrease in insulin, HOMA-IR and increase in HDL ( $p < .05$ ) while IL-8 decreased in all participants.

**Conclusions:** Youth with PWS presented a better cardiometabolic profile than youth with nonsyndromic obesity, despite similar overall adiposity level and participation in less moderate to vigorous physical activity. The intervention elicited more favorable changes in youth with nonsyndromic obesity than in youth with PWS potentially as those without PWS exhibited a more deleterious cardiometabolic profile at baseline. Supported by US Army Medical Research and Materiel Command Contract W81XWH11-1-0765.

P2-1136

#### VALIDATION OF SURROGATE MARKERS FOR METABOLIC SYNDROME AND CARDIOMETABOLIC RISK FACTOR CLUSTERING IN CHILDREN AND ADOLESCENTS: A NATIONWIDE POPULATION-BASED STUDY

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**Objectives:** The metabolic syndrome (MetS) has been a concern in children and adolescents. However, there is lack of consensus on predicting the definition and risk factors. The present study is to evaluate the prevalence and to validate the anthropometric and laboratory surrogate markers of MetS and cardiometabolic risk factor (CMRF) clustering among Korean children and adolescents.

**Methods:** We used data from the 2011-2014 Korean National Health and Nutrition Examination Survey (KNHANES), which is the nationally representative database. In total, 2,931 subjects (boys 1537, 52.6%) aged 10-19 years were assessed. MetS was defined by the International Diabetes Federation criteria for children and adolescents. The presence of two or more CMRFs among abdominal obesity, hypertension, hyperglycemia, elevated triglyceride (TG), and decreased high density lipoprotein cholesterol (HDL-C) was classified as CMRF clustering. Anthropometric and laboratory parameters including body mass index (BMI) z-score, waist-to-height ratio (WHR), HbA1c, TG/HDL-C ratio, non-HDL-C and alanine aminotransferase (ALT) was evaluated for predicting MetS and CMRF clustering.

**Results:** The prevalence of obesity was 12.7% (boys 15.0% and girls 10.1%). The prevalence of MetS and CMRFs were 1.8% and 8.7% respectively. There were no significant difference between both boys and girls. On multiple logistic regression analysis adjusted for age and gender, predictors for MetS were BMI z-score [OR 12.2 (95% CI 6.8-21.6),  $p < 0.001$ ], HbA1c [OR 6.2 (95% CI 1.3-29.8),  $p = 0.022$ ]. TG/HDL-C ratio [OR 2.4 (95% CI 1.9-3.2),  $p < 0.001$ ] and WHR [OR 1.4 (95% CI 1.3-1.5),  $p < 0.001$ ] were also significantly associated with MetS. Similar patterns were observed when applying the logistic regression analysis to CMRF clustering. In receiver operating curve analysis, area under the curve for MetS and CMRF clustering was largest in WHR and TG-HDL-C ratio.

**Conclusions:** This study demonstrated that the prevalence of MetS and CMRF clustering was 1.8 % and 8.7% in Korean children and adolescents. Most reliable predictors for MetS and CMRF clustering were WHR in anthropometric parameters and TG/HDL-C ratio in laboratory markers. Long-term follow up is needed for evaluation for further validation.

P2-1137

#### TO STUDY THE ASSOCIATION BETWEEN IUGR AND GROWTH PATTERNS AND THE ONSET AND PREVALENCE OF METABOLIC SYNDROME

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**Objectives:** To establish the association between IUGR and growth patterns and the onset and prevalence of metabolic syndrome, also to study the clinical spectrum of metabolic syndrome in childhood and adolescence with relation to risk factors.

**Methods:** This cross sectional observational study was conducted in the Department of Pediatrics, Manipal Hospital, Bangalore (MHB) between July 2014 to October 2016. 27 Infants born with IUGR in MHB in the specified period were recalled for follow up and were subjected to clinical examination for assessment of components of metabolic syndrome such as anthropometric parameters, presence of acanthosis nigricans, measurement of blood pressure and Tanners staging. After obtaining an informed consent, OGTT was performed after an overnight fast, along with lipid profile.

**Results:** In the present study, the age distribution was between the age of 6 to 16 years and mean age of the children in the study group was  $10.59 \pm 2.63$  years. Of the 27 children, 14 (51.8%) were male and 13 (48.2%) were female with a ratio of 1.07:1. The mean value of birth weight and Ponderal Index (PI) were  $2177g \pm 269g$ ,  $2.2 \pm 0.23$  respectively. Positive family history of components of metabolic syndrome was noted in 18 children. 13 (48.1%) were observed in the normal weight for age, 2 (7.40%) were overweight and 12 (44.4%) were found to be obese based on BMI centile cut-offs. Fifteen (55.5%) children had waist hip ratio  $> 0.85$ . Blood pressure was in the normal range for age in 26 (96.3%) children and elevated ( $> 2$  SD) in 1 (3.7%) child. Acanthosis nigricans was present in 11 children (40.7%). OGTT was overtly abnormal in 1 (3.7%) child with elevated fasting and post prandial blood glucose values. 12 (44.4%) children had elevated total cholesterol levels, 6 (22.2%) children had hypertriglyceridemia, and a low HDL level was present in 4 (14.8%) children.

**Conclusions:** On following up children with IUGR status at birth, it was found that the incidence of one of more components of metabolic syndrome was 55.5%. The earliest components of metabolic syndrome to develop are obesity and insulin resistance. Increased catch up growth as evidenced by overweight or obesity after 6 years, increased

calorie intake and positive family history were significant risk factors for the development of metabolic syndrome.

P2-1138

**A MECHANISTIC EXAMINATION OF DIETARY COMPOSITION ON METABOLIC FUEL AVAILABILITY**

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**Objectives:** Weight loss is difficult to maintain, and dietary composition may be a driving factor. A prior study showed that during weight loss maintenance on iso-caloric diets varying in carbohydrate to fat ratio, a higher carbohydrate diet was associated with lower energy expenditure (Ebbeling, JAMA 2012). In a related pilot study, the combined energy availability (circulating level multiplied by relative energy content) of glucose, free fatty acids and ketones was significantly lower 180-300 minutes post-prandially in those on the higher carbohydrate diet (Walsh, PLoS One 2013). For the current study, we hypothesize that during weight loss maintenance, the combined energy availability of metabolic fuels in the late post-prandial period will be lowest and reported hunger will be highest on a high-carbohydrate diet compared to a moderate or low-carbohydrate diet.

**Methods:** This study was conducted within an ongoing large-scale feeding trial in which following weight loss on a standard diet, overweight or obese adults with high BMI were randomized to one of three weight-loss maintenance test diets varying in macronutrient energy contribution as follows: high-carbohydrate diet (HI: 60% carbohydrate, 20% fat, 20% protein), moderate-carbohydrate diet (MOD: 40% carbohydrate, 40% fat, 20% protein) or low-carbohydrate diet (LOW: 20% carbohydrate, 60% fat, 20% protein). 10-15 weeks into the test diet, each subject underwent a 24-hour admission while consuming test diet meals. Blood samples to measure glucose, free fatty acids, beta-hydroxybutyrate, lactate, insulin and glucagon were drawn pre-meal (time 0); at 30, 60, 120, 180, 240 and 300 min post-meal, and overnight. Hunger and satiety levels were measured using a 10 cm visual analog scale. Energy availability was calculated according to Table 1.

**Results:** A total of 30 subjects (18 women, 12 men, aged 19-65 yrs) were enrolled over two cohort-years of the parent study from August 2014 to May 2016. Data analysis is currently ongoing.

**Conclusions:** Utilizing the infrastructure of a large-scale feeding trial, our study may uncover fundamental evidence regarding aims to explore the underlying biological mechanisms contributing to obesity and weight re-gain.

Table 1: Energy Availability (EA) from Metabolic Fuels

Metabolic Fuel	EA (kcal/L)	*= measured level
Glucose	( <sup>*</sup> mg/dL) x (1 g/1000 mg) x (10 dL/1L) x (4 kcal/g)	
Beta-Hydroxybutyrate	( <sup>*</sup> mmol/L) x (1 mol/1000 mmol) x (104 g/mol) x (4.2 kcal/g)	
Free Fatty Acids	( <sup>*</sup> mmol/L) x (1 mol/1000 mmol) x (270 g/mol) x (9 kcal/g)	
Lactate	( <sup>*</sup> mmol/L) x (1 mol/1000 mmol) x (90 g/mol) x (3.6 kcal/g)	

P2-1139

**ASSOCIATION OF SCLEROSTIN AND OSTEOPROTEGERIN WITH GROWTH AND INSULIN RESISTANCE IN CHILDREN AND ADOLESCENTS**

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**Objectives:** Various adipokines are associated with the growth, obesity and insulin resistance. Recently, it has been shown that sclerostin and osteoprotegerin, primarily associated with bone metabolism, are associated with insulin resistance in adults. We aimed to evaluate the association of sclerostin and osteoprotegerin levels with growth, body composition, and parameters of insulin resistance in lean and obese children and adolescents.

**Methods:** We measured sclerostin and osteoprotegerin levels in fasting serum samples of 1377 children and adolescents aged 0.9-18 years from the Leipzig LIFE-Child cohort. We have correlated the sclerostin and osteoprotegerin levels with parameters of growth, body composition, and insulin resistance (based both on the fasting and oGTT values).

**Results:** Sclerostin and osteoprotegerin correlated with height SDS and IGF1 SDS (R=0.140, p<0.001 and R=0.062, p=0.023 for sclerostin, and R=-0.057, p=0.035 and R=-0.100, p<0.001 for osteoprotegerin). Both sclerostin ( $\beta$  = 0.09  $\pm$  0.03, p=0.002) and osteoprotegerin ( $\beta$  = -0.06  $\pm$  0.03, p=0.039) were beside BMI SDS, IGF1-SDS, gender, and pubertal status independent predictors of height SDS. Sclerostin (R=0.136, p<0.001) and osteoprotegerin (R=-0.098, p<0.001) correlated mildly with the BMI SDS corrected for height SDS, and osteoprotegerin also with body fat content (R=-0.256, p=0.001, controlled for age, sex, height SDS, BMI SDS and pubertal development). Independent of this association with obesity, both cytokines also correlated with 2h oGTT insulin (R=0.139, p=0.05 for sclerostin, and R=0.183, p=0.009 for osteoprotegerin), and AUC<sub>INS</sub>/AUC<sub>GLU</sub> (R=0.143, p=0.042 for sclerostin, and R=0.142, p=0.045 for osteoprotegerin), both controlled for age, sex, height SDS, BMI SDS and pubertal development.

**Conclusions:** Beyond the known association of the bone-derived cytokines sclerostin and osteoprotegerin with height, we found them mildly related to obesity and glucose induced insulin secretion.

P2-1140

**LONG-TERM SAFETY STUDY ON STATIN TREATMENT IN CHILDREN WITH SEVERE HYPERCHOLESTEROLEMIA**

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**Objectives:** One of the most serious side-effects of statin treatment reported in adults is rhabdomyolysis, which can be



detected by a laboratory finding of elevated levels of creatine phosphokinase (CPK). With the American Academy of Pediatrics' guidelines for treating children with severe hypercholesterolemia with pharmacologic therapy, an increasing number of children are being treated with statins. Although statin treatment is generally considered safe, limited study has been conducted on whether children on this treatment could develop serious side effects, such as rhabdomyolysis. The purpose of this study is to investigate the effect of statins on rhabdomyolysis in children with hypercholesterolemia.

**Methods:** This is a retrospective study of 106 pediatric patients ( $\leq 18$  years) with severe hypercholesterolemia and on statin treatments. CPK levels used as a proxy for rhabdomyolysis were measured at five intervals (in months): 0, 1-6, 7-12, 13-24, and 25-36. Tests of between and within group differences were conducted using the independent and dependent *t*-tests, respectively. Data represented as M (sd) with respective *t* and *p* values.

**Results:** There were no statistically significant differences in CPK levels from baseline to 1-6 mo: 105.75 (49) and 109.70 (63), respectively (*t* (121) = 1.75, *p* = .710). Similarly, no differences were observed at the baseline and other time intervals: 7-12 mo [127.08 (76); *t* (111) = 1.70, *p* = .09], 13-24 mo [125.45 (77); *t* (102) = 1.37, *p* = .175] and for 25-36 mo [115.13 (66); *t* (93) = .501, *p* = .62]. For paired data, no statistically significant differences were noted in CPK levels from baseline to 1-6 mo: 104.78 (49) and 107 (62), respectively (*t* (37) = .359, *p* = .721). Similarly, no differences were observed at the baseline and 7-12 mo [123.17 (76); *t* (26) = 1.83, *p* = .08], 13-24 mo [117.61 (77); *t* (18) = 1.67, *p* = .112] and for 25-36 mo [115.13 (66); *t* (7) = .999, *p* = .351].

**Conclusions:** According to the present study there is no clinical evidence of rhabdomyolysis in children being treated with statins for up to 3 years. This suggests that statin treatment is safe for children with severe hypercholesterolemia. Specifically, children treated with statins do not seem to have increased risk of rhabdomyolysis.

P2-1141

#### EFFECT OF TNF-ALPHA TREATMENT ON MIRNA EXPRESSION IN ADIPOCYTES

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**Objectives:** MicroRNA (miRNA) are small, non-coding RNAs that bind to complementary sequences within the 3' untranslated region of mRNAs and thereby modulate protein production, typically degrading or repressing translation of targeted mRNAs. A recent study has shown that several miRNAs are differentially expressed in subcutaneous adipose from obese individuals. It is known that obesity results in an inflammatory milieu which may drive some of the changes

seen in miRNA expression. In the present project, we tested the hypothesis that the observed increase in miRNA expression in adipose tissue is due, in part, to inflammatory cytokines specifically TNF- $\alpha$ .

**Methods:** Fully differentiated 3T3-L1 adipocytes were treated with 250 pM TNF- $\alpha$  for 96 hours. Media was changed every 24 hours and conditioned media from the final 24 hours of exposure was collected for exosome extraction. RNA was then extracted from the adipocytes as well as the cell culture supernatants and quantified by PCR. Transcription of GLUT4 and IL-6 were measured to assess for inflammatory changes related to TNF- $\alpha$ .

**Results:** TNF- $\alpha$  reduced GLUT4 transcription by 64% ( $p < 0.001$ ), and IL-6 was increased 23-fold ( $p < 0.001$ ), both consistent with an inflammatory response. miR-155 increased 19-fold in adipocytes exposed to TNF- $\alpha$  ( $p = 0.004$ ). There was no difference in miR-130b or miR-210 with exposure to TNF- $\alpha$ . In the exosomes secreted into the media by 3T3L1 cells, miR-130b and miR-210 were increased after TNF- $\alpha$  exposure by 2.4- and 3.1-fold ( $p = 0.0013$  and  $p = 0.0047$ ), respectively.

**Conclusions:** The results suggest that inflammatory cytokines such as TNF- $\alpha$  display differential effects on miRNA expression and secretion in the adipocyte. miR-155 has been implicated in inflammation and predicted to target HIF-1 $\alpha$  suggesting a potential link between inflammation and energy metabolism. Future work is needed to understand the mechanisms behind the differential expression of miRNAs within adipose tissue as well as the impact of the differentially expressed miRNAs on their targets and downstream signaling.

P2-1142

#### PHYSICAL ACTIVITY DIFFERENCES AND RELATIONSHIP WITH VISCERAL ADIPOSITY IN YOUTH WITH AND WITHOUT DOWN SYNDROME

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**Objectives:** Reduced physical activity (PA) likely contributes to childhood prevalence of excess adiposity. In typically developing children, PA declines with age and is lower in girls. Children with Down syndrome (DS) are at increased obesity risk, particularly adolescent DS females. We aim to determine if youth with and without DS are similar in their age and sex-related PA patterns, and if PA is associated differently with BMI and visceral adiposity (VFAT) in DS.

**Methods:** Moderate to vigorous activity min/d (MVPA,  $\geq 3.0$  METs) was compared between youth with DS and typically-developing youth of comparable age, sex, race, and BMI%ile using accelerometry (Sensewear®). Armband wear  $\geq 20$  hrs/d

for ≥2 weekdays and ≥1 weekend days over a 7-d period was required for inclusion in analyses. Linear regression models tested group differences in the associations between 1)age and 2)sex with MVPA and MVPA with 1)BMI and 2)BMIZ adjusted VFAT (measured by dual x-ray absorptiometry) adjusted for age, sex, and race.

**Results:** DS youth [28M/49F,age 15.1±3.4y,14% African-American (AA),median (min, max)73min(0, 290)] were compared to typically-developing peers [23M/20F,age 15.4±3.1y,23% AA,109min(6, 339)] of similar BMIZ(p=0.38). In a BMI, age, and sex-adjusted model, MVPA was lower in females(p=0.04) and DS(p=0.009). A DS\*age but no DS\*sex interaction was present: MVPA declined less in DS with increasing age(p=0.03), and females with DS did not show greater decline in MVPA vs controls(p=0.18). As expected, MVPA was negatively associated with BMI(p=0.02) and VFAT(p=0.03); given the recruitment strategy, DS and controls did not differ in the association of MVPA with BMI(p=0.9). However, despite similar BMIZ and a tendency toward lower MVPA, VFAT was lower in DS(16.9 cm2,p=<0.0001), but with no DS\*MVPA interaction(p=0.94). **Conclusions:** We demonstrate sex differences and age declines in MVPA and less MVPA in DS. However, DS females did not show as great of declines in MVPA with increasing age, suggesting further reduction in MVPA with age in DS females does not fully explain their greater increase in BMI during later adolescence. MVPA is associated with VFAT, a cardiometabolically active depot, suggesting MVPA may help maintain lower VFAT in both DS and typically developing peers.

P2-1143

**POLYCYSTIC OVARY SYNDROME IN OBESE ADOLESCENTS: ANOTHER RISK FACTOR FOR METABOLIC SYNDROME?**  
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**Objectives:** To evaluate the association between polycystic ovary syndrome (PCOS) and metabolic syndrome (MS) in obese adolescents from the Weight and Management Outpatient Clinic.  
**Methods:** We performed a cross-sectional study with 49 postmenarcheal obese adolescents, with mean age of 15.6 years and mean BMI of 34.6kg/m2. Clinical, anthropometric and medical records were reviewed. PCOS was considered when both menstrual irregularity and hyperandrogenism were present. Clinical hyperandrogenism was considered as severe hirsutism, quantified through the Ferriman-Gallwey index ≥ 8. Serum hyperandrogenism was considered when the androgen levels were above the cut-off values for the method. MS was considered when the patient presented with waist circumference > p95 associated with at least two of the

following parameters: high density lipoprotein (HDL) < 40 mg/dl; triglycerides (TG) > 130 mg/dl; high blood pressure; fasting blood glucose > 100 mg / dl.  
**Results:** We found 18.4% of PCOS in our population of obese adolescents. Irregular menstrual cycles were found in 65.3% of the patients. Clinical hyperandrogenism was observed in 16.3% of the girls, and 18.4% had total testosterone concentrations above the normal range (Table 1). When we analyzed the presence of MS in obese adolescents with PCOS and without PCOS (Table 2), we found 4/9 (44.4%) vs. 4/40 (10%), respectively, with p value of 0.028. The only variable of MS that differed statistically between the groups was TG ≥ 130 (p = 0.028).

**Conclusions:** Obese adolescents with PCOS had a higher prevalence of MS than obese adolescents without PCOS.

Table 1. Variables used to diagnose polycystic ovarian syndrome.

Variables	n (total: 49) (%)	CI (95%)
Chronic anovulation	Irregular menstrual cycle	32 (65.3%)
Clinical Hyperandrogenism	Hirsutism (F-G ≥ 8)	8 (16.3%)
Serum Hyperandrogenism	Total Testosterone > 48 ng/dl	9 (18.4%)
	Free Testosterone > 37 pmol/l	5 (10.2%)

n: number of subjects with abnormality; F-G: Ferriman-Gallwey index;

Table 2. Comparison of continuous variables (mean ± SD) and categorical variables (absolute number and percentage) of polycystic ovary syndrome (PCOS), using Witchel *et al.* consensus, and metabolic syndrome.

	OAwithoutPCOS (n=40)	OAwithPCOS (n=9)	p
Age (years)	14.6 ± 2.2	15.3 ± 2	0.387
Weight (kg)	90.2 ± 19	96.9 ± 17.5	0.245
BMI (kg/m²)	34.4 ± 6.5	35.5 ± 5.6	0.453
Total Testosterone (ng/dl)	30 ± 14.7	49.2 ± 22.9	0.013
Free Testosterone (pmol/l)	18.1 ± 15.4	31.4 ± 19.6	0.036
Irregular menstrual cycle	8/40 (20%)	9/9 (100%)	0.001
Hirsutism (F-G>8)	3/40 (7.5%)	5/9 (55.6%)	0.003
Total testosterone > 48 (ng/ml)	4/40 (10%)	5/9 (55.6%)	0.006
Free Testosterone > 37 (pmol/l)	2/40 (5%)	3/9 (33.3%)	0.037
Waist Circumference > p95	37/40 (92.5%)	6/9 (66.7%)	0.067

P2-1144

**EARLY OBESITY AND FUTURE CARDIOMETABOLIC RISK IN A LATINO COHORT: A MATTER OF TIMING OR TRACKING?**  
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**Objectives:** Early obesity (EO) is associated with obesity, insulin resistance (IR) and cardiometabolic (CM) risk later in

life. Prenatal nutritional environment determines epigenetic programming of metabolism that allows adaptation to the external environment. In affluent environments, however, it predisposes to CM disorders. We compared the CM profile in adolescence and emerging adulthood of youths with and without EO (defined by an onset ≤5y) and explored the association of age of onset and persistence of obesity with the CM profile of adolescence and emerging adulthood.

**Methods:** Observational prospective study in 328 22y (51% males) from an infancy cohort in Chile. BMI was measured at 5y, 10y, 16y, 22y. Waist circumference (WC), fat mass (FM%; DEXA), arterial blood pressure (BP), triglycerides (TG), HDL, glucose, insulin and leptin were measured at 16y and 22y. BMIz, HOMA, and Metabolic Syndrome z-score (zMetS) were calculated. Four groups were defined: participants who were never obese (NOB); participants who were obese at 5y but not at 16y and 22y (formerly obese,FOB); participants diagnosed with obesity at 16y or 22y (recent onset obese,ROB); and participants who were obese at 5y and remained obese in subsequent assessments (persistently obese,POB). ANCOVA examined the associations of age of onset and persistence of obesity with CM markers at 16y and 22y.

**Results:** In the sample 19% had EO, of whom ≈50% were no longer obese in adolescence. EO was associated with higher prevalence of obesity ( $P<0.001$ ), higher BMIz, WC, FM, BP, TG, leptin and zMetS at 16y and 22y ( $P<0.001$ ) and higher insulin and HOMA-IR at 16y ( $P<0.001$ ). After controlling obesity status group, ROB and POB participants had the greatest deterioration in their CM profile at 16y and 22y, with significantly higher values in all CM markers and lower values of HDL compared to NOB participants. Compared to NOB participants, FOB ones only had higher ( $P<0.01$ ) BMIz, WC and BP.

**Conclusions:** In this Latino cohort, current and persistent obesity were more important than EO in predicting CM profile in adolescence and emerging adulthood. Early intervention of obese children might be key to prevent future CM risk. **Funding:** NHLBIHL088530;CONICYT79140003

P2-1145

**METFORMIN: EFFECTIVENESS IN WEIGHT LOSS IN ADOLESCENTS WITH INSULIN RESISTANCE AFTER 12 MONTHS OF TREATMENT COMPARED TO THE CONTROL GROUP**

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**Objectives:** The aim of this study is to demonstrate our experience related to use of metformin in obese children and adolescents with IR, and evaluate the benefits in weight loss after 12 months of treatment compared to the control group.

**Methods:** Retrospective study of 41 children and adolescents followed in the Pediatric Endocrinology Clinic ICR-FMUSP, due to obesity and IR, at baseline and after a year of use of metformin, compared to the control group. Exclusion criteria: T2DM, Neurological disorders with or without mental impairments and use of other weight related medications. Clinical (age, gender, weight, height, waist circumference, BMI, pubertal stage) and biochemical (fasting glucose, insulin, cholesterol and its fractions) data were analyzed. IR was identified by HOMA-IR.

**Results:** Metformin cohort: Mean age  $11\pm2.2$ , 50% female. At baseline and one year after metformin, the values of the studied variables were, respectively: HOMA-IR:  $4.7\pm2.5$ ,  $3.56\pm1.8$ ( $p=0.005$ ); Fast insulin  $23\pm9.5$ ,  $17.3\pm9.1$ ( $p<0.001$ ); BMI score  $3.2\pm0.67$ ,  $2.9\pm0.58$ ( $p<0.001$ ). Fasting glucose decrease ( $p=0.005$ ), as well as abdominal circumference ( $p=0.029$ ). There were no significant differences in outcomes after analyzing only the control group.

**Conclusions:** Metformin improves IR, and provides a statically significant, but very modest reduction in BMI and abdominal circumference. Subgroup analyses in a large scale trial is needed to know if there is any specific group who may have clinical and not just statistical benefit from treatment with metformin.

P2-1146

**METABOLIC SYNDROME (MS) AND CARDIOVASCULAR RISK (CV) IN PERIPUBERTAL AND ADOLESCENT CHILDHOOD CANCER SURVIVORS (CCS)**

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**Objectives:** Pediatric CCS have greater CV risk than healthy children, but data are limited. Aim of the study was to

Table 1 Anthropometric and cardiometabolic profile in adolescence and emerging adulthood by presence of early obesity (EO)

	Adolescence (16-17y)				Emerging adulthood (22-23y)			
	EO (+)		EO (-)		EO (+)		EO (-)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (y)	16.8	0.3	16.8	0.3	22.4	0.5	22.5	0.2
BMI	28.7	5.5	22.3	3.3	32.4	6.4	25.3	4.7
Total Fat Mass (%)	35.9	11.0	26.5	11.0	41.3	8.4	34.6	9.2
Waist circumference (cm)	92.9	13.4	77.8	8.8	94.5	13.9	79.7	10.2
Systolic BP (mm Hg)	117.0	12.4	110.4	9.8	117.0	11.7	110.3	11.3
Diastolic BP (mm Hg)	72.0	7.6	68.7	6.9	73.3	7.9	68.6	7.7
Glycaemia (mg/dl)	87.6	10.4	87.5	10.4	91.1	11.3	90.2	9.4
Insulin (uU/ml)	11.1	8.5	7.4	4.9	15.8	12.4	14.3	9.9
HOMA-IR	2.5	2.0	1.6	1.2	3.6	2.9	3.2	2.3
SPIN Index	5.7	1.8	8.0	1.9	4.8	1.6	7.0	2.0
Triglycerides (mg/dl)	98.9	59.1	83.5	47.5	113.4	59.9	96.6	62.6
HDL (mg/dl)	35.8	10.1	38.0	16.0	41.6	14.3	45.2	12.7
TG:HDL Index	3.2	2.5	2.4	1.8	3.3	2.5	2.4	1.9
Metabolic Syndrome (z score)	0.47	0.7	0.05	1.1	0.05	0.8	-0.48	0.7
Leptin (males) (µg/L)	9.7	10.5	7.0	10.5	12.4	10.6	5.6	7.7
Leptin (females)(µg/L)	27.4	21.5	18.3	12.2	40.6	17.3	24.3	7.4

Early obesity defined by an onset ≤5y. Statistical significance (Student's t test): \* $P<0.05$ , \*\* $P<0.01$ , \*\*\* $P<0.001$

evaluate the prevalence of the MS based on the IDF 2007 criteria and of the CV risks in a large single center cohort of young CCS.

**Methods:** Two-hundred and six adolescents (111M, 95F) were evaluated after a median off-therapy of 8.1 years since cancer diagnosis. All subjects underwent height, weight, BMI, waist and hip circumference-WC and HC, blood pressure, tryglicerides-TG, HDL and LDL cholesterol, glycemia, insulin, fT4 evaluations. The IDF 2007 criteria were applied for MS definition (CV>90th percentile plus at least 2 of the following: TG>150 mg/dl, HDL130/85 mmHg, baseline glycemia>100 mg/dl or type 2 diabetes).

**Results:** We found a 3.9% prevalence of MS (n=8,3F,5M) that increased up to 9.9% (n=8/81,53M,28F) in the obese population (BMI-SDS>2), and no associations between the MS and type of tumor or previous cancer treatment; subjects with brain tumor displayed an increase of LDL, TG and WC/HC ratio (all P values<0.05) compared to other cancer groups. Multiple logistic regression analyses demonstrated that the model with a BMI-SDS>2.24 and a baseline insulin >10.8μU/mL perfectly predicted the MS; subjects with a WC/height ratio>0.53 (OR<sub>adj</sub>:41.6;p<0.0001) and fT4 adj:10.6;p=0.007) presented also a higher MS risk compared to patients not satisfying these cut-offs. Central adiposity (WC>90<sup>th</sup> percentile) was found in 52.4% of the cohort (n=108/206,n=61M,n=47F);BMI-SDS>2.24(p<0.0001), insulin>10.8μU/mL (p<0.0001) and prepubertal Tanner stage (p=0.012) were associated to it. A perfect prediction of central adiposity was obtained by a systolic BPvalue >130 mmHg; furthermore, subjects with a BMI-SDS >2.24 (OR<sub>adj</sub>: 148.7; p<0.0001) and a follow-up since cancer diagnosis 9.7 years (OR<sub>adj</sub>: 2.6; p=0.014) presented an increased risk of having a WC>90<sup>th</sup> centile.

**Conclusions:** In our cohort we found a MS prevalence of 3.9%, 8 years after off-therapy, that increased up to 10% in the obese cohort. Central adiposity was found in 52.4% of the population, highlighting an early potential CV morbidity. Specific cut-off for BMI, insulin, fT4 and WC/height ratio could be predictors for developing a MS or CV risk.

## POSTER SESSION 2

Friday, September 15, 2017, 11:30am-12:30pm

P2 - Other

P2-1200 – P2-1208

P2-1200

### ASSESSING OVARIAN FUNCTION AFTER PEDIATRIC CANCER TREATMENT – WHAT DOES ANTI-MULLERIAN HORMONE ADD?

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University and Children's Healthcare of Atlanta, Atlanta, GA, United States

**Objectives:** This study describes ovarian reserve in pediatric cancer survivors at risk for infertility using anti-mullerian hormone (AMH) and follicle-stimulating hormone (FSH).

**Methods:** A retrospective analysis of 11-21 year old females ≥2 years since cancer treatment seen in our survivor clinic (n=341) between 1/2014-8/2016 was performed. FSH and AMH levels were measured in patients who received gonadotoxic therapies: bone marrow transplant (BMT), ovarian radiation, alkylators (cyclophosphamide equivalent doses (CED)), heavy metals, and/or oophorectomy. Those on hormone therapy or who received ≥30 Gy cranial radiation were excluded. Ovarian reserve was classified as normal, diminished (AMH below assay age-specific normal range) or depleted (AMH below assay sensitivity limit). Ovarian function was classified as menopausal (FSH >40mIU/mL) or non-menopausal. Univariate associations of demographic and treatment variables with AMH-FSH subgroups were performed.

**Results:** Among all survivors seen in clinic, 89% were at risk for infertility; of those, 180 were eligible for this analysis (55% non-Hispanic white and 41% leukemia survivors). Low AMH was found in 34% (15% diminished, 19% depleted). Non-menopausal FSH was found in 56% of survivors with low AMH. Blacks and Hispanics were more likely than whites to have low AMH with non-menopausal FSH (26%, 32% vs 10%, p=0.01) as were those diagnosed ≥13 years old (35% vs 16%, p=0.04). Additionally, all treatment groups were significantly more likely to have low AMH with non-menopausal FSH as compared to CED <7.5 gm/m<sup>2</sup> except those treated with heavy metals only or those who received low dose CED with ovarian radiation. Menopausal FSH was found in 27 survivors and was more likely after BMT or >15 gm/m<sup>2</sup> CED with ovarian radiation as compared to those who received CED <7.5 gm/m<sup>2</sup> (68%, 55% vs 1%, respectively, p<0.001).

**Conclusions:** Current survivor care guidelines recommend screening for infertility in at risk cancer survivors with FSH. However, AMH detects a decline in ovarian reserve, even when FSH is normal. Adding AMH to screening could result in early referral of survivors to specialists for counseling while others could be cautiously reassured.

P2-1201

### ADHERENCE TO TREATMENT WITH ZOMAJET, A NEEDLE-FREE DEVICE TRANSJECTING GROWTH HORMONE: RESULTS OF A FRENCH OBSERVATIONAL SURVEY

Mohita Kumar, MD, Ferring Pharmaceuticals Inc., Parsippany, NJ, United States; Jacques Weill, MD, Lille University Hospital, Lille, France; Bradley S. Miller, MD, PhD, University of Minnesota Masonic Children's Hospital, Minneapolis, MN, United States; Phillipe Niez, MD, Ferring SAS, Gentilly, France

**Objectives:** Injection pain and needle phobia compromise treatment compliance in growth hormone deficiency (GHD). Needle-free devices may improve compliance. This study

evaluated pediatric compliance with somatropin (Zomacton™) delivered via ZomaJet needle-free devices (ZomaJet Vision X or ZomaJet 2 Vision).

**Methods:** This 3-year multicenter, longitudinal, observational study followed subjects with GHD or Turner syndrome according to usual practice. Primary endpoint was mean compliance rate (cumulative treatment duration/total duration). Reasons for noncompliance/stopping treatment were recorded. Missing durations were matched to zero (maximum bias method). The intent-to-treat (ITT) population received  $\geq 1$  ZomaJet transjection, and the per-protocol (PP) population comprised ITT subjects without protocol violations.

**Results:** Eighteen pediatric endocrinologists enrolled 83 subjects; mean (SD) age was 9.5 (3.8) years, and mean (SD) height SD score was  $-2.2$  (1.0) cm. Most subjects (79 [95.2%]) were GH therapy naïve, and median duration of ZomaJet use was 1.8 years. Fifty-seven subjects (68.7%) used ZomaJet Vision X 10 mg, and 26 (31.3%) used ZomaJet 2 Vision 4 mg; baseline mean (SD) weekly dose was 0.25 (0.04) mg/kg. Over 3 years, mean (SD) compliance rates were 96.6% (9.1%; 95% CI: 94.6–98.6) in ITT (n=83) and 96.8% (8.1%; 95% CI: 95.0–98.7) in PP (n=74). Rates were high among children aged  $<11$  years (years 1–2: 91.1% [15.5%]; years 2–3: 99.5% [1.2%]) and adolescents aged  $\geq 11$  years (96.5% [6.8%]; 97.6% [4.9%]) in PP. Mean (SD) annual height gain was 8.8 (2.2), 7.8 (1.8), and 5.8 (1.8) cm after 1, 2, and 3 years, respectively. Seventeen subjects (20.5%) reported technical difficulties using the device; 3 (3.6%) stopped treatment. Treatment was generally well tolerated, although 22 subjects (26.5%) poorly tolerated  $\geq 1$  injection and 14 (16.9%) had injection-site reactions (ISRs; ie, hematoma, pain, bleeding, or edema). Local intolerance was attributed to the medication in 1 subject (1.2%) and the device in 7 (8.4%).

**Conclusions:** Subjects receiving somatropin administered via ZomaJet needle-free devices had high compliance rates and good clinical outcomes, despite some reports of poor tolerability and ISRs.

P2-1202

#### PREDICTORS OF LONG-TERM GLYCEMIC CONTROL IN CHILDREN WITH CHRONIC PANCREATITIS AND INTRACTABLE PAIN, FOLLOWING TOTAL PANCREATECTOMY & ISLET CELL AUTOTRANSPLANTATION (TPIAT).

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**Objectives:** To investigate the predictors of long-term insulin requirements in Children with chronic Pancreatitis (CP) who underwent TPIAT.

**Methods:** Thirteen patients (Pts) (7 males), age range 7-17 (median 10.3) years with CP underwent TPIAT between 2009-2016. Islet cells were separated after TP and infused into the portal vein. All Pts had normal glucose parameters before TPIAT (fasting glucose, HbA1C, and, in a subgroup, response to a mixed-meal tolerance test). Six (46 %) had a PRSS1

(protease, serine, 1) mutation, 2 (15.4 %) had a CFTR (Cystic fibrosis transmembrane conductance regulator) mutation, 2 (15.4 %) had combined CFTR/SPINK1 (serine protease inhibitor, Kazal-type, 1) mutations.

**Results:** All Pts were evaluated 6 months after TPIAT. Five Pts (38 %) required no insulin (HbA1c 5.5-6.1%), 3 Pts (23 %) required basal insulin only (0.03-0.35 U/Kg/day), with HbA1c of 5.5-6.7%, and 5 Pts (39 %) required MDI (0.5-1 U/Kg/d, median 0.6) with HbA1c of 6.8-10.2%, median 7.6%. Insulin requirements (U/kg/d) did not correlate with patients' age at time of presentation ( $r=0.14$ ) or at time of surgery ( $r=0.12$ ), duration of symptoms prior to surgery ( $r=-0.04$ ), BMI SDS ( $r=0.18$ ) or HbA1c prior to surgery ( $r=0.2$ ), or the number of islets/kg infused ( $r = -0.21$ ) (All:  $p>0.10$ ). ). Of the 6 patients with PRSS1 mutation, 4 required no insulin at 6 months, 1 required  $<0.1$  U/Kg/D of basal insulin and 1 required 0.6 U/Kg/d as MDI. All 4 patients with CFTR/SPINK mutations required insulin (MDI in 2 Pts) at doses of 0.23-0.75 U/Kg/d. Thus, Pts with PRSS1 mutation had borderline lower ( $p=0.05$ , t-test) insulin requirements (0.1 U/kg/day) than Pts with CFTR/SPINK mutation (0.46 U/kg/day).

**Conclusions:** 1) Children with CP undergoing TPIAT after years of symptoms were able to maintain normal glucose homeostasis before surgery, and the majority (61%) did not require insulin, or just required basal insulin, 6 months after surgery.

2) Variables associated with endocrine outcome in adults with CP (duration of symptoms, the number of islet cell/Kg infused, BMI) did not predict such outcome in children.

3) Genetic markers (PRSS1 vs. CFTR and SPINK mutations) may be important as predictors of endocrine outcome in children with CP.

P2-1203

#### PERMANENT NEONATAL DIABETES MELLITUS (PNDM) CAUSED BY 6Q24 ABNORMALITIES

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**Background:** Transient Neonatal Diabetes Mellitus (TNDM) is the more common type of Neonatal Diabetes Mellitus (NDM). In most of the cases, gradual improvement of hyperglycaemia and spontaneous remission are seen at the age of 3 months, but in approximately 50% of those patients, diabetes, usually type 2 diabetes mellitus, recurs during puberty or adulthood. Abnormalities in the imprinted locus on chromosome 6q24 are the most common causes of TNDM. However, PNDM is consistent with no remission, the main causes of which are KCNJ11 and ABCC8 mutations. There are also over 20 rarely-seen genetic mutations including GCK and INS. This research reports a case of NDM who is small for gestational age and found to have hyperglycaemia one day after birth with no other systematic congenital anomaly.

**Methods:** The patient was followed up from birth to 5.5 years old. Sequencing analysis of the KCNJ11, ABCC8 and INS genes in the baby has failed to identify a mutation. SNP array (

HumanCytoSNP-12 chips(31K)) was used to detect methylation abnormalities. A next-generation sequencing to sequence whole genome to find whether there was coding and non-coding mutation.

#### Results:

1. Methylation-Specific PCR (MS-PCR) found out the defect of DNA methylation in the differentially methylated region (DMR) on chromosome 6q24 and hence, the patient was predicted to have TNDM. After the follow-up till 5.5 years old showed no remission of diabetes and the patient's reliance on insulin, the patient was diagnosed with PNDM. SNP array and highly polymorphic short tandem repeat (STR) analysis identified UPD6, and genome-wide analysis ruled out mutations in coding and Non-coding regions. Therefore, the patient was confirmed to have methylation defects at chromosome 6q24 – UPD6-induced PNDM.

**Conclusions:** This report expands the varieties of diabetes that is induced by methylation defect at chromosome 6q24. This indicates that 6q24 abnormalities might also cause PNDM, so it is recommended that 6q24 abnormalities should be tested when the cause of PNDM is unknown.

P2-1204

#### A CASE OF TRANSIENT NEONATAL DIABETES ASSOCIATED WITH A NOVEL KCNJ11 MUTATION

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**Objectives:** Neonatal diabetes (ND) is a rare type of diabetes that presents in the first 6 months of life. Alterations in 23 genetic loci have been reported so far to be associated with ND. Activating mutations of the *KCNJ11* gene encoding for the Kir6.2 subunit of the  $K_{ATP}$  channel can lead to transient (TNDM) or permanent neonatal diabetes mellitus (PNDM).

**Methods:** A female infant presented at the 22<sup>nd</sup> day of life with severe hyperglycemia and ketoacidosis (glucose: 907mg/dl, blood gas pH: 6.84,  $HCO_3^-$ : 6mmol/l). She had a septic screen and was managed with intravenous (IV) fluids, IV insulin and IV antibiotics. Ketoacidosis resolved within 48 hours and she was started on subcutaneous insulin injections with intermediate acting insulin NPH twice daily, requiring initially 0.75-1.35 IU/kg/d.

**Results:** Pre-prandial C-peptide levels were 0.1 ng/ml (normal:1.77-4.68) and all diabetic autoantibodies (DAA) were negative. Growth and psychomotor development were normal. Insulin requirements were gradually reduced and insulin administration was discontinued at the age of 10 months. Subsequent glucose levels and HbA1c levels were normal. C-peptide levels had normalized (pre-prandial: 1.6 ng/ml, postprandial > 2 ng/ml; normal:1.1-4.4). Genetic analysis revealed a novel missense mutation (p.P254Q) in the *KCNJ11* gene confirming the diagnosis of TNDM.

**Conclusions:** We report a novel *KCNJ11* mutation in a patient who presented in the first month of life with a phenotype of ND, that subsided at the age of 10 months. It seems that the novel p.P254Q mutation results in mild impairment of  $K_{ATP}$  channel function leading to TNDM.

P2-1205

#### ISLET-AFTER-LUNG AND LIVER TRANSPLANTATION IN A PEDIATRIC PATIENT WITH CYSTIC FIBROSIS-RELATED DIABETES

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**Objectives:** We report the case of an islet-after-lung and liver transplantation in an adolescent aged 14 years, for cystic fibrosis-related diabetes (CFRD).

**Methods:** The patient was diagnosed with cystic fibrosis (CF) at the age of 14 months, due to a homozygous delta F508 *CFTR* mutation. Lung function, weight gain and growth were acceptable during the first 10 years of life, until diagnosis of CFRD. After this, BMI and lung function began to decline despite insulin treatment and nocturnal enteral feeding via a gastrostomy. Pulmonary transplantation was needed because of severely impaired forced expiratory volume, 2 pulmonary hemorrhages and necessity of  $O_2$  administration over night. Liver transplantation was decided due to cholestatic liver cirrhosis and severe portal hypertension.

**Results:** At the age of 13 years and 8 months, the patient's BMI was 14.9kg/m<sup>2</sup> (< 3<sup>rd</sup> percentile). Pubertal development was Tanner stage II. Antibodies against GAD65, IA2, insulin and islet cells were negative. He received insulin at a dose of 1.11 units/kg/day and HbA1C was 7.3% (57.4 mmol/mol). Lung and liver were transplanted at the age of 14 years and 6 months. The first islet transplantation was performed 10 days later, after reducing glucocorticoids. Six months later, peak C-peptide secretion after arginine stimulation was disappointing with peak values of 371 pmol/l (versus 569 pmol/l before transplantation) and insulin doses were unchanged (1.4 units/kg/day). A second islet transplantation was performed at the age of 15 years and 2 months, a third at 16 years and 2 months. After this, peak arginine-stimulated C-peptide secretion increased to 2956 pmol/l and insulin doses could be reduced to 0.82 units/kg/day, while prednisone treatment was 5mg/day. HbA1C decreased to 5.9% (41.0 mmol/mol). BMI increased to 18.8kg/m<sup>2</sup> (25<sup>th</sup> percentile).

**Conclusions:** Islet transplantation after lung and liver transplant is feasible but several islet transplants may be necessary to improve C-peptide secretion, decrease insulin needs and decrease HbA1C. Absence of diabetes being associated to improved long term function of liver and lung grafts, we hypothesize that improved diabetes control thanks

to islet transplantations will improve long term outcome of the patient.

P2-1206

#### **HYPOGLYCEMIA DUE TO HYPERINSULINEMIA RELATED TO 6-MERCAPTOPYRINE (6-MP) IN A CHILD WITH ACUTE LYMPHOBLASTIC LEUKEMIA**

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**Objectives:** Hyperinsulinemia probably due to 6-MP has been rarely reported in the world. This is the first case who developed hyperinsulinemia by 6-MP in Korean children with leukemia.

**Methods:** Medical records were reviewed retrospectively

**Results:** A 8 yrs old boy with acute lymphoblastic leukemia (ALL) who treated with 6-MP experienced recurrent hypoglycemic symptoms such as drowsiness and general weakness for 3 months. He was hospitalized to identify the cause of hypoglycemia. No focal lesion was found in pancreas USG and MRI. Blood ketone bodies and blood insulin/C-peptide ratio was normal. HbA1c was 4.9%. there was no specific abnormal findings in glucagon stimulation test. Blood pancreatic enzymes levels were normal. Administration time of the 6-MP was changed to morning, and corn starch was given for the treatment of hypoglycemia. Hypoglycemia disappeared after withdrawal of 6-MP.

**Conclusions:** It has been rarely reported that 6-MP can be associated with hypoglycemia due to hyperinsulinemia. This report is the first case in Korean children. Further gene study is necessary on the basis of pathogenesis in patients susceptible to 6-MP.

P2-1207

#### **PRIMARY HYPERPARATHYROIDISM COMPLICATED BY SUPERIOR SAGITTAL SINUS THROMBOSIS: A RARE COMPLICATION IN CHILDHOOD**

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**Objectives:** Primary hyperparathyroidism (PHPT) is uncommon in childhood. Cardiovascular events in the course of paediatric PHPT are rarely documented. We report our experience with a 13 year old girl who presented with symptomatic primary hyperparathyroidism due to a parathyroid adenoma inferior to the thyroid gland. Two weeks after successful parathyroidectomy she presented with depressed conscience, paresis of the left arm, left facialis paresis and incomprehensible slurry speech.

**Methods:** Coagulation tests were done and Computed Tomography Angiography and Magnetic Resonance Venography were performed. A comprehensive

literature search was undertaken, in order to evaluate the relation between PHPT and the incidence of cardiovascular events.

**Results:** This girl showed evidence for superior sagittal sinus thrombosis without signs of venous infarction. After venepuncture she was immediately started on anticoagulation therapy. Coagulation tests did not demonstrate an increased risk for cardiovascular events. She was discharged without any neurologic deficit after three weeks of hospitalisation.

Adults with PHPT have a higher risk for cardiovascular events through abnormalities in coagulation and fibrinolysis pathways, but evidence is still conflicting. This risk appears to decrease with time after parathyroidectomy. Higher plasma levels of tissue type plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1) and lower tissue factor pathway inhibitor (TFPI) levels are reported and may play an important role in this phenomenon (Erem et al.). Evidence concerning cardiovascular complications in childhood PHPT is not available.

**Conclusions:** There may be an increased risk for cardiovascular events in childhood PHPT. Further larger incidence and intervention studies are needed that directly investigate the haemostatic and fibrinolytic disorders in childhood PHPT in order to determine the need for anticoagulation therapy in this specific paediatric population. Investigation of plasma t-PA, PAI-1 and TFPI levels may be helpful.

P2-1208

#### **AN OVARIAN SERTOLI-LEYDIG CELL TUMOR MAY BE THE FIRST SIGN IN THE DETECTION OF THE DICER1 SYNDROME**

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**Objectives:** The DICER1 gene encodes an endonuclease involved in the production of microRNAs that regulate gene expression. Patients with germline DICER1 mutations are predisposed to a rare cancer syndrome called DICER1.

**Methods:** We present a case of an adolescent with an ovarian Sertoli-Leydig cell tumor (SLCT), and a multinodular goiter (MNG), who was diagnosed with DICER1 syndrome.

**Results:** A 15-year-old girl was referred to evaluate a goiter. She was euthyroid and antithyroid antibodies were negative. Thyroid ultrasound (US) showed multiple complex nodules, but the fine-needle aspiration ruled out malignancy. Family history was significant for the patient's mother who had been thyroidectomized as an adolescent for a MNG.

At the age of 17, our patient had amenorrhea, rapid onset of acne, hirsutism, and a deep voice. Laboratory tests showed very high serum testosterone levels (467 ng/dl), androstenedione (21.5 nmol/L) and free androgen index (21). 17-OH-progesterone (9.8 nmol/L) and dehydroepiandrosterone sulfate (8.39 µmol/L) were slightly



increased. An abdominal ultrasound and MRI revealed the presence of a solid cystic mass (about 11 X 8 cm) attached to the left ovary. The alfa-fetoprotein, carcinoembryonic antigen and CA 125 were negative.

The mass was completely removed by a left salpingo-oophorectomy. A pathological exam showed a SLCT with intermediate differentiation. Few hours after surgery androgens levels were almost normal. Menstruation normalized a month later.

Genetic testing confirmed DICER1 syndrome with an heterozygous pathogenic change c.2804+1G>A in the DICER1 gene, which hadn't been displayed previously. The same mutation was found in the mother.

Given the risk of developing differentiated thyroid carcinoma (DTC) in patients with DICER1 mutations, a total thyroidectomy was performed. A thoracic computerized tomography and a body MRI did not reveal additional tumors.

**Conclusions:** SCLT is a very rare form of ovarian tumor and DICER1 syndrome should be suspected. Proper diagnose is key for appropriate screening of other possible associated tumors.

## POSTER SESSION 2

Friday, September 15, 2017, 11:30am-12:30pm

### P2 - Puberty

#### P2-1300 – P2-1326

P2-1300

#### METHYLATION PROFILE OF THE MKRN3 GENE IN PATIENTS BORN SMALL FOR GESTATIONAL AGE (SGA) AND/OR PRETERM (PT)

*Elisângela Araujo, MS/MA, Santa Casa de São Paulo Medical Sciences College, São Paulo, Brazil; Carlos A Longui, PhD, Santa Casa de São Paulo, São Paulo, Brazil*

**Objectives:** Children born SGA or PT frequently present pubertal anticipation with unknown mechanism. Methylation abnormalities were previously described in this group of patients. *MKRN3* gene was recently recognized as a major inhibitor of puberty, with paternal expression and maternal allele silencing by methylation. Precocious puberty occurs in cases where paternal expression is reduced. In this study, we propose to establish the quantitative pattern of methylation of *MKRN3* gene. Our working hypothesis is that an additional mechanism could be related to hypermethylation of the alleles, determining the loss of its inhibitory activity upon pubertal initiation.

**Methods:** We studied SGA patients born with less than 2kg and/or PT with less than 32 weeks of gestation (n:10). A control group (n:10) included patients born term and adequate for gestational age. Methylation analysis of the two *MKRN3* CpG islands was performed by employing the Cells to CpG Bisulfite Conversion Kit (Applied Biosystems™ 4445554, USA) followed by both DNA sequencing and quantitative PCR (MeltDoctor HRM kit running in Step One

Plus thermocycler). BSP primers were designed employing the Methyl Primer Express v1.0 software.

**Results:** The methylation status of the second CpG island of *MKRN3* was obtained with High Resolution MeltSoftware v3.0.1. Mean(SD) methylation was 0.72(0.1) and 0.66(0.1) for patient and control groups, respectively. The difference between groups was not significant (p:0.19; t- test), but the power of the test was low (0.12), suggesting inadequate sample size.

**Conclusions:** In conclusion, we standardized the assay for determination of *MKRN3* methylation status. Increase sample size analyses of the 50 available individuals from each group will possibly allow the recognition of the role of *MKRN3* gene methylation in pubertal anticipation of SGA and/or PT born conditions.

P2-1301

#### DIFFERENTIAL IMPACT OF GENETIC LOCI ON AGE AT THELARCHE AND MENARCHE IN HEALTHY GIRLS

*Alexander S Busch, MD; Casper P Hagen, PhD, Rigshospitalet, Copenhagen, Denmark; Maria Assens, MD; Katharina M Main, MD, PhD, Professor, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; Kristian Almstrup, PhD, Rigshospitalet, Copenhagen, Denmark; Anders Juul, PhD, Rigshospitalet, Copenhagen, Denmark*

**Objectives:** Age at onset of puberty exhibits a large variation largely reflecting genetic factors. Recent genome-wide association studies (GWAS) of age at menarche and candidate gene studies of age at thelarche observed partially divergent associations. Results pointed to a potential differential impact of genetic variants on timing of early versus late pubertal events (thelarche vs menarche). We aimed to investigate the association of genetic variation of *LIN28B*, *INHA*, *MKRN3*, *TMEM38B* and *ZNF483* (highly significant signals in GWAS on age at menarche) as well as *FSHB* and *FSHR* (age at thelarche signals) with age at thelarche and menarche in a cohort of healthy girls.

**Methods:** 1388 healthy Danish girls were recruited as part of two population-based and cross-sectional and longitudinal studies (COPENHAGEN Puberty Study and Copenhagen Mother-Child Cohort). Clinical examinations, including pubertal breast stage by palpation, were performed. Menarche status was assessed by status quo method. Subjects were genotyped for genetic variations by competitive PCR.

**Results:** Genetic variation of *LIN28B* (rs77599386) was significantly associated with age at thelarche and menarche (corrected for BMI z-score, p < 0.001 and p = 0.005, respectively). Minor allele counts of *FSHB* -211G>T (rs10835638) and *FSHR* -29G>A (rs1394205) were significantly associated with age at thelarche (corrected for BMI z-score, p = 0.004, previously published), but not menarche (unpublished). Genetic variations of *INHA* (rs41411537), *MKRN3* (rs1214876915), *TMEM38B* (rs104532259) and *ZNF483* (rs109809219) were not associated with age at thelarche or menarche.

**Conclusions:** We suggest differential impact of distinct genetic loci on the age at appearance of early (thelarche) versus late (menarche) pubertal markers in healthy girls.

P2-1302

#### RESPONSES TO KISSPEPTIN IN BOYS AND GIRLS WITH DELAYED PUBERTY

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**Objectives:** The goal of this study was to assess GnRH neuronal responses to exogenous kisspeptin in boys and girls with delayed puberty.

**Methods:** Subjects had delayed puberty (no breast development by 12 y for girls or testicular enlargement by 13.5 y for boys) or stalled puberty (no change in breast development or testicular size for >6 months) with no identified pathological cause. All subjects and their parents gave written informed assent/consent, and study procedures were approved by the IRB.

Subjects were admitted for frequent blood sampling to measure LH secretion at baseline (assessed overnight), after kisspeptin 0.24 nmol/kg IV x1, and after GnRH 75 ng/kg IV x1. Because prepubertal children may not initially respond robustly to GnRH, we then administered GnRH 25 ng/kg SC q2h x6d to enhance pituitary responsiveness to GnRH. Subjects returned for a second visit to measure LH responses to kisspeptin and GnRH after this pituitary "priming."

**Results:** Fourteen subjects (10 boys, 4 girls) completed both visits. We observed three patterns based on the presence or absence of spontaneous overnight LH pulses, pre-priming responses to GnRH ( $\Delta LH_{GnRH}$ ), and post-priming responses to kisspeptin ( $\Delta LH_{kisspeptin}$ ). Six children exhibited Pattern 1, characterized by presence of overnight LH pulses,  $\Delta LH_{GnRH} > 1.5$  mIU/mL (range 1.7-15.4 mIU/mL), and  $\Delta LH_{kisspeptin}$  ranging from 0.8-1.7 mIU/mL. Pattern 2, seen in six children, was characterized by absence of overnight LH pulses,  $\Delta LH_{GnRH}$  kisspeptin = 0. Two children exhibited Pattern 3, an intermediate pattern with no overnight LH pulses,  $\Delta LH_{GnRH} = 1.6$  and 7.5 mIU/mL, and  $\Delta LH_{kisspeptin} = 0.2$  and 0.4 mIU/mL. Kisspeptin was well-tolerated by all subjects.

**Conclusions:** Some children with delayed puberty exhibit responses to kisspeptin similar to those seen in healthy adults (Pattern 1), and some resemble adults with IHH (Pattern 2). It is unclear if Pattern 3 (intermediate response to kisspeptin) is a static pattern that is insufficient to drive pubertal maturation or a transient pattern that could be followed by increasing responsiveness to kisspeptin and progression through puberty. Further follow-up will determine whether kisspeptin responsiveness in children with delayed puberty predicts later pubertal entry.

P2-1303

#### IDIOPATHIC CENTRAL PRECOCIOUS PUBERTY IN PRADER-WILLI SYNDROME IN KOREA

*Chong Kun Cheon, MD, Pusan National University Children's Hospital, Yangsan, Korea, Republic Of; Yoo-Mi Kim, MD, Pusan National University Children's Hospital, Yangsan si, Korea, Republic Of*

**Objectives:** Prader-Willi syndrome (PWS) is characterized by infantile hypotonia, childhood obesity, growth hormone deficiency, short stature, and hypogonadotropic hypogonadism. Delayed pubertal development as well as premature adrenarche are usually detected in PWS, whereas central precocious puberty (CPP) is very rare in PWS. This study aimed to report the clinical and biochemical follow-up of PWS patients with idiopathic CPP.

**Methods:** A total 70 PWS patients was diagnosed with PWS by molecular genetic testing and clinical manifestations. Among them, 33 PWS patients (20 boys, 13 girls) aged 5-12 years were enrolled in the present study. Two individuals were confirmed as having UPD and 31 individuals had a deletion. Thirty-three PWS individuals have been treated with growth hormone (GH) for more than four years.

**Results:** Among 33 PWS patients, five (15.1%) patients (2 boys, 3 girls) were diagnosed with idiopathic CPP in whom a deletion was observed. CPP patients showed normal height and weight range for age but the growth rate was accelerated ( $8.7 \pm 0.6$  cm/year). Physical examination revealed a Tanner stage II for breast/testicular development and a Tanner stage I for pubic hair development. Body mass index at gonadotropin-releasing hormone analog (GnRHa) start was  $20.6 \pm 2.0$ . Routine hematological and biochemical analyses were normal. Endocrine evaluation revealed a random luteinizing hormone level of  $0.3 \pm 0.3$  IU/L, a follicle-stimulating hormone level of  $3.7 \pm 2.9$  IU/mL, and elevated DHEA-S  $146.5 \pm 51.8$  ug/dL. GnRH stimulation test was consistent with the diagnosis of CPP (LH peak  $11.8 \pm 8.0$  IU/L). Skeletal maturation, evaluated by a left wrist X-ray, was advanced, relative to chronological age, by  $2.6 \pm 0.5$  years according to the Greulich and Pyle method. Pituitary MRI scan was normal. Combined therapy with GnRHa and GH was done, the treatment was beneficial in terms of halting the progress of pubertal development.

**Conclusions:** CPP tends to be underdiagnosed in PWS individuals during GH treatment. Considering CPP-diagnosis rate (15.1%) in this study, thorough recognition and monitoring of pubertal development in PWS may be an important for the early diagnosis and individualized treatment of CPP.

### SENSITIVITY AND SPECIFICITY OF BASAL LH LEVELS IN THE DIAGNOSIS OF CENTRAL PRECOCIOUS PUBERTY IN GIRLS

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**Objectives:** Distinction between Central Precocious Puberty (CPP), premature thelarche and Pseudo Puberty is traditionally based on the GnRH stimulation test. More recently stimulation testing with GnRH analogues (GnRHa) has become an interesting alternative. The advent of sensitive third generation tests with gonadotrophin detection levels of

**Methods:** The medical records of girls aged more than 2 years referred to our clinic for sexual precocity from July 2007 to December 2016 were reviewed. CPP was suspected on clinical (history and Tanner staging) and radiological criteria (uterus  $\geq$  35mm and/or ovaries  $\geq$  25mm on pelvic ultrasounds). The diagnosis of CPP was confirmed by a GnRHa test (Basal/Peak LH  $>0.3/>5$  UI/I). LH was measured using a Chemiluminescence assay.

**Results:** Of 261 patients referred for precocious puberty, 140 were included in the study. Diagnosis of CPP was made in 57 (40.7%) patients at a mean (SD) age at diagnosis of  $6.03 \pm 2.07$  years. CPP was idiopathic in 54 (94.7%) patients and caused by brain tumour (hamartoma) in 3 patients. Basal LH level  $\geq 0.35$  UI/I correlated with CPP with a sensitivity of 72% and a specificity of 85%. Peak LH level  $>4.85$  UI/I on GnRHa test had a 100% sensitivity and specificity for the diagnosis of CPP. Correlation test between basal LH levels and LH Peak was  $0.58$  IC  $0.95$  [0.44-0.69].

**Conclusions:** Basal LH level is a useful tool in the diagnosis of CPP, basal levels  $>0.35$  UI/L was strongly correlated with the diagnosis of CPP, GnRHa may be used in situations where GnRH is unavailable although the GnRH test remains the gold standard.

P2-1305

### ENERGETIC COSTS OF GAMETOGENESIS - WHO SPENDS THE MOST?

Shai Z. Fuchs, MD/PhD, The Hospital for Sick Children, Toronto, ON, Canada; Miki Goldenfeld, Medical student, Tel-Aviv University, Tel-Aviv, Israel

**Objectives:** The ability to reproduce comes with an energetic price tag. In humans, pre-fertilization reproductive strategies are radically different between sexes, and systematic comparison of even sub-segments such as cost of gamete

pool maintenance, cost of hormonal regulation et cetera has not taken place. Our study looks at comparative energetic cost of supporting the gamete pool. Females are born with mean 600,000 oocytes in non-growing follicles that over life undergo progression and/or atresia. This oocyte pool is gradually exhausted until menopause. Male gamete strategy is based on constitutive differentiation of gametes far smaller in mass, with onset at puberty and a significantly slower decay. We sought to compare the lifetime energetic cost of those disparate strategies.

**Methods:** Our approach was based on equating energetic cost to area-under-the-curve (AUC) of the gamete mass supported over a lifetime. This value was calculated based on integration of published quantitative data. *For females*, we analyzed probabilities of alternative oocyte life histories which effect their mass and longevity. *For males* we independently analyzed sperm production rate as well as data on dynamics of ejaculation frequency and sperm content.

**Results:** The AUC of oocyte mass over a lifetime is  $\approx 100$  gr\*days of supported gamete mass. Remarkably, half of this AUC is reached by age 10 years and  $\approx 90\%$  by age 24. For males we found that a mean of 3 trillion sperm cells are produced over a lifetime. Accounting for mass and gamete lifespan, we find that overall the male strategy produces 100-1,000 fold larger AUC of supported mass.

**Conclusions:** When accounting for the energy directly allocated to support cell mass, the cost of the male continuously renewing gamete pool exceeds that of the female oocyte reservoir maintenance by 2-3 orders of magnitude. The significance of our account lies in setting a methodology that can be further used to elicit other segments of energetic components of human reproduction. Comparative quantitative accounts based on this approach may bear relevance to unsolved observations such as sex-specific age of puberty onset and interactions between fecundity and longevity. We also provide the community with a comprehensive quantitative compendium of the dynamics of gamete number and mass.

P2-1306

### MKRN3 LEVELS IN GIRLS WITH CENTRAL PRECOCIOUS PUBERTY AND CORRELATION WITH SEXUAL HORMONE LEVELS

Anna Grandone, PhD, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy; Grazia Cirillo, DO; Marcella Sasso, MD, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy; Gianluca Tornese, MD, Istituto pediatrico Burlo Garofalo, Trieste, Italy; Caterina Luongo, MD; Michela Mariani, MD; Giuseppina r Umamo, MD; Emanuele Miraglia Del Giudice, Professor; Laura Perrone, Professor, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy

**Objectives:** Recently, mutations of makorin RING-finger protein 3 (MKRN3) have been described in familial central precocious puberty (CPP). Serum levels of this protein decline

before the pubertal onset in healthy girls and boys. The aim of the study is to investigate MKRN3 circulating levels in patients with CPP.

**Methods:** We performed an observational cross-sectional study. We enrolled 17 patients with CPP aged 7 years (range: 2-8 years) and breast development onset

**Results:** No MKRN3 mutation was found among CPP patients. MKRN3 levels were lower in patients with CPP compared to prepubertal age matched ones ( $p: 0.0004$ ) and comparable to those matched for pubertal stage. MKRN3 levels were inversely correlated to BMI SD ( $r: -0.35$ ;  $p: 0.02$ ), LH ( $r: -0.35$ ;  $p: 0.03$ ), FSH ( $r: -0.37$ ;  $p: 0.02$ ) and (17)estradiol ( $r: -0.36$ ;  $p: 0.02$ ).

**Conclusions:** We showed that girls with CPP had lower peripheral levels of MKRN3 compared to age matched pairs and that they negatively correlated to gonadotropins, estrogen and BMI. Our findings support the MKRN3 involvement in CPP also in absence of deleterious mutations. In addition our data suggest the role of MKRN3 in the complex mechanism controlling puberty onset and its interaction with other factors affecting puberty such as nutrition.

P2-1307

#### MAKORIN RING FINGER 3 GENE ANALYSIS IN KOREANS WITH FAMILIAL PRECOCIOUS PUBERTY

Hwalrim Jeong, MD, Hallym university, Chuncheon sacred heart hospital., Chuncheon, Korea, Republic Of; Jinsoo Hwang, PhD; Haesang Lee, PhD, Ajou University, School of Medicine, Suwon, Korea, Republic Of

**Objectives:** To identify *MKRN3* gene mutations or polymorphisms in Korean patients with familial CPP.

**Methods:** We recruited 26 patients with CPP and their parents (13 families). We measured endocrine and auxological parameters, and sequenced all *MKRN3* exons.

**Results:** We found no *MKRN3* mutations. Two *MKRN3* exon polymorphisms were identified. The g.23566445 C/T polymorphism was found in 8 families; a novel single nucleotide polymorphism (SNP) g.23567001 A/C was found in 1 family. These variants are synonymous SNPs; their functional roles remain unknown.

**Conclusions:** *MKRN3* mutation is uncommon in Korean patients with familial CPP. Ethnic variation in *MKRN3* mutational status is thus evident.

P2-1308

#### URINARY EXCRETION OF FSH AND LH IN NORMAL AND DISORDERED PUBERTY

Nanna Kolby, BSc; Alexander S Busch, MD; Lise Aksglaede, MD, PhD; Jørgen H. Petersen, MSc, PhD; Anna-Maria Andersson, MSc, PhD, Rigshospitalet, Copenhagen, Denmark; Anders Juul, PhD, Rigshospitalet, Denmark, Copenhagen, Denmark

**Objectives:** The complex and pulsatile secretion of LH and FSH in the transitional phase of puberty challenges the measurement of gonadotropins in serum. However, first morning voided (FMV) urine has been proposed to collect and integrate these fluctuating gonadotropin levels and therefore possibly gives a better and more 'true' reflection of the activity in the hypothalamic-pituitary-gonadal-axis (HPG-axis). The aims of this study were to describe and evaluate urinary and serum FSH and LH levels according to age, sex and pubertal stage in a large group of healthy children. In addition, the study aimed to test whether FMV urine analysis could serve as a non-invasive substitute for the GnRH-stimulation test.

**Methods:** A large cohort of healthy Caucasian children and adolescents ( $n=924$ , age 5.8-19.4 years) and a group of girls referred for precocious puberty ( $n=35$ ) all collected FMV urine, had blood samples drawn and a clinical examination performed. GnRH-stimulation test results were available in 25 patients.

Percentile curves were calculated to find reference ranges for urinary and serum concentrations of FSH and LH according to age, sex and pubertal stage using the General Additive Model for Location Scale and Shape (GAMLSS). ROC-curves were performed to evaluate the utility of the FMV urinary FSH and LH to separate central puberty from premature thelarche.

**Results:** Urinary gonadotropins were detected in FMV urine before physical signs of puberty. FMV-urinary LH correlated strongly to basal ( $r=0.87$ ) and stimulated serum-LH levels ( $r=0.81$ ). Urinary LH concentrations were superior in differentiating the pubertal stage of the children. A cut-off value of FMV-urinary LH 0.75 IU/l gave a sensitivity of 83.3% and a specificity of 84.6% in predicting a positive GnRH-stimulation test (e.g. LHmax  $>5$  IU/l). A cut-off z-score of 2 to FMV-urinary LH (IU/8hrs) gave a sensitivity of 75% and a specificity of 76.9% in predicting a positive GnRH-stimulation test.

**Conclusions:** Detectable urinary FSH and LH levels herald the onset of puberty and may be used to reveal imminent puberty. The strong correlation between urinary and serum FSH and LH concentrations further support the potential use of urine as an alternative non-invasive method for testing the activity of the HPG-axis in children with disordered puberty.

P2-1309

#### EFFECT OF GONADOTROPIN-RELEASING HORMONE AGONISTS ON AUXOLOGICAL OUTCOMES OF BOYS WITH EARLY PUBERTY

Jong Seo Yoon, MD; Hae Sang Lee, PhD; Jin Soon Hwang, MD, PhD, Ajou University School of Medicine, Ajou University Hospital, Suwon, Korea, Republic Of

**Objectives:** To determine the effect of gonadotropin-releasing hormone agonist (GnRHa) treatment on auxological outcome of Korean boys with early puberty (EP).

**Methods:** Patients diagnosed with EP were retrospectively divided into two groups. Group 1 subjects ( $n = 17$ ) received GnRHa treatment between 9.0 and 9.9 years of age. Group 2

subjects ( $n = 16$ ) received GnRHa treatment between 10.0 and 10.9 years of age.

**Results:** The mean chronological age (CA) and mean bone age (BA) of patients in Group 1 at the start of treatment were  $9.82 \pm 0.22$  years and  $12.43 \pm 0.59$  years, respectively. Their predicted adult height (PAH) at the start of treatment was  $168.49$  cm ( $-0.88 \pm 0.99$  PAH standard deviation score [SDS]). After 2 years of treatment, it was  $173.49 \pm 6.07$  cm ( $-0.03 \pm 1.06$  PAH SDS) ( $p < 0.001$ ). The mean CA and mean BA of patients in Group 2 at the start of treatment were  $10.44 \pm 0.30$  years and  $12.67 \pm 0.45$  years, respectively. The PAH at the start of treatment was  $168.79 \pm 5.59$  cm ( $-0.82 \pm 1.01$  PAH SDS) in Group 2. After 2 years of treatment, it was  $172.06 \pm 5.88$  cm ( $-0.24 \pm 1.05$  PAH SDS) ( $p < 0.001$ ). The PAH after 2 years of treatment was influenced significantly by the PAH at the start of treatment.

**Conclusions:** GnRHa treatment significantly improved the growth potential of boys with EP.

P2-1310

#### EFFECT OF ANTIANDROGEN, AROMATASE INHIBITOR, AND GONADOTROPIN-RELEASING HORMONE ANALOG ON THE ADULT HEIGHT OF BOYS WITH FAMILIAL MALE-LIMITED PRECOCIOUS PUBERTY (FMPP)

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**Objectives:** Treatment with antiandrogen (AA), aromatase inhibitor (AI), and gonadotropin-releasing hormone analog (GnRHa) normalizes growth rate and bone maturation and increases predicted adult height in boys with familial male-limited precocious puberty (FMPP). To determine the effect of this treatment regimen on final adult height, 28 boys with FMPP were treated with this regimen and followed until attainment of adult height.

**Methods:** We evaluated adult height in 28 boys with FMPP following long-term treatment with AA (spironolactone), AI (testolactone/anastrozole), and GnRHa (deslorelin/leuprolide). Mean  $\pm$  standard deviation (SD) age at treatment onset was  $4.9 \pm 1.5$  years (y) for AA and AI and  $6.9 \pm 1.5$  y for GnRHa. At treatment discontinuation, chronologic age (CA) was  $12.2 \pm 0.5$  and bone age (BA) was  $14.4 \pm 1.3$  y. Adult height was assessed at CA of  $16.4 \pm 1.3$  y and BA of  $18.5 \pm 0.6$  y (all BAs  $\geq 17$  y).

**Results:** Adult height (mean  $\pm$  SD) for all treated subjects was  $173.6 \pm 6.8$  cm ( $-0.4 \pm 1.0$  SDS relative to US males at age 19). For the 25 subjects with pretreatment predicted adult height measurement, adult height significantly exceeded predicted adult height at treatment onset ( $173.8 \pm 6.9$  vs.  $164.9 \pm 10.7$  cm,  $p < 0.001$ ), but fell short of predicted adult height at treatment discontinuation ( $177.3 \pm 9.0$  cm,  $p < 0.001$ ). For the

11 subjects with maternal/sporadic inheritance, adult height did not differ significantly from sex-adjusted mid-parental height (MPH) ( $175.4 \pm 5.8$  vs.  $178.5 \pm 3.1$  cm [MPH],  $p = 0.10$ ). For the 16 subjects with affected untreated fathers, adult height was significantly greater than their fathers' adult height ( $172.8 \pm 7.4$  vs.  $168.8 \pm 7.2$  cm,  $p < 0.05$ ).

**Conclusions:** Long-term treatment with AA, AI, and GnRHa in boys with FMPP results in adult height modestly below sex-adjusted MPH and well within the range for adult males in the general population.

P2-1311

#### PRECOCIOUS PUBERTY: CLINICAL, PARACLINICAL AND ETIOLOGICAL PRESENTATION IN A REFERENCE CARE CENTER IN SUB-SAHARAN REGION

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**Objectives:** We aimed to describe clinical and paraclinical features, then identify causes of precocious puberty among children attending a reference center in Cameroon.

**Methods:** We performed a cross-sectional study including 36 children received for sexual maturation before 8 years for girls and 9 years for boys. We collected data about anthropometric parameters, tanner staging, hormone assays and morphologic (pelvic ultrasound, bone age) results.

**Results:** The median age was 7 years with a majority of girls. Stage 2 breast development was the main clinical presentation. An advanced bone age of 2 years was found in 19.6% of cases. The basal luteinizing hormone level was greater than 0.1 UI/L in 66.7% of children. Central precocious puberty was more frequent than peripheral form. Ovarian tumors (71.4%) were mainly involved in peripheral precocious puberty.

**Conclusions:** Precocious puberty mostly affects girls under 8 in our setting as mentioned in previous studies. Moreover, stage 2 breast development is mainly reported at diagnosis. Peripheral involvement is mainly due to ovarian tumors.

P2-1312

#### ANDROGEN RECEPTOR GENE CAG REPEAT POLYMORPHISM IN GIRLS WITH HIGH DHEAS: ASSOCIATION WITH PUBERTAL EVENTS AND BODY COMPOSITION

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**Objectives:** High DHEAS (HD), defined by plasma [DHEAS] >42 µg/dl before 8y in girls, can be accompanied by signs of androgenic action. The Androgen Receptor (RA) harbors a variable repeat of 9 to 36 glutamine residues (codified by CAG) in the AF1 domain which seems to affect inversely RA transcriptional activity. We aimed to assess whether the number of CAG repeats affects the sequence of androgen-sensitive pubertal events and body composition in girls with HD.

**Methods:** A case-control association study of HD girls (n=58) at  $6.8 \pm 0.4$ y and 107 age-matched normal DHEAS girls from the Chilean Growth and Obesity longitudinal cohort (GOCS). The methylation weighted mean of CAG repeats, mw(CAG)n, was calculated through X-chromosome methylation-sensitive enzyme restriction treatment in peripheral DNA, followed by PCR and fluorescent capillary electrophoresis (ABI prism 310 Applied Biosystem®). Age of pubarche (P2) and telarche (T2) were calculated by censoring method. Adiposity indicators, BMI in SDS (BAZ), %fat mass (bioimpedanciometry), waist circumference (WC) and waist-to-height ratio (W/H), were measured by standardized procedures at age 7y and at T2.

**Results:** Similar median AR mw(CAG)n were observed in cases and controls (21.9 range 17–27.5 and 22.7 range 13.7–27) and mw(CAG)n correlated positively with age of P2 ( $r=.261$ ,  $P=.001$ ). Cases with P2 ( $9.1 \pm 0.9$ y) before than T2 ( $10.2 \pm 0.8$ y) presented a trend to more frequent (27%) shorter alleles (<20mwCAGn) compared to cases (19%) with T2 ( $7.4 \pm 0.5$ y) before than P2 ( $9.3 \pm 0.7$ y) and controls (11%;  $P=.08$ ; Pearson's chi-square). BAZ, %fat mass and WC were positively correlated with DHEAS at 7y ( $r=.165$ ,  $.211$ ,  $.223$ ;  $P<.05$ ). Among cases (HD), those with <20mw(CAG)n had lower BAZ, %fat mass, WC and W/H compared to cases with  $\geq 20<25$ mw(CAG)n ( $P<.05$  Mann-Whitney test). In contrast, adiposity indicators did not show association with mw(CAG)n at age of T2.

**Conclusions:** Our results suggest that shorter CAGn polymorphisms favor the onset of pubarche before than telarche in girls with HD and this genetic polymorphism affects positively the androgen dependent modulation of body composition before puberty. FONDECYT grant#1140447 and SOCHED 2015-05

P2-1313

#### NOVEL MATERNALLY IMPRINTED DEFECTS IN THE MKRN3 GENE IN PATIENTS WITH FAMILIAL CENTRAL PRECOCIOUS PUBERTY

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**Objectives:** Premature activation of the gonadotropin releasing hormone (GnRH) secretion in Central Precocious Puberty (CPP) may arise either from gain-of-function mutations of the *KISS1* and *KISS1R* genes or loss-of-function mutations of the makorin RING-finger protein 3 (*MKRN3*) gene leading to MKRN3 deficiency. The main objective was to identify loss-of-function mutations in the makorin RING-finger protein 3 (*MKRN3*) gene or gain-of-function mutations in the *KISS1* and *KISS1R* genes that lead to CPP.

**Methods:** In the present study, we genotyped by DNA sequencing a cohort of 54 index girls with CPP for the presence of genetic variations in the intronless *MKRN3*, the *KISS1* and *KISS1R* genes.

**Results:** Familial CPP have been reported for the six out of 54 index cases. Genotypic analysis of the *KISS1* and *KISS1R* genes did not identify any genetic defect. However, *MKRN3* gene mutations were identified in one sporadic and three familial cases of CPP. The novel g.Gly312Asp (p.G312D) missense mutation was identified in two nonrelated familial index cases with CPP. Similarly, the also novel p.Glu298Term (p.E298\*) nonsense mutation was identified in one familial index case with CPP. Additionally, in a sporadic case with CPP the known frameshift p.Met268ValfsTer23 (p.M268Vfs\*23) mutation was identified. As expected the novel *MKRN3* mutations identified in this study were also identified in the unaffected fathers following an imprinted mode of inheritance. We verified the pathogenicity of the p.G312D missense mutation at the protein level by *in silico* structural analysis. A phenotype-genotype correlation between the patients with and without *MKRN3* mutations revealed that the onset of puberty was earlier among the patients with *MKRN3* mutations compared to those without *MKRN3* mutations.

**Conclusions:** Our results confirm the role of *MKRN3* in the onset of pubertal development and support the fundamental role of this gene in the suppression of the hypothalamic GnRH neurons. Furthermore, these results indicate the involvement of additional genes in the regulation of pubertal timing in humans and genetic screening of more genes is under investigation. In conclusion, *MKRN3* gene analysis should be considered as an additional critical tool for the diagnosis of familial CPP.

P2-1314

#### EFFECTS OF HISTRELIN AND LEUPROLIDE ON BMI IN CHILDREN WITH IDIOPATHIC CENTRAL PRECOCIOUS PUBERTY

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**Objectives:** Gonadotropin-releasing hormone agonists (GnRHa) are the gold standard for treatment of central

precocious puberty (CPP), yet effects on BMI and association with obesity have not been clearly defined in the literature. The most recent Pediatric Endocrine Society consensus statement does not currently comment on the role of GnRHa in the promotion of weight gain. The aim of this study is to compare the effects of two GnRHa (histrelin and leuprolide) on BMI in children with idiopathic CPP at 12 and 24 months after initiation of treatment.

**Methods:** In a retrospective chart review from Oct 2006 to Dec 2015, 31 patients were identified. Criteria included girls <8 and boys <9 years old prior to starting treatment with either histrelin (n=12) or leuprolide (n=19) for idiopathic CPP. BMI was recorded prior to treatment, and 12 and 24 months post treatment (visit 1 and 2 respectively). Data was analyzed to assess changes in BMI among the 2 treatment groups over time. Results were summarized by mean  $\pm$  standard error of mean (SEM). The linear mixed effects model was used to compare the histrelin vs leuprolide treatment groups at each visit and BMI changes within each treatment group; a p-value < 0.05 was statistically significant.

**Results:** The BMI (Mean  $\pm$  SEM) at baseline, visit 1, and visit 2, were  $18.66 \pm 1.21$ ,  $19.15 \pm 1.21$  and  $20.20 \pm 1.23$  for the histrelin group and  $19.31 \pm 0.96$ ,  $20.24 \pm 0.96$  and  $23.23 \pm 1.07$  for the leuprolide group. The between-group comparisons were not statistically significant with the mean differences (mean BMI of histrelin – mean BMI of leuprolide) -0.65, -1.09, and -3.03 at baseline, visits 1 and 2. The corresponding p-values were 0.679, 0.487, and 0.071, respectively. In the histrelin group, the mean difference in BMI was 0.49 (p=0.679) between visit 1 and baseline, and 1.54 (p=0.045) between visit 2 and baseline. In the leuprolide group, the mean difference in BMI was 0.93 (p=0.121) between visit 1 and baseline, and 3.92 (p<0.0001) between visit 2 and baseline.

**Conclusions:** Our results show a mean BMI increase after 2 years of treatment in both the histrelin and leuprolide groups. There was no significant difference in the change in BMI between the two groups.

P2-1315

#### THE INFLUENCE ON METABOLISM OF PRECOCIOUS PUBERTY IN FEMALE RATS

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**Objectives:** To observe the metabolism and gonadal axis in female precocious puberty SD rats during their puberty and early adulthood.

**Methods:** The female rats were randomly divided into 2 groups: control group (C group) and precocious puberty group (PP group). In PP group, rats were injected danazol in day 5<sup>th</sup> after birth, and only those whose vaginal open day were -2SD earlier than C group can be enrolled. Two groups were randomly divided into 3 batch, which were sacrificed respectively in vaginal open day 3<sup>rd</sup> (which stands for puberty

of rats), 7 weeks and 12 weeks. Blood, perirenal fat, uterus and ovary were collected. OGTT was carried out in 12 weeks. **Results:** The vaginal open time were  $36.00 \pm 2.34$  (33~42) days in C group and  $24.79 \pm 2.04$  (23~29) days in PP group ( $t=16.937, P<0.001$ ). At 3<sup>rd</sup> day of vaginal open, insulin and HOMA-IR were significantly higher in PP group than in control group, while HOMA -ISI was significantly lower ( $P<0.05$ ); moreover, eight rats (100%) in PP group were hyperinsulinemia (INS>+2SD of control group) and insulin resistance (HOMA-IR>+2SD of control group), while none of control group were hyperinsulinemia or insulin resistance. But at 7 weeks and 12 week there were no significant difference between two groups. At 3<sup>rd</sup> day of vaginal open, the amounts of perirenal fat cells was significantly higher ( $P<0.05$ ), while cholesterol and low density lipoprotein were lower in PP group than in C group ( $t=4.082, P=0.001$ ), while no difference at 7 weeks and 12 weeks. At 3<sup>rd</sup> day of vaginal open, there were no corpus luteum was found in ovary of PP group, while 1~2 were found in C group. No difference was found in ovary at 7 weeks and 12 weeks. There were no significant differences in serum estrogen, Lee index, perirenal fat/body weight, size of perirenal fat cell, and serum leptin and adiponectin level between two groups at three time points ( $P>0.05$ ).

**Conclusions:** During puberty, precocious puberty rats had temporary and reversible hyperinsulinemia and insulin resistance, which disappeared in adulthood. They had more amounts of adipocytes in puberty, but not in adulthood. Their ovary was not as mature as that of control group in their puberty, while well developed in adulthood.

P2-1316

#### ANTHROPOMETRIC, METABOLIC AND REPRODUCTIVE OUTCOME OF PATIENTS WITH CENTRAL PRECOCIOUS PUBERTY DUE TO HYPOTHALAMIC HAMARTOMA IN ADULT LIFE

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**Objectives:** Hypothalamic hamartoma (HH) represents the main cause of organic central precocious puberty (CPP). Long-acting GnRH analogs (GnRHa) are the first-line for treatment of CPP. Reports of long-term follow-up are scarce in HH. Our aim was to describe the anthropometric, bone density, metabolic and reproductive parameters of patients after treatment with GnRHa.

**Methods:** Fourteen patients (7 boys) with CPP due to HH treated exclusively with depot GnRHa from a single tertiary center were reviewed. Final height, body mass index (BMI), bioimpedance, bone densitometry, hormonal and biochemical evaluation, pelvic ultrasound and a reproductive function questionnaire were utilized at the cross-sectional evaluation.



**Results:** The mean duration of GnRHa treatment was  $7.7 \pm 2.4$  yr in boys and  $7.9 \pm 2.1$  yr in girls. GnRHa treatment was interrupted at  $12.1 \pm 1.1$  yr in boys and  $10.7 \pm 0.5$  yr in girls. At the last visit, the mean CA of the male and female patients was  $21.5 \pm 3.2$  yr and  $24 \pm 3.9$  yr, respectively. Eleven of 14 patients reached normal final height (SDS  $-0.6 \pm 0.9$  for males and  $-0.6 \pm 0.5$  for females), all of them within target height (TH) range. The remaining 3 patients had predicted height within TH range. Mean BMI-SDS and the percentage of body fat mass was significantly higher in females, with higher prevalence of metabolic disorders. All patients presented normal gonadal function at adulthood and 3 males fathered a child.

**Conclusions:** All patients with CPP due to HH reached normal final or near final height. A higher prevalence of overweight/obesity and hypercholesterolemia was observed in the female patients. Finally, no reproductive disorder was identified in both sexes, indicating that HH *per se* has no deleterious effect on gonadotropic axis at adulthood.

P2-1317

#### EVALUATION OF FINAL HEIGHT IN PRECOCIOUS PUBERTY AND FAST PROGRESSIVE EARLY PUBERTY GIRLS WITH GNRH ANALOG TREATMENT

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**Objectives:** OBJECTIVE: In this study, we aimed to evaluate of final height and to investigate the factors acting on the final height in central precocious puberty and fast progressive early puberty under GnRH analog treatment.

**Methods:** METHOD: Female cases diagnosed with precocious puberty which had started  $< 8$  years of age constituted Group 1 ( $n=19$ ) and fast progressive early puberty with  $\geq 8$  years of age constituted Group 2 ( $n=35$ ). All patients were given GnRH analog treatment and viewed until they reaches the final height.

**Results:** RESULTS: The average chronological age in diagnosis is  $7.26 \pm 0.53$  years in Group 1,  $8.97 \pm 0.51$  years in Group 2. Height sds, weight sds, BMI sds were similar between the groups. Bone age/chronological age ratio is  $1.22 \pm 0.14$  in Group 1,  $1.19 \pm 0.11$  in Group 2. The median duration of treatment is 27.8 (37-59) months in Group 1 and 15.2 (2-48) months in Group 2. Significant difference between final height and height sds in diagnosis was not found in groups. Significant difference between final weight sds, BMI sds and weight sds, BMI sds in diagnosis was not found. While first year growth velocity sds was similar to second year growth velocity in Group 1, second year growth velocity sds was

lower than first year growth velocity in Group 2. Bone age/chronological age in follow up years is significantly lower than the diagnosis in both groups. Final heights were similar to target heights in two groups. Target height, first year predicted adult height, second year predicted adult height and final height were similar in two groups (Table 1). 74% of final size variable was responsible for age and height in diagnosis.

**Conclusions:** CONCLUSION: In this study, we found that patients with central precocious puberty at 6.5-9.5 years of age given GnRH analog treatment reached final height compatible target height. In this age group, the principal factors which influence the final height were age and height in diagnosis.

Table 1. Target height, predicted adult height in diagnosis and follow up years and final height in groups

	Group 1 n=19	Group 2 n=35	p
Target Height (cm)	$157.9 \pm 5.14$	$158.4 \pm 4.45$	0.683
Predicted height in diagnosis (cm)	$157.3 \pm 7.68$	$157.7 \pm 6.45$	0.835
Predicted height in first year (cm)	$156.6 \pm 8.53$	$158.4 \pm 6.2$	0.462
Predicted height in second year (cm)	$158.5 \pm 7.1$	$159.5 \pm 7.08$	0.558
Final height (cm)	$159.2 \pm 5.94$	$157.8 \pm 5.59$	0.409

P2-1318

#### INVESTIGATION OF MAKORIN RING FINGER PROTEIN 3 MUTATION IN PATIENTS WITH FAMILIAL CENTRAL PRECOCIOUS PUBERTY: SINGLE CENTER EXPERIENCE

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**Objectives:** Objectives: The onset of puberty is influenced by many genetic factors such as stimulators and inhibitors. Activating mutations in Kiss1 and Kiss1R and loss of function mutations in the Makorin Ring Finger Protein 3 (MKRN3) gene cause premature activation of GnRH secretion. In this study, it was aimed to investigate MKRN3 mutation in familial idiopathic central precocious puberty (icPP) cases.

**Methods:** Methods: Thirty children from 15 families with icPP were enrolled in this study. All gene sequence analysis in the MKRN3 gene was performed.

**Results:** Results: The ages of the cases ranged from 5 to 11 years. Three sisters in two families, two siblings in one family,

two siblings in one family, a male patient with early puberty father story in a family, and two sisters in the other family were diagnosed with iCPP. Twenty eight of them were girls, two of them were boys. A heterozygous mutation in the MKRN3 gene (c.630\_650delinsGCTGGGC) was detected in only one male patient. Mutation caused the frame shift, leading to premature stop codon and genetic loss of function. The mutation was detected at 11.5 years old, one and a half years ago, with the complaint of the emergence of the beards. On admission, his puberty was stage 4 and height was 159 cm. Her father had a story about getting an early beard.

**Conclusions:** Conclusion: In this study, 30 patients with familial iCPP had MKRN3 mutation in only one case. We think that father's pubertal history, especially from patients with iCPP diagnosis, may be important in patient selection for the possibility of MKRN3 mutation.

P2-1319

#### THE RELATIONSHIP BETWEEN PLASMA KISSPEPTIN LEVEL AND EARLY DEVELOPMENT OF INFANT PREMATURE THELARCHE

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**Objectives:** To investigate the correlation between PT with the onset of progression and plasma kisspeptin levels, which may be possible to pave a way to a new direction of the early diagnosis and prognosis for the precocious puberty in infants and toddlers.

**Methods:** 42 PT female children (the age of first visit is less than 2 years old) were recruited as patient group and followed up for 2 years, thelarche of 18 cases completely disappeared (CD group), 11 cases were no regression or reappeared (RA group), and 13 cases were transformed into ICPP (ICPP group). 35 age-matched cases were recruited as the normal control group. ELISA are performed in measuring kisspeptin level.

**Results:** The level of plasma kisspeptin in ICPP group is higher than that in RA, CD, and control groups. The difference is statistically significant ( $P < 0.05$ ). The level of plasma kisspeptin in RA group is higher than that in CD and control groups ( $P < 0.05$ ). The levels of plasma kisspeptin do not have significantly difference between the CD and control groups ( $P = 0.792$ ). Plasma kisspeptin levels show positive correlation with P-LH, P-LH/P-FSH, E2, and PRL levels. For the analysis of related risk factors, there are significantly differences between patient and control groups in terms of the inharmonious relationship in parents, menarche of younger age, PT existing in parents' brothers and sisters, infants' sleeping with light on in the night and habitual residence near factories of discharging pollutants, all of them are risk factors to PT.

**Conclusions:** Our study suggested that plasma kisspeptin level is closely related to precocious puberty of infants, and can be regarded as a critical reference for the diagnosis and differential diagnosis of ICPP and PT in infants. Inharmonious relationship in parents, menarche of younger age, PT existing

in parents' brothers and sisters, infants' sleeping with light on in the night and habitual residence near factories of discharging pollutants are risk factors to PT.

P2-1320

#### PRECOCIOUS PUBERTY IN RENAL TRANSPLANT RECIPIENTS

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**Objectives:** Hypogonadism and delayed puberty are common endocrine complications of chronic kidney disease, but precocious puberty in this population has rarely been reported. We describe four girls from our pediatric nephrology service who presented with precocious and/or early-onset, rapidly progressing puberty following renal transplantation.

**Methods:** Children with chronic kidney disease followed in the pediatric nephrology unit at our center are routinely seen by a pediatric endocrinologist for assessment of growth and pubertal development. Between the years 2010 and 2015 we saw four girls (ages 7-2/12, 7-4/12, 8-0/12, and 8-8/12 years) with precocious or rapidly progressing early puberty following autologous kidney transplantation for Finnish type congenital nephrotic syndrome, single dysplastic kidney, polycystic kidneys and primary hyperoxaluria. Clinical evaluation included measurements of height, weight, BMI, and Tanner staging. Bone age was determined according to Greulich and Pyle. Hormone measurements were performed using standard ELISA assays. Gonadotropin levels were measured after testing with GnRH or triptorelin.

**Results:** Physical signs of puberty (breast Tanner stage 3 and pubic hair Tanner stage 1-2) were noted at 2-6 years following renal transplantation. Medications included prednisone, mycophenolate mofetil (Cellcept), tacrolimus, mycophenolic acid (Myfortic), vitamin D, and calcium. BMI ranged from 75th-95th percentiles. Bone age was 1-2 years greater than chronological age in 3 girls. Basal LH levels were 0.6, 0.1, 2.6 and 0.4 mIU/ml, and basal FSH levels were 5.1, 2.1, 3.2 and 2.0 mIU/ml, respectively. Peak LH and FSH levels were 6.5 and 13, 20.2 and 8.3, 7.83 and 8.01, and 19.1 and 7.5 mIU/ml, respectively. Treatment with intramuscular triptorelin acetate (Decapeptyl CR) every 4 weeks slowed progression of breast development and bone age advancement.

**Conclusions:** Although delayed puberty is more common in children with renal transplants, precocious puberty is also seen. Evaluation of growth and puberty by a pediatric endocrinologist should be considered as routine care for all children with chronic kidney disease.

# **PRESERVED FERTILITY DESPITE LIFE-LONG UNDETECTABLE FSH AND LH LEVELS IN A PATIENT WITH ACTIVATING P.ASP578TYR MUTATION IN THE LH RECEPTOR GENE (TESTOTOXICOSIS)**

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**Objectives:** Testotoxicosis (OMIM176410) is an autosomal dominant, male limited disorder causing constitutive activation of the LH receptors in the Leydig cells, resulting in highly increased autonomous testosterone synthesis.

**Methods:** The patient presented at 10 months of age with pubic hair and growth of genitals. Bone age was advanced by 3.5 years. Testosterone was markedly elevated to 35.1 nmol/L, the GnRH test showed a prepubertal response. The ACTH test and s-17-OH-progesterone were normal. Bilateral testis biopsy at 1.5 years showed extensive Leydig cell hyperplasia with fully differentiated Leydig cells, spermatogonia and a few primary spermatocytes which had entered meiosis. He was diagnosed with testotoxicosis (heterozygous for c.1732G>T, p.Asp578Tyr mutation in the *LHCGR* gene). Throughout infancy and childhood, he underwent available anti hormonal therapies and Growth hormone.

**Results:** Final adult height was 164 cm (target height 172.6 cm). Bone mineral density (BMD) was normal (T-score -0.8 SD (L1-L4)). Testicular vol. by orchidometry was 8 mL. Testosterone was 24 nmol/L, Estradiol 117 pmol/L, Inhibin B 22 pg/ml, AMH 23 pmol/L, FSH < 0.05U/l and LH. A heterogeneous testicular echo pattern was observed by ultrasonography, which was repeated every 6-12 months. At age 25 ultrasound of testes revealed a tumor suspicious mass, biopsy showed benign Leydig cell tumor but with widespread germ cell neoplasia in situ.

Despite life-long undetectable levels of LH and FSH, the patient fathered a son by natural conception at 23.8 years. The son virilized in infancy (Testosterone 18.4 nmol/L at 9 months), was diagnosed with an identical mutation, and therapy was initiated.

## **Conclusions:**

- The patient ended up with reduced height but normal BMD.
- We observed meiotic entry of some germ cells already in infancy, spermatogenic activity in adulthood and an ability to conceive despite documented undetectable levels of LH and FSH throughout life.
- Development of Leydig cell tumor with germ cell neoplasia in situ, suggest regular follow up of such patients. Long term consequences of lifelong increased concentration of sex steroids and LH receptor activation remain to be seen.

# **CLINICAL PRESENTATION OF A NOVEL MKRN3 MUTATION IN TWO SIBLINGS WITH CENTRAL PRECOCIOUS PUBERTY**

*Marek Niedziela\*, MD, Poznan University of Medical Sciences, Poznan, Poland; Johanna EM Kansakoski\*, MS; Kirsi T Vaaralahti, PhD; Taneli Raivio, Professor, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*

**Objectives:** Idiopathic central precocious puberty (ICPP) is defined as early activation of the hypothalamic–pituitary–gonadal axis in the absence of identifiable central lesions. *MKRN3* is one of the gatekeepers of the postnatal activation of the pubertal axis, and paternally inherited *MKRN3* mutations are currently the most common known genetic cause of ICPP. We analyzed *MKRN3* as a potential candidate gene for precocity in two siblings.

**Methods:** A boy aged 9 years and 3/12 was diagnosed with ICPP with initial clinical status such as testes 20 ml A2P3 and growth acceleration. Clinical signs were as follows: pubarche at 7 yrs, axilarche at 9 yrs; the onset of testicle enlargement was not known. His younger sister had precocious thelarche and growth acceleration at the age of 4 yrs and 4/12. In both, ICPP was confirmed by LHRH test, and MRI of the pituitary excluded organic cause. Mother (170cm) had menarche at the age of 13 yrs. All family members were screened for mutations in the *MKRN3* coding sequence. The endocrine phenotype was compared between *MKRN3* mutated and non-mutated family members.

**Results:** Both children had a novel heterozygous paternally inherited frameshift mutation in *MKRN3*, c.1237\_1252delGGAGACACATGCTTTT p.(Gly413Thrfs\*63), predicted to result in a premature stop codon. Age at puberty onset varied among affected patients and puberty occurred at 7yrs in a son and 4 yrs and 4/12 in a daughter. Predicted adult height (calculated according to B&P method) in the fully pubertal son (A3 P5 testes 25 ml) at the age of 12.1 yrs and final height in the father were in both normal, 182.5-183 cm (TH=184.5 cm) and 186 cm, respectively. The daughter was the only one treated with GnRH analog (GnRHa) soon after diagnosis. Her PAH was 173 cm and 169 cm at the age of 5 yrs 4/12 and 6 yrs and 4/12 respectively (TH=171.5 cm).

**Conclusions:** The question arises whether the conventional treatment with GnRHa is superior to “wait and see” option. Long-term observation is mandatory in these treated and untreated patients to calculate benefits vs. risks in affected patients.

\*Both are first authors

# **PREMATURE OVARIAN FAILURE (POF) ASSOCIATED WITH HETEROZYGOUS POLYMERASE GAMMA (POLG) MUTATION – CAUSE OR ASSOCIATION?**

*Colina Mckeown, MBChB; Rosemary Hall, MBChB, FRACP; Katherine Neas, MBChB, FRACP; David Bourke, MBChB, FRACP, Capital and Coast District Health Board, Wellington, New Zealand; David Thorburn, PhD, Royal Children's Hospital,*

**Objectives:** A 16 year old presented with primary amenorrhea. Puberty commenced age 12-13 with pubic hair, acne and breast development but did not progress. She was otherwise well, with normal growth, nutrition and exercise levels. Family history included late menarche and autoimmune thyroid disease. Examination included height 162.4cm (50th centile); BMI 27 (95th centile); tanner stage 2 (breast and pubic hair); no dysmorphism; no goiter; normal fundi, visual fields and pupils; no signs of chronic disease.

**Methods:** POF was confirmed with elevated FSH (65.9 U/L), LH (16.9 U/L) and low estradiol (31 pmol/L). Karyotype, ovarian antibodies, fragile-X and thyroid function were normal, with weakly +ve thyroid antibodies. Ultrasound showed a pre-pubertal uterus and small ovaries. Pubertal induction commenced with estradiol valerate in slowly increasing doses and subsequent cyclical provera.

**Results:** Her progress was complicated by scoliosis requiring posterior fusion at 18. At almost 19 she developed left ptosis, diplopia and reduced upward gaze. MRI, MR angiogram, acetylcholine receptor and ANCA antibodies were normal. mtDNA analysis in blood was normal. Sequencing of *POLG* revealed a heterozygous variant of uncertain significance (c.380A>T; p.His277Leu) in the exonuclease domain. Involved muscle (from ophthalmic surgery) was tested for mtDNA depletion and was normal.

**Conclusions:** POF has been described with mitochondrial disorders involving both nuclear (eg *POLG*, *COX10*, *LARS2*, *ACAD9* and *AARS2*) and mitochondrial (*MT-CO1*) genes with a range of phenotypes. Heterozygous *POLG* mutations in the polymerase domain cause progressive external ophthalmoplegia (PEO) and reports have also associated POF with these mutations. Homozygous/compound heterozygous mutations in *POLG* cause multisystem mitochondrial disease. The oocyte has the highest number of mtDNA copies of any human cell. Oocytes of women with ovarian insufficiency have lower mtDNA copy number and heterozygous *POLG* mutations could lead to POF by limiting mtDNA replication.

Mitochondrial disorders should be considered in POF and we speculate a heterozygous *POLG* mutation may cause POF as well as PEO. A study in a large cohort of patients with POF would provide stronger scientific validity to this observation.

P2-1324

#### A RARE CASE OF A GIRL WITH GROWTH HORMONE DEFICIENCY AND A PHENOTYPE OF GENETIC ABNORMALITY OF FSH RECEPTOR

Maria Xatzipsalti (Chatzipsalti), MD; Ioulia Polychroni, MD, "P & A Kyriakou" Children's Hospital, Athens, Greece; Helen Fryssira, MD, National and Kapodistrian University of Athens, Athens, Greece; Foteini-Eleni Karachaliou, MD, Attikon University Hospital, Athens, Greece; Lela Stamoyannou, MD, "P & A Kyriakou" Children's Hospital, Athens, Greece

**Objectives:** Follicle stimulating hormone (FSH) is one of the two pituitary gonadotrophins involved in the regulation of gonadal function. Abnormalities of FSH receptor (FSHR) in patients with Growth hormone deficiency (GHD) are rare. We describe a girl with hypergonadotropic hypogonadism and a phenotype of genetic abnormality of FSH receptor and GHD.

**Methods:** A 4 years old girl was referred to our Department because of short stature. She showed a stature of 91cm (-2.1SDS), weight of 14kg (BMI 16.9, 0.87 z-score) reduced growth rate (3.3 cm/year) and she was on pre-pubertal maturation stage. Physical examination was normal.

Hypothyroidism, chronic diseases, malabsorption and skeletal dwarfism were excluded. GH deficiency was diagnosed by two stimulation tests: insulin (GH peak: 6.2 ng/ml) and L-dopa administration (GH peak: 4.6 ng/ml) and confirmed by low IGF-1 levels (138ng/ml (90-474)). Bone age was delayed (1.6 years). The MRI of the hypothalamic-pituitary region was normal. Karyotype of cultured lymphocytes showed 46, XX. A replacement therapy with GH (0.02 mg/Kg/week) showed a good response on linear growth.

At the age of 10 years her height was 134cm (-0.4SDS) and she was still on pre-pubertal stage. Her blood tests showed high plasma levels of gonadotropins, especially FSH (FSH=112.5miu/ml, LH=26.3miu/ml), low levels of estradiol (4.9pg/ml) and normal levels of androgens.

**Results:** The ultrasound analysis showed small uterus for her age, hypoplastic left ovary with no right ovary. Comparative Genomic hybridization (CGH) was normal. Sequencing analysis of FSHR gene using multiplex PCR of the coding regions and independent Sanger sequencing detected no mutations in the analyzed regions. This analysis however did not exclude variants outside the analyzed regions or variants not detected by this methodology

**Conclusions:** we report here the case of a girl with GHD and a phenotype of abnormality of FSHR. Patients presented with similar phenotype have been observed previously with unknown etiology, as well. Such cases may not be uncommon but FSHR abnormalities in patients with GHD are extremely rare.

P2-1325

#### IT SMELLS LIKE PRECOCIOUS PUBERTY, BUT IT IS NOT ALWAYS TRUE

Federico Baronio, MD, S.Orsola-Malpighi University Hospital, Bologna, Italy; Valentina Assirelli, MD, AOU S.Orsola-Malpighi, University of Bologna, Bologna, Italy; Rita Ortolano, MD, S.Orsola-Malpighi University Hospital, Bologna, Italy; Giulio Maltoni, MD; Ilaria Bettocchi, MD; Alessandra Cassio, Professor, AOU S.Orsola-Malpighi, University of Bologna, Bologna, Italy

**Objectives:** Precocious thelarche (PT) leads to investigations to rule out precocious puberty (PP) in girls, however in many cases it may not represent the beginning of complete pubertal development. The aim of this study is to retrospectively evaluate the clinical and biochemical features

of a series of girls referred to our Centre for precocious thelarche in the last 10 years

**Methods:** Between 2004 and 2014, 244 girls were examined at our Centre for PT at a mean age of 6.9 years: they underwent auxological, biochemical and radiologic work up for pituitary gonadal and thyroid axes function; moreover 147 patients agreed to complete a questionnaire for family history and endocrine disrupters exposure.

**Results:** 143 girls (group 1, true precocious puberty, TPP) (58%) fulfilled the standard criteria for TPP and started aGnRH treatment; 60 girls (group 2, abortive precocious puberty, APP) (24%) showed incomplete PP features that regressed within 12 months; 41 girls showed only isolated precocious thelarche (group 3, IPT) (18%). Group 1 girls had significant higher LH/FSH ratio after GnRH test, bone age, uterine volume (UV) and uterine longitudinal diameter (ULD) compared to group 2 and 3 ( $p<0.05$ ). UV and ULD were higher in girls of group 2 than group 3 ( $p<0.05$ ). Where available, family history of TPP resulted positive in higher % in group 2 (60%) than in group 1 (43%) and 3 (44%) ( $p<0.001$ ). Hyperthyreotropinemia was found in 13% of cases of group 1 and in 28% of group 2. Final height SD was higher than midparental target height SD in group 2,3. In all groups about 50% of patients utilized sometimes homeopathic drugs, and we cannot exclude the exposure to some endocrine disruptors. The incidence of APP showed an increasing trend across the decade considered.

**Conclusions:** Our results showed that: PT should be carefully evaluated to rule out TPP (58% of our cases); APP is increasing and it could be considered a new nosographic entity, that generally would not progress to TPP; in APP and TPP, hyperthyreotropinemia is more frequent than in the general pediatric population.

P2-1326

#### OUTCOMES OF GONADOTROPIN-RELEASING HORMONE AGONIST TREATMENT IN OBESE GIRLS WITH CENTRAL PRECOCIOUS PUBERTY

*Hye Ryun Kim, MD, Korea University College of Medicine, Seoul, Korea, Republic Of; Hyo-Kyoung Nam, MD, College of Medicine, Korea University, Seoul, Korea, Republic Of; Young-Jun Rhie, MD, College of Medicine, Korea University, Seoul, Korea, Republic Of; Kee-Hyoung Lee, MD, College of Medicine, Korea University, Seoul, Korea, Republic Of*

**Objectives:** The aim of this study was to investigate the influence of obesity on the clinical course and the effect of Gonadotropin-releasing hormone analogs (GnRHa) treatment in girls with central precocious puberty (CPP).

**Methods:** We reviewed the medical records of 182 girls with CPP who had been treated with GnRHa. The patients were classified as normal weight ( $n=108$ ) and overweight/obesity group ( $n=74$ ). Chronological age (CA), bone age (BA), the difference between BA and CA (BA-CA), standard deviation score (SDS) of height, BMI, predicted adult height (PAH) and laboratory findings were compared at baseline, after 1 year and the end of GnRHa treatment in both groups.

**Results:** Mean BMI at baseline were  $16.87\pm1.28$  kg/m<sup>2</sup> in normal weight group and  $20.81\pm1.36$  kg/m<sup>2</sup> in overweight/obesity group. At initiation of GnRHa treatment, the CA, BA, midparental height and PAH were similar between the two groups. At the end of treatment, BA and BA-CA were significantly higher in overweight/obesity group than normal weight group. The BA-CA after GnRHa treatment were significantly decreased compared with baseline in both groups ( $P<0.001$ ). The end PAH was significantly increased compared to baseline in both groups ( $P<0.001$ ). The end PAH in overweight/obesity group ( $159.88\pm3.41$  cm) was similar to that of the normal weight group ( $159.19\pm3.25$  cm). Remarkably, BMI SDS for CA was significantly increased in normal weight group, but not in overweight/obesity group after treatment ( $P<0.001$ ).

**Conclusions:** The GnRHa treatment in obese girls with CPP improved height outcome similarly to those of normal weight girls. Obesity may not affect the efficacy of GnRHa in CPP girls.

## POSTER SESSION 2

Friday, September 15, 2017, 11:30am-12:30pm

### P2 - Sex differentiation/gonads and disorders of sex development

P2-1500 – P2-1533

P2-1500

#### A HIGH RATE OF NOVEL CYP11B1 MUTATIONS IN PATIENTS WITH 11- $\beta$ HYDROXYLASE DEFICIENCY FROM A HIGHLY INBRED POPULATION

*Doha S. Alhomaidah, MD, Farwanya Hospital, Sabah Al-Naser, Kuwait; Ali S Alzahrani, MD, King Faisal Hospital and research center, Riyadh, Saudi Arabia*

**Objectives:** 11  $\beta$ -hydroxylase deficiency (11- $\beta$  OHD) due to *CYP11B1* mutations is the second most common form of congenital adrenal hyperplasia (CAH). We report a high rate of novel mutations in this gene from a highly inbred population and describe their clinical and biochemical features and gender assignment decisions.

**Methods:** We studied 11 patients with 11- $\beta$  OHD from 6 unrelated families. DNA was isolated from peripheral blood. The 9 exons and exon-intron boundaries of *CYP11B1* were PCR-amplified and directly sequenced.

**Results:** Family 1 (Three 46XX and one 46XY siblings) had a novel single nucleotide insertion mutation in codon 18 (c.53\_54insT) leading to frameshift and truncation 21 codons downstream. Family 2 (two siblings) presented with clitoromegaly and had a novel missense mutation (c.1343 G>C, p.488R>P). They were raised as females. Family 3 (One 46XX and one 46XY siblings) had also a novel missense mutation (c.1394 A>T, p.465 H>L). A 46 XX patient had a recently described non-sense mutation (c. 780G>A, p.260W>X). Her family chose to raise her as a male. Another 46 XX patient had a novel missense mutation (c.617 G>T, p.206 G>V) and was raised as a female. The last patient had the same novel

mutation (c.1343 G>C, p.448 R>P) that was found in family 2 and was raised as a male.

**Conclusions:** We describe the clinical, biochemical and molecular genetics of 11 cases with 11- $\beta$  OHD from 6 unrelated families. A high rate of novel missense and nonsense mutations was found in this series.

P2-1501

**COMPARISON OF CLINICAL AND METABOLIC EFFECTS OF TESTOSTERONE AND ESTRADIOL IN ADULT GONADECTOMIZED PATIENTS WITH 46,XY DSD DUE TO COMPLETE ANDROGEN INSENSITIVITY SYNDROME (CAIS) - (EUDRACT-NR: 2010-021790-37).**

*Wiebke Birnbaum, MD; Olaf Hiort, PhD; Louise Marshall, Psychologist, University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany*

**Objectives:** Primary objective: To detect differences in the effects of testosterone versus estradiol treatment on quality of life and wellbeing in patients with CAIS due to mutation of the androgen receptor.

Secondary objectives: To compare endocrine profiles between both treatments and to determine levels of SHBG, Insulin, Cholesterol (total, HDL, LDL), Triglycerides, Hematocrit, Haemoglobin as control parameters and to investigate the correlations with quality of life and hormones.

**Methods:** We designed a national multicenter, controlled, double-blind randomized cross-over clinical trial (phase III) according to the German Medicines Law. The study was coordinated and conducted at our national centre of referral for disorders of sex development in Lübeck/ Germany. After a run-in-phase with estradiol (Gynokadin, 1,5mg transdermal application) all probands received 6 months estradiol (Gynokadin, 1,5mg transdermal application) and 6 months testosterone (Testogel, 50mg transdermal application) in a cross-over design. According to the study protocol all patients were seen for 7 visits, including follow-up. Psychological wellbeing and sexual functioning was assessed using the SF36, BSI and FSFI respectively. Steroid profiles in serum and urine were measured by mass spectrometry. Molecular genetic analysis of the AR-gene was mandatory before exposure to study medication.

**Results:** From November 2011 to July 2014 26 patients have been randomized. 9 patients left the study before completion of the whole trial.

We will present the first results of 118 data sets including evaluation of wellbeing, sexual functioning and measuring CAIS specific clinical findings and endocrine profiles.

**Conclusions:** This study is the first standardized assessment of endocrine treatment performed in CAIS and the first controlled pharmaceutical trial in the field of DSD. The results of this study could lead to a different recommendation for hormone replacement therapy in patients with CAIS. The mechanisms for testosterone-induced effects need to be elucidated in detail.

P2-1502

**EUROPEAN CONSENSUS ON THE STANDARDIZED FOLLOW-UP OF INDIVIDUALS WHO HAVE A DSD ACROSS THE LIFE SPAN**

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**Objectives:** As Differences of Sex Development (DSD) comprise rare to very rare variable conditions, sharing expertise among healthcare workers and international collaboration in prospective studies is essential to gain insight in health-related outcome of affected individuals. The aim of our work was to develop guidance for healthcare workers on data that should be collected routinely and longitudinally, and which could be incorporated into a detailed registry, such as the I-DSD registry.

**Methods:** A multidisciplinary working group of European clinical experts in DSD and patient representatives was created in the framework of "DSDnet", a network granted by the EU-funded program European Cooperation in Science and Technology (COST). Through round-table discussions and literature review, consensus was reached on optimal long-term follow-up of individuals with atypical sex development and on standardized collection of outcome data, reflecting phenotypical aspects, associated morbidities, mental health and gender contentedness across ages.

**Results:** The age (ranges) of 1 month after birth, 4 and 8 years, prepuberty, at end of puberty and between ages 18-25, 25-40, 40-60 and 60-75 were identified as critical milestones for clinical assessment. Per age category, a core dataset was developed, with pre-specified outcomes and an option to include limited free text for each variable. Emphasis was placed on a non-binary and holistic approach of DSD conditions, covering a broad range of physical (e.g. external genitalia, cardiovascular health, bone strength) as well as psychological (e.g. gender development, received psychosocial support) determinants of health and well-being that could be quickly captured objectively as part of routine clinical practice.

**Conclusions:** Consensus on best practices for standardised follow-up of individuals who have a DSD was developed by a group of professionals and patient representatives. This will provide clinical guidance for new multidisciplinary teams and enable standardised and routine collection of outcome data at all developmental ages, facilitating large-scale multicenter studies.

PLEASE SEE TABLE ON THE FOLLOWING PAGE

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P2-1503

# **DEFINING THE DOSE, TYPE AND TIMING OF GLUCOCORTICOID AND MINERALOCORTICOID REPLACEMENT IN 256 CHILDREN AND ADULTS WITH CONGENITAL ADRENAL HYPERPLASIA (CAH) IN THE I-CAH REGISTRY**

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**Objectives:** Physiological replacement is important for optimal control of congenital adrenal hyperplasia (CAH). We examined glucocorticoid and mineralocorticoid replacement in children and adults with CAH.

**Methods:** Data were extracted in February 2017 for 22 centres in 14 countries from the international I-CAH registry ([www.i-cah.org](http://www.i-cah.org)). 1501 events from 269 patients seen between 1987 and 2017 were analyzed.

**Results:** 256 patients had information on glucocorticoids (F 136, M 116, 4 sex not assigned; 0-1y n=130, 69F, 1-8y n=153 82F, 8-12y n=42 26F, 12-18y n=39 23F, 18-30y n=27 12F, 30-60y n=26 14F). The majority of pediatric patients were treated with hydrocortisone (HC) and adults with prednisolone (Pred) and some with cortisone acetate (CA) and dexamethasone (DEX); 0-1y: HC 92%, CA 8%, Dex 1%, 1-8y: HC 93%, CA 6%, Pred 1%, 8-12y: HC 83%, CA 7%, Dex 5%, Pred 5%, 12-18y: HC 69%, CA 3%, Dex 18%, Pred 10%, 18-30y: HC 33%, CA 4%, Dex 26%, Pred 37%, 30-60y: HC 31%, Dex 12%, Pred 54%. The HC-equivalent dose varied significantly between age groups,  $p=0.02$  (mean $\pm$ sd in mg/m<sup>2</sup>/day); 0-1y (15.3 $\pm$ 8.3), 1-8y (13.6 $\pm$ 12.3), 8-12y (15.2 $\pm$ 5.9), 12-18y (15.7 $\pm$ 6.8), 18-30y (16.0 $\pm$ 5.1), 30-60y (12.2 $\pm$ 5.8). Information on mineralocorticoids was available in 22We hab7 patients (F 119, M 105, 3 sex not assigned). Average fludrocortisone dose and frequency of administration was (mean $\pm$ sd, frequency in % of patients); 0-1y (101.2 $\pm$ 62.1mcg, od 59%/ bd 32%/ tds 11%), 1-8y (91.07 $\pm$ 61.7mcg, od 70%/ bd 26%/ tds 4%), 8-12y (84.41 $\pm$ 44.1mcg, od 82%/ bd 32%/ tds 3%), 12-18y (111.4 $\pm$ 52.6mcg, od 81%/ bd 19%), 18-30y (134.5 $\pm$ 68.2mcg, od 90%/ bd 10%), 30-60y (152.9 $\pm$ 74.4mcg, od 71%/ bd 29%). Total fludrocortisone dose mcg/m<sup>2</sup>/day was significantly higher in children younger than 8y,  $p<0.0001$  (mean $\pm$ sd): 0-1y (274.2 $\pm$ 181.7), 1-8y (146.7 $\pm$ 129.7), 8-12y (63.3 $\pm$ 34.3), 12-18y (66.43 $\pm$ 34.3), 18-30y (77.1 $\pm$ 37.1), 30-60y (74.8 $\pm$ 37.9).

**Conclusions:** Data from a large international cohort of CAH patients confirm variations in the hormonal replacement regimens between pediatric and adult patients. Glucocorticoid doses were high in some age groups compared to recommendations in current guidelines.

P2-1504

# **PSYCHOSOCIAL SCREENING IN THE DSD POPULATION: PSYCHOMETRIC PROPERTIES OF THE PSYCHOSOCIAL ASSESSMENT TOOL IN A CLINICAL SAMPLE.**

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Hospital Medical Center, Cincinnati, OH, United States; David E Sandberg, PhD, University of Michigan, Ann Arbor, MI, United States

**Objectives:** This study evaluated the psychometric properties of the Psychosocial Assessment Tool (PAT), a screening tool for psychosocial risk validated in other chronic illness populations, with the purpose of promoting efficient and effective comprehensive care for patients with DSD and their families.

**Methods:** Study sites were health care institutions comprising the DSD-TRN, a US NIH-sponsored clinical research network. 197 caregivers of DSD patients completed the PAT as part of standardized, routine care during clinic visits. The PAT is scored into 7 subscales and provides an overall total level of family risk. Subsets of these caregivers also completed the PHQ4, a brief screening measure of adult depression/anxiety. Statistical plan included descriptive analysis and internal consistency of the PAT scale, and correlational analysis of the PAT with the PHQ4 as a measure of convergent validity.

**Results:** The average PAT Total score was  $0.89 \pm 0.66$ , indicating universal (low risk). However, 65% of caregivers scored in the low risk category, 28.9% scored in the medium risk and 6.1% scored in the high risk. Internal consistency for the PAT Total score was high ( $\alpha = 0.86$ ), with 6 of the 7 subscales having  $\alpha > 0.60$ . Highest scores among subscales were for child emotional-behavioral problems and caregiver emotional-behavioral problems. Caregiver PHQ4 score was associated with the PAT Family Problems subscale ( $r = 0.47$ ,  $p < 0.01$ ), and the PAT Total score ( $r = 0.43$ ,  $p < 0.01$ ).

**Conclusions:** The PAT demonstrated good internal consistency in this DSD sample, and was correlated as expected with caregiver psychosocial distress. One-third of families scored in at-risk categories, highlighting the role of psychosocial support. Children with DSD and their families may face a range of challenges including medication/hormone management, coping with medical exams/procedures, gender concerns, fears of stigmatization and complicated treatment decision-making. Current DSD care guidelines emphasize the importance of providing routine psychosocial assessment and intervention for patients and families, yet lack of psychosocial resources may compromise implementation. Use of a validated psychosocial screener such as the PAT has the potential to effectively identify at-risk families so that care teams can provide targeted psychosocial care.

P2-1505

#### **NORMALIZING OVULATION RATE BY PREFERENTIAL REDUCTION OF HEPATO-VISCERAL FAT IN ADOLESCENT GIRLS WITH POLYCYSTIC OVARY SYNDROME**

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**Objectives:** Polycystic Ovary Syndrome (PCOS) is an increasingly prevalent disorder in adolescent girls, commonly presenting with hirsutism/oligomenorrhea, commonly treated with an oral contraceptive (OC), and commonly followed by oligo-anovulatory subfertility. We tested whether an intervention targeting the reduction of hepato-visceral adiposity is followed by a higher ovulation rate than OC treatment.

**Methods:** This randomized, open-label, single-center, pilot proof-of-concept study (12 months on treatment, then 12 months off) was performed in adolescent girls with hirsutism and oligomenorrhea (PCOS by NIH; no sexual activity; N=36; mean age 16 years, BMI 23.5 Kg/m<sup>2</sup>; 94% study completion). Compared treatments were OC (ethinylestradiol-levonorgestrel) versus low-dose combination of spironolactone 50 mg/d, pioglitazone 7.5 mg/d, and metformin 850 mg/d (SPIOMET). Primary outcome was post-treatment ovulation rate inferred from menstrual diaries and salivary progesterone (12 + 12 weeks). Secondary outcomes included body composition (DXA), abdominal fat (MRI), insulinemia (oGTT), and androgenemia (LC-MS/MS).

**Results:** SPIOMET was followed by a 2.5-fold higher ovulation rate than OC ( $P \leq 0.001$ ), and by a 6-fold higher normovulatory fraction (71% vs 12%;  $P \leq 0.001$ ); oligo-anovulation risk after SPIOMET was 65% lower (95%CI, 40-89%) than after OC. Higher post-treatment ovulation rates related to more on-treatment loss of hepatic fat ( $r^2 = 0.27$ ;  $P < 0.005$ ). Visceral fat and insulinemia normalized only with SPIOMET; androgenemia normalized faster with OC, but rebounded more thereafter. Body weight, lean mass, and abdominal subcutaneous fat mass remained stable in both groups.

**Conclusions:** Early SPIOMET treatment for PCOS normalized post-treatment ovulation rates more than OC. Focusing PCOS treatment on early reduction of hepato-visceral fat may prevent part of later oligoanovulatory subfertility.

P2-1506

#### **DISORDERS OF SEX DEVELOPMENT IN A SINGLE ACADEMIC CENTER**

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**Objectives:** Disorders of sexual development (DSDs) are a diverse group of congenital deviations in chromosomal, anatomic and gonadal sex development (Hughes et al., 2006). We describe the phenotypic spectrum of DSD patients treated in a single pediatric tertiary center (HUHC) with special attention in the diagnostic effectiveness of the most common sex chromosome DSDs (Turner [TS] and Klinefelter [KS] syndromes), and report a shift in the management of bilateral during the 11-yr survey period.

**Methods:** The patients who had visited HUCH between 2004 and 2014 were identified based on an ICD 10 inquiry. Patients with the mildest forms, *i.e.* unilateral cryptorchidism or distal hypospadias were excluded.

**Results:** We identified 523 patients with a DSD; 52% had 46,XY DSD; 39 % had sex chromosome DSD, and 9% had 46,XX DSD. Patients with TS or KS were most frequently referred based on deceleration of growth or the special needs of the child, and there were no significant trends in the age at diagnosis in either patient groups. Bilateral cryptorchidism was operated at an older age before 2007 than thereafter ( $P=0.0001$ ).

**Conclusions:** DSD patients comprise a large and vulnerable patient group, which is characterized by delayed diagnostics, and for whom evidence-based treatment guidelines are scarce. We propose age at bilateral cryptorchidism and age at diagnosis of TS and KS as simple indices for monitoring the diagnostic efficiency and management of DSD patients within and between different centers.

P2-1507

#### ACCURACY AND CLINICAL IMPLICATIONS OF THE PRENATAL DIAGNOSIS OF ABNORMAL GENITALIA.

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**Objectives:** Disorders of sex development (DSD) are increasingly commonly diagnosed by prenatal abnormalities of external genitalia.

**Objective:** to evaluate the role of the prenatal ultrasound in the diagnosis of DSD and our practices in terms of additional prenatal examinations and communication of the diagnosis.

**Methods:** A retrospective study was conducted between 2006 and 2014

**Results:** Results: A retrospective study was conducted between 2006 and 2014. A genital anomaly was prenatally diagnosed in 30 cases : 73% 46, XY DSD (26 %posterior hypospadias , 6% bifid scrotum , 20 % micropenis, 13% chordee and 13% undescended testis) and 27% 46, XX DSD. 93% are isolated DSD. Overall, 83.3% of the cases (86% 46,XY DSD/75% 46,XX DSD) were confirmed at birth. The gestational age at diagnosis was 24.4 weeks (16-32). Prenatal diagnostic testing varied widely, from no tests to multiple molecular tests with amniotic fluid hormone concentrations : sex testing was performed in 84% of cases (karyotype in 54% of cases, fluorescent in-situ hybridisation (FISH) in 46% of cases), while hormone levels in amniotic fluid were measured in 63% of the cases (68% of 46,XY and 50% of 46,XX). Nearly two-thirds of cases (63%) were screened for 21 hydroxylase deficiency

and androgen receptor abnormalities. A questionnaire evaluating the communication of the diagnosis was sent to 25 families (address information being missing for 5 families) and 18/25 (72%) responded. All parents considered that the information delivered before birth allowed them to be more prepared (60% 'very', 40% 'moderately'). The quality of the information given prenatally was judged as 'good' in most cases.

**Conclusions:** Conclusion: Prenatal diagnosis of external genital abnormalities by ultrasound seems to be an effective tool in both sexes. To assess the sensitivity and specificity of this examination more exactly, prospective studies are necessary. Parents reported being generally satisfied with the quality, accuracy and timing of the communication of the diagnosis

P2-1508

#### MASS SPECTROMETRY: THE MAGIC BULLET IN CLINICAL STEROID ANALYSIS? HETEROGENEITY OF MASS SPECTROMETRY BASED REFERENCE VALUES FOR 17-HYDROXYPROGESTERONE (17OHP) SIGNALS URGENT NEED FOR HARMONIZATION

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**Objectives:** The use of mass spectrometry (MS) for measurement of 17-hydroxyprogesterone (17OHP) is increasingly common. This survey was conducted to compare the reference intervals reported by laboratories using MS assay.

**Methods:** This study analysed a subset of data belonging to a larger survey examining the preanalytical, analytical and post-analytical phases of MS-based 17OHP laboratory methods. Participants were invited via national and international laboratory medicine societies. In total 44 valid survey responses were received globally, of which, 26 provided data regarding reference intervals and were summarised in this study.

**Results:** Twenty-one laboratories reported their results in Système International units. The paediatric reference intervals showed marked heterogeneity. The starting age of the reference intervals varied from 26 weeks pre-term to day-7 post-delivery. Only 3 laboratories accounted for Tanner staging. The paediatric reference intervals were partitioned between one and twelve groups. The upper reference limit differed by more than 10 folds between laboratories in some instances.

**Conclusions:** When comparing the reference values of serum 17OHP for various age groups produced by MS-based

techniques, the huge extent of heterogeneity is striking. With one exception of gas chromatograph MS, liquid chromatography MS was the preferred analytical technique. The differences found are worrisome because they are most likely due to variations in assay quality than to physiological differences of individuals analyzed. As long as harmonization and standardization are not implemented, reference ranges cannot be automatically transferred between methods, even though MS is the underlying analytical principle.

P2-1509

#### REDUCED PRENATAL WEIGHT GAIN AND/OR AUGMENTED POSTNATAL WEIGHT GAIN PRECEDE POLYCYSTIC OVARY SYNDROME IN ADOLESCENT GIRLS

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**Objectives:** Hepato-visceral fat excess is a feature of Polycystic Ovary Syndrome (PCOS). Risk factors for such excess include a reduced prenatal weight gain and an augmented postnatal weight gain. We studied whether PCOS in adolescent girls was preceded by a relatively low birth weight and/or a relatively high body mass index (BMI) at PCOS diagnosis.

**Methods:** The adolescent study population consisted of 298 non-obese and 169 obese girls with PCOS diagnosed respectively in Barcelona/Spain and Datteln/Germany; 87 healthy girls served as controls. Z-scores for weight-at-birth and for BMI-at-PCOS-diagnosis were derived from country-, age- and sex-specific references; individual changes between these Z-scores were calculated.

**Results:** Healthy control girls had mean birth weight and BMI Z-scores close to nil, as expected. Non-obese Spanish and obese German PCOS girls had mean birth weight Z-scores of -0.7 and 0.0, and mean BMI Z-scores of +0.4 and +2.7, so that mean Z-score increments amounted to +1.1 and +2.6 ( $P < 0.001$  versus controls).

**Conclusions:** PCOS in adolescent girls was found to be preceded by a marked Z-score rise between weight-at-birth and BMI-at-PCOS-diagnosis, thus corroborating the notion that prenatal and postnatal weight gain have opposing influences on PCOS development, as they have on adrenarche and on age at menarche. PCOS is not a gynecological syndrome, but an outcome of a metabolically unfavorable sequence of early weight gains.

P2-1510

#### SEXUAL FUNCTIONING OF ADULT GONAECTOMIZED CAIS

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**Objectives:** Sexuality plays a major role in caring for people with Differences of Sex Development (DSD). Sexual functioning might be impeded due to the given anatomy, medical interventions or hormonal therapy. Women with complete androgen insensitivity (CAIS) voice severe complaints after gonadectomy about reduced life quality. A questionnaire that polled amongst others issues for sexual activity and problems gave insight into this topic in adult women with CAIS.

Primary objective: to investigate sexual satisfaction and sexual problems in adult women with CAIS after gonadectomy.

Secondary objectives: to compare sexual satisfaction and sexual problems of patients with CAIS to other DSD diagnoses  
**Methods:** The questionnaire derived from the German Network Study of Disorders of Sex Development (Thyen et al. 2010) Sexual functioning was expressed in 13 items. Within the CAIS study the questionnaire was applied before the beginning of study medication to elucidate individual baseline parameters. Participants were on an Estradiol-Monotherapy at the time.

Data sets from 26 participants of the CAIS study and 74 participants of the German Network Study (42/ CAH; 24/gonadal dysgenesis; 7/ deficiency in androgen synthesis) were analyzed.

**Results:** Sexual satisfaction in women with CAIS is significantly lower than in persons with other DSD diagnoses. Within the compared groups only 10 % were satisfied, followed by gonadal dysgenesis (35%), CAH (50%). Persons with deficiency in androgen synthesis achieved 60% in the satisfaction score. These scores express e.g. sexual inappetency (61.5%), lack of arousal (57,7%), pain during intercourse (65.4%).

**Conclusions:** It seems likely that vaginal hypoplasia, problems with arousal and pain impede sexual life in women with CAIS. So far the impact of hormone treatment on sexual satisfaction has not been elucidated. The data presented emphasize the importance for the clinical trial investigating hormone treatment in gonadectomized women with CAIS.

# ETHICS CLINICAL COMMITTEE AND THE AGREEING WITH ETHICS PRINCIPLES RECOMMENDATIONS IN THE MANAGEMENT OF DISORDER OF SEX DEVELOPMENT IN SOME COUNTRIES OF LATIN AMERICA

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**Objectives:** To know the extent of use of Ethics Clinical Committee (ECC) and the agreeing with ethics principles recommendations (EPR) in the management of disorder of sex development (DSD) (*Eur J Pediatr.* 2010).

**Methods:** Adult and pediatric endocrinologist, gynecologist, geneticist, and pediatric urologist from some countries in Latin America were invited to answer an electronic survey. Data from Likert scale was reduced into two categories of "accept" and "reject".

**Results:** A total of 46 survey were returned: Argentina (3), Brazil (2), Chile (31), Colombia (5), Mexico (3), Venezuela (1), USA (1). The ECC was reported to be consulted in the management of DSD: Always (8), in some patients (21), non-exist (1) and never (15). The level of agreement with the following statement were: 1) DSD do not *per se* require correction and for new-borns, do not represent a surgical emergency: Accept 91.5%. 2) The health-care team must comprehensively involve the parents in the decision-making and therapy-planning process: Accept 97.8%. 3) The child's well-being is not automatically ensured by determining an external and/or biologically unambiguous sex: Accept 89.1%. 4) A therapeutic stance of openness and acceptance is to be encouraged: Accept 93.5%. 5) All interventions must be based upon the most exhaustive diagnostics and the best possible prognosis: Accept 100%. 6) Explicit reasoning and justification are necessary when interventions are being considered that are not substantiated by any satisfactorily conclusive scientific evidence: Accept 97.8%. 7) The child should be given information about its condition that is commensurate with its age: Accept 82.6%. 8) The right of the future adult to obtain information about the treatment it received during childhood: Accept 100%. 9) Ethical research should help evaluate whether they can be feasibly put into practice and to what extent the affected persons, their parents, or the health-care team find them to be helpful and appropriate: Accept 95.7%.

**Conclusions:** A highly acceptance to the EPR suggested by Wiesemann *et al.* in the management of DSD was observed in this sample. The ECC should always consider as part of the inter-disciplinary team.

# EXOME SEQUENCING IDENTIFIES NEW GENES INVOLVED IN HUMAN GONAD DEVELOPMENT

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**Objectives:** Disorders of sex development (DSD) are a group of rare complex orphan diseases of errors of gonadal development and hormone synthesis or action. This includes the rare disorders of sex-determination – a failure of testis-determination (46,XY gonadal dysgenesis) or testis formation on a 46,XX background (46,XX testicular or ovotesticular DSD). 40% of all cases of 46,XY gonadal dysgenesis can be explained by mutations involving *SRY*, *NR5A1* or *MAP3K1*. Rare cases are caused by mutations involving *GATA4* or its partner *FOG2/ZFPM2*. Most non-syndromic 46,XX DSD patients carry the *SRY* gene or have rearrangements involving different *SOX* gene *loci*. However, the majority of *SRY*-negative 46,XX DSD cases and 46,XY gonadal dysgenesis cases do not have a molecular diagnosis. Unbiased genomic approaches, such as exome sequencing should reveal new gene mutations causing DSD.

**Methods:** We performed whole exome sequencing on 250 cases of DSD at a coverage of x50. This included 180 cases with either 46,XY gonadal dysgenesis or 46,XX-*SRY* negative (ovo)testicular DSD. This also included 20 familial cases of DSD and 37 syndromic forms of DSD.

**Results:** Analysis of datasets revealed novel mutations in genes known to be associated with syndromic and non-syndromic forms of DSD including *RSPO1*, *WT1*, *ARX*, *SRY*, *GATA4*, *FOG2*, *WNT4*, *MAP3K1* and *NR5A1*. In additional novel and likely pathogenic mutations were identified in *SOX* genes, extra-cellular matrix proteins, and genes involved in the WNT signalling pathway.

**Conclusions:** Exome sequencing is a powerful, cost-effective and rapid approach to identify known causes of DSD as well as new genetic factors involved in human urogenital development.

# ALTERED CYP19A1 AND CYP3A4 ACTIVITIES DUE TO MUTATIONS IN THE FLAVIN MONONUCLEOTIDE BINDING DOMAIN OF HUMAN P450 OXIDOREDUCTASE

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**Objectives:** Cytochromes P450 proteins are responsible for the metabolism of many steroid hormones as well as drugs

and xenobiotics. All cytochromes P450s in the endoplasmic reticulum rely on P450 oxidoreductase (POR) for their catalytic activities. Previously it has been shown that mutations in POR cause metabolic disorders of steroid hormone biosynthesis and also affect certain drug metabolizing P450 activities. Human POR has distinct subdomains, which bind flavin molecules and interact with redox partners. We aimed to characterize the mutations identified in flavin mononucleotide (FMN) binding domain of POR that interacts with cytochrome P450 and other partner proteins.

**Methods:** WT and mutant POR proteins as well as cytochrome P450s were expressed in recombinant form in bacteria and purified. We used liposomes to embed the P450 and POR proteins and created a functional P450 metabolic system. Metabolism of Testosterone, androstenedione as well as small molecule dyes and tracer compounds was evaluated by radioactive ligand metabolism, fluorescent substrate metabolism and colorimetric assays using chromogenic substrates. Enzyme kinetic analysis was performed using Prizm.

**Results:** We found that mutations A115V, T142A located close to the FMN binding site had reduced flavin content compared to wild type POR and lost almost all activity to metabolize androstenedione via CYP19A1 and also showed reduced CYP3A4 activity. The variant A284L identified from normal subjects also had severe loss of both CYP19A1 and CYP3A4 activities, indicating this to be a potentially disease causing mutation. The mutation Q153R initially identified in a patient with disordered steroidogenesis showed remarkably increased activities of both CYP19A1 and CYP3A4 without any significant change in flavin content, indicating improved protein-protein

interactions between POR Q153R and some P450 proteins.

**Conclusions:** These results indicate that effects of mutations on activities of individual cytochromes P450 can be variable and a detailed analysis of each variant with different partner proteins is necessary to accurately determine the genotype-phenotype correlations of POR variants.

P2-1514

**FREQUENCY OF METABOLIC SYNDROME IN PATIENTS WITH KLINEFELTER SYNDROME FROM THE DSD-LIFE COHORT**

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**Objectives:** to determine the frequency of MBS in patients with Klinefelter Syndrome (KS) from DSD Life cohort

**Methods:** This study was part of the DSD life study ([www.dsd-life.eu](http://www.dsd-life.eu)). After completion of paperwork, signed consent, biometric screenings (height, weight, body mass index (BMI), waist circumference (WC) and blood pressure

were completed. Given the tall men, we chose to retain the waist to height ratio. Fasting laboratory values were measured, Triglycerides (TG), HDL cholesterol, glucose levels were performed. Drug list was requested. The American heart Association (AHA)/National Heart, lung and blood institute (NHLBI) definition requires three of the following risk factors be present for diagnosis of MBS: WC to height ratio >0.5, TG ≥150 mg/dl, HDLc < 40 mg/dl or taking medication, diastolic blood pressure ≥ 130 mmhg and systolic ≥ 85 mmhg or taking medication, fasting glucose ≥ 100 mg/dl or taking antidiabetic medication.

**Results:** 218 patients with KS (median 38 (15-75) years) were included, median of height was 184 m (157-208 cm), BMI was 25.75 kg/m<sup>2</sup> (13.9-47.3). Overweight and obesity were respectively in 35.8% and 16.0 % of cases. Their karyotype was a 47XXY (94%), mosaicism and other in 6% of cases.

	WC/H ratio N (%)	High Syst or treated N (%)	High Diastolic or treated N (%)	High Glucose N (%)	Low HDL N (%)	High Triglyceride N (%)
Missing data	68 (32)	67 (30)	72 (33)	114 (52)	110 (50)	91 (41.7)
No	47 (33.5)	73 (33.5)	86 (39)	62 (28.5)	63 (29)	89 (40.8)
Yes	103 (35.8)	78 (35.8)	60 (27.7)	42 (19.5)	45 (20.6)	38 (17)

Everyday life activity was less than 3 hours in 23%, 3 hours and more in 58% of cases. About smoking behavior we noted 17% of current smoker and former smoker in 13.7%. We noted the importance of missing data for MBS in 55 cases (25%). On the complete files, 66 patients (30%) had 3 criteria or more; 33 patients (15%) had 2 positive criteria, 64 patients presented 0 or 1 criteria of MBS (29%).

**Conclusions:** It is imperative that metabolic syndrome be identified and treated to preserve the health and well-being. In our cohort, one third of patients a complete MBS with at least 3 factors. We emphasize on practiced regular physical activity and dietary advice.

P2-1515

**CURRENT SURGICAL PRACTICE IN DSD: RESULTS OF THE COST/DSDNET SURGERY SURVEY**

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**Objectives:** Differences in Sex Development (DSD) describe a heterogeneous group of conditions with unusual sex development, often with effect on the appearance of the genitalia and function of the reproductive system. Surgical treatment of these conditions is not standardized and controversial. The purpose of the survey was to delineate

current surgical practice in DSD within the dedicated surgical community.

**Methods:** A surveymonkey® survey consisting of 49 items was developed by a working group of COST BM1303/DSDNet and spread among the surgical DSD community using an email invitation to subspecialty organisations, personal contacts, and social media. There were 124 responders: 76%/24% male/female; >80% pediatric surgeons and pediatric urologists; from all regions of the world (Europe 56%).

**Results:** 90% of the participants work in a multidisciplinary DSD team (67% always with endocrinologists, 35% always with psychologists). In only 20% the surgeon is clinical lead of the team. In 19% of participants surgical options cannot be discussed in the team. However, in 15% support groups are involved in the decision making process. There is no standardized tool how DSD surgical activity is recorded. More than 70% of the DSD centers do not take part audit or quality improvement exercises. Case load in diagnostic procedures as well as feminizing surgery was around 2-4 cases per doctor per year. In contrast to optimal sexual functioning and fertility issues, cosmesis was regarded as least important outcome parameter. Stratification according to geopolitical criteria, sex, subspecialty or year of graduation showed no significant differences except for timing of feminizing surgery which was postponed significantly more often (29%) to adolescence or adulthood by surgeons from Western countries ( $p < 0.05$ ). Almost all respondents preferred masculinizing surgery during the first 24 months of life.

**Conclusions:** This survey shows that there is considerable variation in the surgical treatment of DSD. Multidisciplinary management, audit and prospective patient registries still have to be developed.

P2-1516

#### CREATION OF AN E-RESOURCE REPOSITORY FOR DIFFERENCES/DISORDERS OF SEX DEVELOPMENT (DSD): COLLABORATION BETWEEN CLINICIANS AND ADVOCATES IN THE DSD TRANSLATIONAL RESEARCH NETWORK

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**Objectives:** To create an e-resource repository for people affected by Differences/Disorders of Sex Development (DSD) and DSD providers, by collaboration between affected

individuals and advocates, and interdisciplinary DSD health providers and scientists.

**Methods:** The project was a collaboration between advocates, health providers and scientists who were members of the DSD Translational Research Network (DSD-TRN), a network of 10 interdisciplinary DSD teams in the US committed to standardizing care based on evolving evidence for best practice in DSD. The e-resource repository was developed in three stages: 1) creation of the initial repository by the project team (workgroup of three advocates and one physician), 2) evaluation and feedback of the resources by interdisciplinary teams in the DSD-TRN (a survey by the DSD-TRN Psychosocial workgroup), and 3) achieving consensus. Twitter-like descriptions were written, and resources were categorized by target age, audience, and specific condition.

**Results:** Forty resources, including educational and informational, peer support and advocacy groups, young adult- and clinician-oriented resources were reviewed and categorized. Seven of 10 centers responded to the survey. Awareness and familiarity about the resources varied between centers from complete lack to full awareness, and teams provided feedback regarding which resources to include. A consensus was achieved when opinions differed, and 30 resources were eventually included in the repository. The repository will be available to the public online and as a printable brochure.

**Conclusions:** This e-resource repository was created to increase awareness and access to resources that provide information, education and support for those affected by DSD. It represents collaboration and communication between advocates and health providers, an important shift towards transforming care in DSD. As knowledge about DSD grows, it is hoped that the repository will continue to evolve.

P2-1517

#### DISORDERS OF SEX DEVELOPMENT IN CAMEROON: DIFFICULT QUESTIONS, WHICH ANSWERS?

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**Objectives:** Describe epidemiological clinical, aetiologies and management aspect of DSD in a developing country

**Methods:** This is a 5 years retrospective study. All patients referred for DSD in the single paediatric endocrinology service of the Mother and Child Centre of Chantal Biya Foundation was reviewed. Socio epidemiological variables, external genitalia were described as so as internal sex organs and tanner stage. 17 hydroxyprogesterone, sexual steroids were measured and genetic testing when possible

**Results:** We included 65 patients with a median age at consultation of 2.6 years. No consanguinity was found. Sex assignment was already done in 89.2% of them. After hormonal assay and genetic testing (when available) congenital adrenal hyperplasia was found in 26 (40%), gonadal dysgenesis in 14 (21 %), 7 (10.5%) ovotestis, were main diagnosis. There was a wrong initial sex assignment in 20% of patients with CAH leading to extreme management difficulties.

**Conclusions:** CAH is the main aetiology of DSD in this single pediatric endocrinologic center. There is a wrong sex assignment in many cases leading in extreme management difficulties questioning the issue of midwives training and neonatal screening in our setting.

P2-1518

#### THE INFLUENCE OF PARENT-RATED SEVERITY OF ILLNESS ON PARENT ANXIETY IN FAMILIES WITH CHILDREN BORN WITH AMBIGUOUS GENITALIA

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**Objectives:** Parents of children born with a disorder/difference of sex development (DSD) including ambiguous genitalia are at risk for negative psychological adjustment. Physician-rated severity of illness (SOI) is associated with parental psychological adjustment in other pediatric chronic illnesses, but the impact of parental perception of SOI on parents' own adjustment has not yet been studied in DSD. We aimed to prospectively examine the effect of subjective parent ratings of their child's SOI on their anxiety prior to, and following, their child receiving early (< 2 years of age) genitoplasty.

**Methods:** Participants were 71 parents ( $M_{age}=33.4$ ,  $SD=6.86$ ; 59.4% female) of 42 children born with ambiguous genitalia prior to undergoing genitoplasty. Participants were recruited from 10 specialized DSD clinics and completed questionnaires within 6-months of diagnosis (baseline), at 6-months post-genitoplasty and at 12-months post-genitoplasty. Multi-level linear modeling was used to account for dependence between observations from the same parent, and between parents from the same family.

**Results:** A likelihood-ratio test after estimation indicated that time accounted for a significant proportion of variance above that accounted for by the unconditional model of anxiety scores, ( $\chi^2(1) = 4.43$ ,  $p < .05$ ) meaning that parent-reported anxiety symptoms decreased over time. A significant positive relationship between SOI ratings at baseline and anxiety scores across time was found ( $b = 0.47$ ,  $SE = 0.19$ ,  $p < .05$ ) and a likelihood-ratio test after estimation indicated that baseline SOI scores accounted for a significant proportion of variance above the model with only time as a predictor,  $\chi^2(1) = 5.50$ ,  $p < .05$ . This indicates that higher baseline SOI scores were related to higher anxiety across 12-months following diagnosis.

**Conclusions:** Overall parent-report of anxiety decreased from baseline to 12-month follow-up, but those parents who rated their child as more ill at baseline experienced greater anxiety that persisted over time. This highlights the need for early intervention aimed at improving skills for coping with illness severity for those parents who are at risk for maladaptive adjustment outcomes.

P2-1519

#### EFFECT OF BLOOD TRANSFUSION ON THE GONADAL AXIS AND SPERM COUNT IN ADOLESCENTS WITH SICKLE CELL DISEASE (SCD)

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**Objectives:** : We evaluated the effect of packed red cell transfusion (PCTx) on serum concentrations of gonadotropins and testosterone (T) levels and measured sperm count in 8 adolescents with sickle cell disease (SCD) on top-up



transfusion (TTx) ( n =3) and those on exchange transfusion (ETx) regimen ( n =5).

**Methods:** Basal serum concentrations of FSH, LH, and T and semen parameters were evaluated before and 7 days after PCTx in 8 adolescents with SCD aged 16-20 years. They had full pubertal development (Tanner’s stage 5), and capacity to ejaculate. They were regularly transfused since early childhood. Chelation therapy was started early during the first 2 years of life using desferrioxamine and was replaced by deferasirox for the last 4-5 years.

**Results:** Packed cell transfusion increased significantly hemoglobin (Hb) from 8.2 ± 0.98 g/dl to 10.4 ± 0.5 g/dl, T from 12.6 ± 1 nmol/L to 14.5 ± 1.1 nmol/L and gonadotropins’ concentrations. Total sperm count increased significantly after PCTx including: total sperm count from 88 ± 6 million/ml to 150 +/- 53 million/ml. Hb concentrations were correlated significantly with sperm count. (table)

**Conclusions:** Our study showed that in adolescent males with SCD blood transfusion is associated with significant increase in concentrations of serum T, LH, and FSH with improving their sperm count. These “acute” effects on spermiogenesis are reached with an unknown mechanism/s and suggest a number of pathways that need further human and/or experimental studies.

	Age	ferritin	LH-1	LH-2	FSH-1	FSH-2	Test 1	Test 2	Sperm count (M/ml) 1	Sperm count (M/ml)2
	16	1664	4	6	6	8	11.6	13.4	96	164
	19	1760	4	5	6	7	12.4	14	84	175
	17	2600	5	6	7	9	12.5	15.5	93	268
	18	1540	5	7	6	7	13.6	15.8	96	127
	17	1150	5	6	5	6	13.4	14.5	85	112
	19	1254	5	5	7	8	12	13.6	81	113
	20	1453	6	7	4	6	11.3	13.6	88	106
	16	825	3	4	5	6	14.2	16	82	136
Mean	17.7	1530.0	4.6*	5.75	5.75	7.1*	12.6	14.5	88.13	150.1*
SD	1.49	526.00	0.92	1.04	1.04	1.13	1.02	1.07	6.13	53.74

1= before blood transfusion 2 = after blood transfusion, \* p < 0.01

P2-1520

**ABOUT A CASE OF 46XX/47XXY GONAD DYSGENESIS.**

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**Objectives:** 46XX/47XXY is an extremely rare mosaicism, just few cases has been reported in the literature . The phenotype is variable and could have several forms of presentation, klinefelter like, ovotestis or female phenotype.We report a case of 46XX/47XXY gonad dysgenesis.

**Methods:** A 14 months consanguineous child assigned us female attended to our unit for management of ambiguous genitalia .Biological and morphological evaluation has been done.

**Results:** On examination, the patient have a dysmorphic face with low implanted ears, arched palate , saddle nose and bulging forehead

Genital examination showed no labioscrotal folds, hypospadiac phallus with one orifice. No gonad has been identified in perianal examination neither in inguinal regions. Biological investigation showed :17OHP :0,45ng/ml(normal value) ,AMH:1,48ng/ml(low value) ,testosterone undetectable which do not increase after long HCG test:0,3ng/ml(<3ng/ml)

Ultrasound found a normal uterus, no gonad has been identified. Genitography showed male urethra and opacification of a posterior cavity.

Karyotype done in 50 mitosis showed 46XX/47XXY chimerism with a predominant population of 46XX .

The patient has been assigned as female after multidisciplinary decision, and attended to surgeon for laparoscopy in order to detect the gonads and their ablation because of the risk of malignancy which occur in 30% of cases.

**Conclusions:** 46XX/47XXY is a very rare form of mixed sex chromosome DSD, with different phenotypes:female ,Klinefelter like and ovotestis .The mosaicism may be explained by chimerism, the lack of Y chromosome in some cells, the double fecundation and the fusion of the fecund embryo with a polar body.

P2-1521

**CHARACTERIZING SEX-REVERSAL IN A 46XY FEMALE WITH PONTO-CEREBELLAR HYPOPLASIA TYPE 7 AND TOE1 MUTATIONS**

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**Objectives:** To characterize endocrine phenotype and hormonal profile of an infant with severe seizures, 46,XY sex-reversal and pontocerebellar hypoplasia type 7 (PCH7; MIM 614969) which have recently been shown to be caused by *TOE1* mutations.

**Methods:** Description of clinical and paraclinical features, endocrine profiling and abdominal findings.

**Results:** Term born girl, birth weight 2900 g, length 50 cm, head circumference 33 cm, Apgar 10-10, healthy non-related parents. Within two months, hypertonia and jitteriness were overt. MRI showed marked hypoplasia of the cerebellum, vermis and corpus callosum. EEG showed multiple spike foci. Severe epilepsy, dystonia, psychomotor retardation and spasticity developed. Metabolic screening was normal; array CGH showed normal result but male sex-chromosomes, the male sex chromosomes were confirmed by QF-PCR analysis on another blood sample. Sequencing of the *SRY*-gene showed normal result. The patient had normally appearing unvirilised female external genitalia . By abdominal surgery in search of gonads, no uterus but both salpinges and a vagina were present. Histology failed to detect gonadal tissue. Before the surgery at five months of age, serum testosterone, anti-Müllarian hormone (AMH) and inhibin B were undetectably low; serum FSH was 8.1 U/L and LH 0.5 U/L, other pituitary hormone axes were normal. Genetic studies (published in *Nat Genet.* 2017 Mar;49:457-464) showed

compound heterozygous mutations in *TOE1* on chr. 1, g.45808081T>G, p.Val173Gly and g.45808798C>A, p.His319Gln. Biallelic mutations in the *TOE1*-gene cause accumulation of abnormal pre-small nuclear RNAs (snRNAs) and henceneurodegeneration.

**Conclusions:** The endocrinological work up showed normal pituitary function despite neurodegeneration and an early fetal arrest of the gonadal function with some development of the internal female genitalia, suggesting initial presence of AMH with partial inhibition of Müllerian structures, but no testosterone effect. In PCH7, abnormal pre-snRNAs may not only lead to neurodegeneration, but also gonadal degeneration already in utero and hence sex-reversal in 46,XY karyotypes.

P2-1522

**CASE REPORT: AROMATASE DEFICIENCY IN TWO ADULT FEMALE SIBLINGS**

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**Objectives:** Aromatase deficiency (AD) results from an inactivating mutation in the aromatase gene, leading to absent or decreased conversion of androgens (testosterone and androstenedione) to estrogens (estriol and estrone). The aromatase enzyme protects the fetus against the virilizing action of fetal adrenal androgens. In addition, aromatase plays a role in the central nervous system, in programming the brain during fetal and neonatal life for noncyclic hypothalamic GnRH function and gender identity. Few cases with AD have been reported, of which only four are adult women.

**Methods:** We report genetic, clinical, biochemical and bone mineral density findings in two adult sisters, 39 and 45 years old, with a genetically confirmed diagnosis of AD in adulthood.

**Results:** Both sisters, 46, XX, had virilized genitalia (Prader V, EMS 6/12) at birth; the oldest was first assigned male, but was reassigned female based upon presence of ovaries and uterus. Reconstructive surgery of the external genitalia had been performed in both sisters. They both recall start and course of puberty as unremarkable, including occurrence of regular menses. At the age of 39, the youngest sister required medical care for an ovarian torsion. Subsequently, both sisters were referred to our DSD center for endocrine work-up at the age of 39 and 45 years. At physical examination, they both had typical breasts, which had developed at the age of 11.5 and 12 years, and had cyclic bleeding through the urethral opening. There were no signs of hirsutism. Menopause occurred at the age of 39 in the oldest sister and 35 in the youngest. Sequencing of the *CYP19A1* gene revealed a novel homozygous missense variant, c.1124G>A, p.(Arg375His), predicted to have deleterious effects on protein function. General biochemistry and data on cardiovascular

risk profile and bone densitometry results are summarized in Table 1.

**Conclusions:** Due to long-term exposure to increased androgens and decreased estrogens adult women with AD are at risk of developing polycystic ovaries or metabolic syndrome. AD has also been associated with low bone mass. We here describe two sisters with AD who were severely virilized at birth but who had, apart from early menopause, apparently no medical problems, underscoring the variability of the phenotype in adulthood.

PLEASE SEE TABLE ON FOLLOWING PAGE

Table 1: Clinical and Biochemical Findings of Subjects with CYP19A1 Mutations		
Clinical features	Patient 1, 39 years	Patient 2, 45 years
Maternal virilization	Absent	Absent
Neonatal phenotype	- Phallic structure 1.5 cm - Urethral meatus at tip of phallus - Labioscrotal fusion - No gonads palpable	- Phallic structure 2 cm - Urethral at tip of phallus - Labioscrotal fusion - No gonads palpable
Puberty	Breast development at 12y No hirsutism Ovarian US: no cysts	Breast development at 11.5y No hirsutism Ovarian US: no cysts
Menopause		
Age of onset (years)	35	39
Blood pressure (mm Hg)	122/84	159/100
Height (cm) (mean ± SD)	168 (164.6 ± 6.8)	165 (164.6 ± 6.8)
Target height (cm) (± SD)	158 (± 8.5)	158 (± 8.5)
Weight (kg) (mean ± SD)	67 (70 ± 13)	70 (70 ± 13)
Body mass index (BMI, kg/m²)	24.5	25.5
Biochemical features		
Estradiol (E2) (<138)	<25.0 ng/L	<25.0 ng/L
Testosterone (8.4-48.1)	21.54 ng/dL	30.81 ng/dL
Follicle stimulating hormone (>26)	92 U/L	130 U/L
Luteinizing hormone (8 – 59)	61 U/L	25 U/L
17 Hydroxy progesterone (0.1-1.98)	<0.2 ng/mL	<0.2 ng/mL
Anti-Müllerian hormone (<2.96)	0.045 µg/L	<0.03 µg/L
Dehydroepiandrosterone sulfate (DHEAS) (60.9 – 337 )	260.1 µg/dL	272.1 µg/dL
D4 androstenedione (13 – 82)	79.7 ng/dL	61.3 ng/dL
Total cholesterol (147 - 253)	255 mg/dL	240 mg/dL
HDL cholesterol (20 - 35)	27.8 %	25.6 %
LDL cholesterol (80 - 191)	165 mg/dL	160 mg/dL
Triglycerides (47 – 209)	97 mg/dL	97 mg/dL
Z-scores DEXA scan		
Femur	0.2	-1.3
Femoral neck	-0.8	-1.3
Lumbar spine	0.0	-2.2

P2-1523

**FAMILIAL OCCURRENCE OF TURNER SYNDROME: INCREASED RISK?**

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**Objectives:** Turner syndrome (TS) is a common chromosomal disorder characterized by complete absence of a sex chromosome or partial deletion of X chromosome and female phenotype. The estimated prevalence is 1 in 2500 live female births. Common features are short stature and premature ovarian failure.

Risk of familial recurrence is not well established. We report an unusual case of familial TS in two siblings with the same genetic alteration from a healthy mother.

**Methods:** N/A

**Results: Clinical case:** First daughter was found to have increased nuchal translucency and postnatal karyotype confirmed 45,X[59]/46,X,i(X)(q10)[3]. Physical examination revealed short stature, low posterior hairline and cubitus valgus. Normal cardiac and renal structures. Puberty was induced at age 12 due to evidence of primary ovarian failure. Her younger sister also had an abnormal fetal ultrasound and postnatally had a confirmed 45,X[96]/46,X,i(X)(p11.2)[4] karyotype which is considered to be the same deletion and breakpoint as her sister. Her clinical features include posterior neck folds, feet edema, nail hypoplasia, hearing loss, mildly dilated ascending aorta and short stature. Mother has had no miscarriages. She gave birth to another healthy daughter.

**Conclusions:** Turner syndrome is a common cause of hypergonadotropic hypogonadism in women. Around 90% of adolescents will have primary gonadal failure and require hormone replacement to initiate puberty and maintain sexual development. Only 2-5% become pregnant spontaneously. The loss or alteration of X chromosome occurs as a random error during cell division in early fetal development. Our two patients share the same deletion. Their mother may be a carrier of the same chromosomal abnormality in a milder mosaic state, without phenotypic manifestation or may have germline mosaicism. Thus, the maternal chromosomes should be evaluated to rule out possible structural chromosomal abnormalities which would be important for the management of further pregnancies and genetic counseling.

Familial recurrence of TS is rare and risk is not established. Only sporadic cases of familial TS have been reported and can be explained by twinning or transmission of X chromosome abnormalities from mother to child, this scenario is unusual.

P2-1524

#### **A 46, XX DISORDER OF SEX DEVELOPMENT DUE TO A MATERNAL ADRENOCORTICAL TUMOR COMPLICATED BY A NEONATAL OVARIAN CYST**

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**Objectives:** Rarely, functional maternal adrenocortical tumors can cause 46,XX disorder of sex development (DSD), to our knowledge only 7 cases were previously reported; on the other hand, prenatal androgen exposure has been proposed led to the development of ovarian cysts. We report a 46,XX DSD allowed to diagnose a maternal adrenocortical tumor that presented a neonatal ovarian cyst during follow-up.

**Methods:** A healthy full-term (2.970g), 2-day-old-newborn assigned as girl was referred due to ambiguous genitalia: 2 cm length phallus, partial fusion of labioscrotal folds, single perineal urogenital orifice and non palpable gonads (Prader III). 21-OH deficiency as well as other steroidogenic

defects including aromatase deficiency were ruled out with normal levels of 17OHP, androgens and E2. Abdominal ultrasound revealed normal uterus. Karyotype 46,XX.

**Results:** Starting from the 5<sup>th</sup> month of gestation the 29-year-old mother had developed progressive hirsutism, severe acne but clinical signs of virilization had gone unnoticed. She became pregnant soon after stopping ACO intake On 3 postpartum-day and thereafter LH and FSH were suppressed in the presence of extremely high testosterone: 4.56 – 5.46 ng/ml, androstenedione: 9 – 22 ng/ml, DHEA-S: 6960 - 16230 ng/ml. Despite normal cortisol levels, Nugent's test revealed autonomous cortisol secretion. Abdominal US, TAC and RMI revealed a 72x60mm right adrenal mass which was laparoscopically removed. Histologically and phenotypically it was an adenoma. Postoperatively androgens returned to normal and adrenal insufficiency was found. Girl's LH and FSH were undetectable at 46 hs of age but increased dramatically (LH:36.2mUI/ml, FSH: 36.3mUI/ml) when maternal circulating steroids disappeared at 12 d. At 1 month of age with significant decrements of LH:1.0 mUI/ml, FSH:2.0mUI/ml and increment of E2:232pg/ml, an US showed a large right ovarian cyst 56x46mm. A month later underwent oophorectomy laparoscopic because US signs of intracystic hemorrhage.

**Conclusions:** Our patient emphasizes the importance of detailed investigation in the mother when a child presents unexplained virilization. The possible role of fetal hyperandrogenism in the development of the ovary cyst, if any, requires further investigation.

P2-1525

#### **A NOVEL NONSENSE MUTATION IN HSD17B3 GENE IN A TUNISIAN PATIENT WITH SEXUAL AMBIGUITY**

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**Objectives:** 17b-hydroxysteroid dehydrogenase type 3 (HSD17B3) isoenzyme is present almost exclusively in the testes and converts delta 4 androstenedione to testosterone. Mutations in the *HSD17B3* gene cause HSD17B3 deficiency and result in 46,XY Disorders of Sex Development (46,XY DSD) This study aimed to present the clinical and biochemical features of a Tunisian patient who presented a sexual ambiguity orienting to HSD17B3 deficiency and to search for a mutation in the *HSD17B3* gene by DNA sequencing.

**Methods:** Polymerase chain reaction (PCR) amplification and subsequent sequencing of all the coding exons of *HSD17B3* gene were performed on genomic DNA from the patient, her family, and 50 controls.

**Results:** Genetic mutation analysis of the *HSD17B3* gene revealed the presence of a novel homozygous nonsense mutation in the exon 9 (c.618 C > A) leading to the substitution p.C206X. The mutation p.C206X in the coding

exons supports the hypothesis of HSD17B3 deficiency in our patient.

**Conclusions:** The patient described in this study represented a new case of a rare form of 46,XY DSD, associated to a novel gene mutation of *HSD17B3* gene. The screening of this mutation is useful for confirming the diagnosis of HSD17B3 deficiency and for prenatal diagnosis.

P2-1526

#### AN UNUSUAL ETIOLOGY FOR AMBIGUOUS GENITALIA: TWO CASES OF PRADER-WILLI SYNDROME

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**Objectives:** Ambiguous genitalia and hypogonadism are two common reasons why primary care providers refer infants to specialized Disorders/Differences of Sex Development (DSD) clinics. When such infants present with additional medical findings (hypotonia, dysmorphic features, other structural malformations), the differential diagnosis needs to be expanded beyond the usual causes of ambiguous genitalia and hypogonadism.

**Methods:** We report two infants who were recently referred to our interdisciplinary pediatric DSD team for evaluation of ambiguous genitalia who were ultimately diagnosed with Prader-Willi syndrome (PWS).

**Results:** The first child presented as a female in the newborn period with a genitourinary exam that revealed an enlarged hooded phallic structure with a urethral opening at the base, fusion of labioscrotal folds with no apparent vaginal opening, and no palpable gonads in the inguinal canal. The child also had intrauterine growth retardation, hypotonia, and respiratory distress secondary to congenital lobar emphysema. The second child was a 7-week-old term male with normal growth parameters, but his extremely poor tone ultimately required gastrostomy tube feeding. His genitourinary exam was consistent with a hypoplastic scrotum with no palpable testes initially, although testes were later palpated within the inguinal canal. Both children had endocrine studies that suggested a normal hypothalamic-pituitary-gonadal axis, normal male 46,XY karyotypes, and a normal fluorescence in situ hybridization study confirming an intact SRY (sex-determining region Y) gene. In each case, a single nucleotide polymorphism array demonstrated long regions of homozygosity on chromosome 15, the chromosome that contains the PWS/Angelman syndrome region. Methylation testing was consistent with a diagnosis of PWS and chromosome 15 microsatellite marker testing confirmed maternal uniparental disomy for both.

**Conclusions:** Although individuals with PWS are often diagnosed in the newborn period because of significant hypotonia and hypogonadism, frank ambiguous genitalia (as seen in our first case) are rarely described but can be seen. Therefore, when children with ambiguous genitalia present to DSD clinics, additional characteristics such as hypotonia

should prompt consideration of syndromic conditions like PWS.

P2-1527

#### AROMATASE EXCESS SYNDROME (AES) IN A 10-YEAR OLD GIRL WITH GIGANTOMASTIA

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**Objectives:** Only 8 female cases of AES have been reported, whose clinical features are highly variable. We aimed to describe a patient harboring gigantomastia due to AES.

**Methods:** Hormone measurements were performed by mass spectrometry. To investigate aromatase excess, *CYP19A1* gene expression was analyzed by RT-qPCR using RNA from skin, adipose tissue, mammary gland and fibroblast cell culture for cDNA synthesis from patient and normal female control. Relative expressions were calculated by the  $2^{-\Delta\Delta CT}$  method. To investigate the molecular etiology, *CYP19A1* promoter and coding region were sequenced by Sanger and CGH array was performed.

**Results:** A 10-year and 11-months (10y11m) girl was referred to our clinic due to gigantomastia with an onset history of only 7 months. The patient presented at first evaluation, besides important bilateral gigantomastia, advanced bone age (13 years), enlarged uterus (4.8x2.0x3.0cm) and ovaries (7.3 and 10.9cc) for age, detected by pelvic US. There was no familial history of gigantomastia. Patient developed menarche at 11y01m. In order to evaluate the hypothalamic-pituitary-gonadal axis, serum hormone levels were measured in different phases of menstrual cycle. Although integrity of the axis was preserved with normal E2 levels and slightly increased E1 levels, E2/T ratio was increased, ranging from 365 (follicular phase) to more than 1800 times (luteal phase). The patient underwent bilateral mastectomy and the histopathology analysis showed pseudoangiomatous stromal hyperplasia with positive expression for estrogen and progesterone receptors. RT-qPCR showed increased *CYP19A1* expression by 2-3 times fold in the patient's skin and 20-40 times fold in patient's fibroblast cell culture compared to normal. Patient maintained advanced bone age (14y with chronological age of 12y). Although the initial height is within the normal range (145,5cm at 11y9m, Z score = 0.0), the prediction for final height is poor owing to acceleration of bone age. Aromatase inhibitor was introduced. No mutations were found neither by *CYP19A1* sequencing and by CGH array.

**Conclusions:** This case shows the importance of endocrine evaluation of patients with gigantomastia and spread the clinical presentation of female cases of AES.

P2-1528

#### AROMATASE DEFICIENCY IN IDENTICAL TWIN GIRLS

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**Objectives:** Estrogens, required for normal sexual development in females, are synthesized from androgen precursors by the enzyme aromatase, a member of the cytochrome P450 family and product of the CYP19A1 gene located on chromosome 15q21.1. In the uncommonly reported cases of aromatase deficiency (AD), homozygous or compound heterozygous mutations in this gene result in absent or diminished production of estrogens and the accumulation of excessive androgens with a range of phenotypes. We present longitudinal clinical, biochemical and radiological data from identical twin girls with AD who were followed intermittently over 15 years.

**Methods:** This is an observational, longitudinal case study.

**Results:** These identical twin girls were born at 29 weeks gestation with genital ambiguity. After other causes of intrauterine virilization were excluded, a clinical diagnosis of AD was made. When seen at 9 4/12 years both were prepubertal, had delayed skeletal maturation and normal gonadotropins. One of the twins had cystic ovaries and normal androgens, while the other had normal ovaries and minimally increased DHEAS and testosterone. At 15 7/12 years both had completed spontaneous puberty and had regular menses. They had mildly elevated androgens, low ultrasensitive estradiol levels, normal gonadotropins, bone age equivalent to chronological age, normal DXA scans and final heights appropriate for the family. Each had at least one ovarian cyst by ultrasound. Genetic analysis revealed an unreported genetic constellation with complete deletion of one CYP19A1 gene and a known c.242A>G mutation of the other.

**Conclusions:** Spontaneous breast development in females with AD has been described, but menarche and regular periods are rare. We propose that the relatively mild clinical phenotype seen in these twins is due to residual aromatase activity of the c.242A>G mutant gene.

P2-1529

#### A CASE OF SEX DEVELOPMENT DISORDER DUE TO A NOVEL MUTATION IN 5 ALPHA REDUCTASE (SRD5A2) GENE

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**Objectives:** Steroid 5 alpha reductase deficiency occurs due to the defect in the enzyme transforming testosterone into dihydrotestosterone (DHT). DHT provides the differentiation of external genitalia towards male. Recessive mutations in SRD5A2 gene in a 46 XY infant may cause ambiguous genitalia in a spectrum from isolated hypospadias to severe masculinization problems (perineal hypospadias, micropenis, bifid scrotum and hypoplastic prostate).

**Methods: Case:** Our patient was born as the third living child from a 21 years old mother in her third pregnancy with a birth weight of 2800 grams through normal spontaneous vaginal delivery. The infant was transferred to our clinic when 8 days old due to sexual differentiation disorder. It was learned that the parents had a second degree cousin marriage. According to the genital examination, the fallus was 1 cm and a bifid scrotum style of labioscrotal fold, 1 ml palpable gonad inside bilateral labioscrotal fold and a singular urogenital clearance were present.

The values checked when the patient was 8 days old were FSH: 4.38 mIU/mL, LH:10.03 mIU/mL and Total Testosterone:0.97 ng/ml. Appearances in line with testicle tissue were present in ultrasonography, with the dimensions of 11x7 mm in the right inguinal area and 12x6 mm in the left inguinal area and uterus and ovaries were not observed. Chromosome analysis was reported as 46,XY. Total Testosterone (T)/ Dehydro Testosterone (DHT) was 14.4 according to the HCG test done when 2.5 months old. 5alpha-reductase deficiency was considered due to these results.

**Results:** Homozygote x.453delC mutation was detected in SRD5A2 gene. Although c.453delC mutation detected in the patient was a change undefined before, it affects all aminoacids after the mutation since it is a base deletion. It was determined as a high disease factor. The same mutation was detected in both parents in heterozygote form. After evaluating the androgen response of the patient, the decision for gender selection was planned.

**Conclusions:** Mutation detected in SRD5A2 gene in the case was undefined before in literature. Gender selection choice in patients with 5α Reductase deficiency is extremely important.

P2-1530

#### CASE REPORT: 46, XY DISORDER OF SEX DEVELOPMENT, NR5A1-RELATED

*Yuliya Shcherbak, PhD, National Specialized Children Hospital "OKHMATDET", Kiev, Ukraine; Nataliya Zelinska, Professor, Ukrainian Scientific Center of Endocrine Surgery, Kiev, Ukraine*

**Objectives:** 46,XY disorder of sex development (DSD), NR5A1-related or 46,XY sex reversal type 3 (OMIM: 612965) is caused by heterozygous mutation in NR5A1 gene (9q33.3). Mutations in the gene NR5A1 lead to 46,XY gonadal dysgenesis, complete or partial, with or without adrenal failure. The clinical features may vary from normal female phenotype with streak-gonads to ambiguous genitalia. Mutations in the gene NR5A1 have autosomal dominant inheritance.

**Methods:** A retrospective analysis of the patient's medical card was conducted. The results of laboratory tests, instrumental examination, cytogenetic analysis, molecular genetic analysis (PCR) were studied.

**Results:** Girl, 4 y.o., was born to healthy parents from 1st normal pregnancy. At the age of 1.5 months was developed salt-loss syndrome and was diagnosed Congenital adrenal hyperplasia, was started hormone replacement therapy. Clinical features: phenotypically female external genitalia, clitoromegaly (II Prader), urogenital sinus; hypoplastic uterus and small gonads (US scan), adrenal hypoplasia (CT with i/v contrast). Karyotype - 46,XY.ish(Xp11.1-q11)CEP(X)x1,Yp11.3(SRYx1). Gonadotropins and sex hormones were normal for age. AMH was normal for boy's parameter. The 21-hydroxylase deficiency was excluded. PCR and direct sequencing NR5A1 gene revealed a heterozygous mutation r.G35D (de novo). The multidisciplinary team chose tactics of dynamic observation, gonadectomy was delayed and surgical plastic of external genital was planned at the age of 9-11 years.

**Conclusions:** 46, XY DSD is not difficult to diagnose, given the differences between karyotype, gonadal and genital sex. Timing of necessary surgery - gonadectomy and/or plastic of external genitalia - determined by multidisciplinary team (consisting of endocrinologist, surgeon, gynecologist, geneticist) in each case individually.

P2-1531

#### SOX9 GENE DUPLICATION-RELATED 46, XX OVOTESTICULAR DISORDER OF SEX DEVELOPMENT

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**Objectives:** SOX9 is a transcription factor with an important role in male sexual differentiation. SOX9 gene duplication causes testicular differentiation in SRY(-) 46, XX individuals and can lead to 46,XX Disorder of Sex Development (DSD). In some of the 46, XX, SRY(-) cases with SOX9 duplication, ovotesticular gonad development is detected, whereas others have normal male external genitalia and may be diagnosed during investigation for infertility.

**Methods:** Herein, we report a case with 46, XX DSD who had SOX9 gene duplication.

**Results:** Patient aged 1 year 7 months was referred for sexual ambiguity. The patient was prescribed 50 mg testosterone enanthate (im) once a month for four months previously. Family history revealed a history of sexual ambiguity in one paternal aunt of the patient. On physical examination, left gonad was in the labioscrotal fold, and right gonad was in the inguinal canal. Fallus was 3.7 cm long and cavernous tissue was well-developed with severe chordee. Urogenital sinus opening was on perineum. Karyotype analysis was consistent with 46 XX and SRY gene was negative. After hCG test (3000

U/m<sup>2</sup>/d, for 3 days), testosterone was 185 ng/dL, dihydrotestosterone was 113.34 pg/mL, testosterone/dihydrotestosterone ratio was 16.3, and androstenedione was <0.30 ng/mL. Uterus was not observed in pelvic ultrasonography. Cystoscopy revealed a blind ending vagina. On laparoscopy, ductus deferentes were present bilaterally and no internal female genital structures was apparent. Gonadal biopsy was consistent with bilateral ovotestis. In microsequencing analysis performed using Agilent SurePrint® G3 CGH 8x60K Human Microarray Kit, 819 kb duplication Arr[hg19]17q24.3(69151003-69970418)X3 was detected in the upstream of SOX9 gene located in the long arm (17q24.3) of chromosome 17.

**Conclusions:** SOX9 gene duplication in 46, XX, SRY(-) individuals can cause testicular or ovotesticular differentiation and can be responsible from 46, XX, DSD.

P2-1532

#### FOUR CASES OF EXTERNAL GENITAL ABNORMALITIES ASSOCIATED WITH WT1 MUTATION.

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**Objectives:** The Wilms' Tumor Suppressor gene (WT1) is the causative gene of Wilms tumor. WT1 mutation also causes disorders of sex development. We reported four cases of boys with external genital abnormalities and WT1 mutations. Case1 and 4 are 5-month-old-boys, Case2 is 6-month-old-boy, Case3 is 2-month-old boy, respectively. Severe hypospadias, microphallus, and bifid scrotum were observed in each case, but no vulvar pigmentation. Palpation revealed bilateral testis within the scrotum in Case 1, 2 and 3. Case 4 has bilateral cryptorchidism.

**Methods:** We analyzed WT1 in four patients with the chief complaint of hypospadias.

**Results:** Case1 and 2 were detected Wilms tumor on further examination. Genetic sequence analysis revealed, c.1201delA, p.Arg401Aspfs\*48 frameshift mutations in WT1 in Case1, c.1086\_1087\_del, p.Phe362 Leufs\*22 frameshift mutation in WT1 in Case2, a c.731G>A: p.G244E mutation in WT1 and a c.557c>t: p.T186M mutation in ZFPM2 in Case3, and a c.425A>G, p.Gln142Arg WT1 mutation in Case4. Abdominal ultrasonography did not indicate abnormal findings at present, and neither kidney function disorder nor proteinuria was detected in Case3 and 4. Endocrinological evaluation, urinary steroid profile and ophthalmologic examination

revealed no abnormal findings. Karyotype was 46, XY, and SRY-FISH positive in all four cases.

**Conclusions:** We identified *WT1* mutations in four patients with the chief complaint of hypospadias. Two of the four cases were complicated with Wilms tumor. It has been reported that *WT1* mutation is more detectable when hypospadias is complicated with cryptorchidism. However, in this study we were able to detect *WT1* mutation in three cases of hypospadias without cryptorchidism. Additionally, mutations within all 10 *WT1* exons have been associated with the development of Wilms tumor, and no specific mutation, hot spots are currently recognized. Therefore, further investigation is necessary to establish the correlation between phenotype and genotype for the *WT1*.

P2-1533

#### THE CHOICE OF SOCIAL SEX IN PATIENTS WITH ATYPICAL GENITALIA

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**Objectives:** Mixed Gonadal Dysgenesis is a congenital disorder of sex development (DSD) that presents a testicle with varying degrees of dysgenesis on one side and a streak on the other. Usually, these patients seek medical attention for atypical external genitalia.

**Objective:** Describe the impact of the choice of social sex in the early childhood in patients with ambiguous genitalia through a case report.

##### **Methods:**

Retrospective review of medical records.

**Results:** S.A.L., 14 days of life, with atypical genitalia (falus 1.5x1.0cm, with no palpable gonads, double opening in urogenital sinus and perineal urethra) and karyotype 46,XY. Laboratorial tests at baseline were: testosterone 58.8 ng / dL and after human chorionic gonadotrophin stimulation test testosterone was 301 ng / dL. Pelvic ultrasound evidenced uterus and vagina and genitogram revealed vagina of normal aspect. Were found in laparoscopic exploration Mullerian remains (body and cervix), Wolffian remains (epididymis and bilateral deferent ducts) and the right testicle. No left gonad was identified. It was chosen to keep the female social sex. For this reason it was then performed a corrective surgery and hormonal replacement was initiated with estrogen hormone in the pubertal period with the development of secondary sexual characteristics. Since early adulthood the

patient has been questioning his sexuality and chosed to assume male social sex, in spite of been raised as female. Patient maintained psychiatric and psychological follow-up throughout the treatment that agreed with the patient's diagnosis and social sex choice. Than opted to initiate testosterone replacement and mastectomy was programmed. The patient is now waiting for surgery.

**Conclusions:** Concerning atypical genitalia treatment, the choice of social sex is as important as the etiological diagnosis. In cases of atypical genitalia this is always the subject of discussion and changes of conduct over the years. Multiprofessional team is an essential pillar of treatment since diagnosis to psychological follow up of the patient and his relatives aiming to help the development of an adult adapted to his social context.

#### POSTER SESSION 2

**Friday, September 15, 2017, 11:30am-12:30pm**

#### **P2 - Syndromes**

#### **P2-1600 – P2-1620**

P2-1600

#### **BEHAVIORAL AND EMOTIONAL PROBLEMS IN GIRLS AND YOUNG WOMEN WITH TURNER SYNDROME**

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**Objectives:** To evaluate the behavioral and emotional problems in a group of girls and adolescent with TS.

**Methods:** 41 TS patients (mean age 16.7±3.3 years, range 11.2-24.9 years) participated in a cross-sectional study. Potential behavioural, emotional and social problems were investigated by a parent report (Child Behaviour Checklist – CBCL) and a self-report (Youth Self report – YSR). Summation of all the problem item scores yielded a “total problem score”. Furthermore, the problem items are divided into two main clusters: “externalizing problems” including conduct, aggressive and antisocial behavioural problems; and “internalizing problems” including withdrawn, depressive, nervous and restrained behavioural problems. Raw scores were compared to Danish norms. According to the CBCL manual raw scores above the 93<sup>th</sup> percentile are considered to indicate a problem behavior.

**Results:** For the TS girls age 11-16 years the CBCL indicated total problem behavior in 11% (2/19), externalizing problem behavior in 5% (1/19), and internalizing problem behavior in 11% (2/19). The YSR indicated total problem behavior in none, externalizing problem behavior in 5% (1/19), and internalizing problem behavior in 5% (1/19). For the TS adolescents age 17-25 years the CBCL indicated total problem behavior in 20% (4/20), externalizing problem behavior in



15% (3/20), and internalizing problem behavior in 25% (5/20). The YSR indicated total problem behavior in 5% (1/22), externalizing problem behavior in 5% (1/22), and internalizing problem behavior in 5% (1/22).

**Conclusions:** The prevalence of problem behavior in general seems low in TS girls both by the parents and by self-evaluation. However, in young adulthood a divergence appears to exist with more problem behavior (total, externalizing and internalizing) being reported by the parents compared to the TS patients themselves. Perhaps these findings imply a level of unrealistic self-perception or self-awareness in the young TS women, or preconceived expectations by the parents or both.

P2-1601

#### **A SHORT COURSE OF TESTOSTERONE IN INFANTS WITH 47,XXY KLINEFELTER SYNDROME HAS ACUTE EFFECTS ON BODY COMPOSITION**

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**Objectives:** Prenatal diagnoses of 47,XXY/Klinefelter syndrome (KS) are rapidly increasing due to non-invasive prenatal screening. KS is associated with a high prevalence of developmental delays, testosterone insufficiency and cardiometabolic disorders. Many parents and professionals advocate for testosterone supplementation during the mini-puberty of infancy in boys with KS, but there have been no prospective randomized trials to evaluate the risks and benefits of this treatment. Our objective was to quantify short-term effects of testosterone on physical parameters in infants with KS.

**Methods:** Infants with a prenatal diagnosis of 47,XXY were enrolled between 6-15 weeks of age and randomized to receive testosterone cypionate 25 mg intramuscularly every 4 weeks for 3 doses or no treatment. Body composition using air displacement plethysmography (PeaPod), growth parameters, and motor development were assessed at enrollment and at 12 weeks. Our primary outcome was change in percent body fat (%BF) z-scores between assessments. Secondary outcomes included change in scores on motor assessments, growth velocity, stretched penile length, and side effects.

**Results:** Sixteen subjects have completed the protocol to date. Baseline infant and maternal factors were similar between groups. The change in body composition was significant higher in participants who did not receive testosterone (n=8), who had an increase in their %BF z-score

of  $+0.9 \pm 0.7$  while the testosterone treated group had no change ( $-0.2 \pm 0.7$ ;  $p=0.005$ ). Growth velocity and increase in stretched penile length were both greater in the treatment group, however between-group differences in motor development did not reach statistical significance. There were no serious adverse effects.

**Conclusions:** This pilot study supports that a three-month course of testosterone injections may have measureable short-term effects on body composition in infants with KS. We do not advise routine testosterone therapy in infants based on these results as our sample size is small and the long-term clinical implications of our outcome measures are uncertain. However, these results support the need for prospective, blinded, and placebo-controlled investigation to confirm these preliminary findings and determine if benefits are sustained.

P2-1602

#### **ASSOCIATIONS BETWEEN PREPUBERTAL AND PUBERTAL ANDROGEN LEVELS AND ADULT HEIGHT OUTCOME IN GROWTH HORMONE TREATED BOYS WITH SILVER-RUSSELL SYNDROME**

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**Objectives:** Severe intrauterine growth retardation and short stature are common features in Silver-Russell syndrome (SRS). Despite growth hormone (GH) treatment poor height gain may be seen during puberty. We have previously shown that high estrogen levels during childhood and early puberty lead to impaired pubertal height gain and adult height (AH) in GH treated SRS patients. The association between AH and androgens during childhood and puberty is not known.

The objective of this study was to evaluate the association between prepubertal and pubertal androgen levels and AH outcome in GH treated boys with SRS. The hypothesis was that altered adrenal and/or gonadal activity increase androgen secretion, which by conversion to estrogens accelerate bone maturation leading to impaired AH outcome.

**Methods:** In 11 GH treated boys with SRS, serum androgens and testicular size were evaluated repeatedly during childhood and puberty. Androgens were determined by liquid chromatography-tandem mass spectrometry with lower limit of detection 0.17 nmol/L, 0.01  $\mu$ mol/L, and 0.10 nmol/L for androstenedione (A), dehydroepiandrosterone sulphate (DHEAS) and testosterone (T), respectively. Subjects with AH equal or less than -1 SDS from target height (TH) were considered responders (R) and subjects with AH above -1SDS from TH were considered non-responders (NR).

**Results:** Pubertal onset at testis  $\geq 3$  mL was seen at age median (range) 11.0 (9.6-12.1) and 12.1 (10.5-15.1) years in the NR and R, respectively. 3/6 NR and 1/5 R did not reach

normal adult testicular size ( $\geq 15$  mL). In NR, A was significantly higher at 10 years median (range) 1.2 (1.0-1.4) versus 0.6 (0.4-1.1) nmol/L,  $p=0.013$  and at 12 years 1.8 (1.2-3.2) versus 0.8 (0.7-1.5) nmol/L,  $p=0.035$  compared to R. T was significantly higher in NR at 14 years median (range) 14.9 (9.1-16.4) versus 6.8 (0.5-13.3) nmol/L,  $p=0.028$ . No difference was seen in DHEAS.

**Conclusions:** Increased A at 10 and 12 years and increased T at 14 years are associated with impaired AH in GH treated boys with SRS. Gonadal dysfunction and testicular insensitivity but not adrenal androgen secretion probably explain increased A and T secretion in early puberty and impaired testis size at AH in this limited number of patients.

P2-1603

#### GENETIC CHARACTERISTICS AND CLINICAL SPECTRUM OF PERMANENT NEONATAL DIABETES: A SINGLE CENTER EXPERIENCE

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**Objectives:** Permanent neonatal diabetes mellitus (PNDM) is rare disease, defined as hyperglycemia needing treatment in the first 6 months of life. Mutations in 22 genes are identified in over 80% of patients resulting in variable phenotypes. The genotype and phenotype is largely influenced by paternal consanguinity. However, studies in consanguineous populations are still limited.

The aim of this study was to identify the genetic causes among a group of patients with PNDM.

**Methods:** Genetic testing was performed in the Exeter Molecular Genetics Laboratory, UK for nine identified patients and their families. DNA was extracted from peripheral blood using the standard methods and direct sequencing of KCNJ11, ABCC8, INS, and EIF2AK3 was initially conducted in all patients. Patients with no identifiable mutations were subsequently analyzed for all known NDM genes using a targeted next generation assay.

**Results:** The genetic cause was detected in 6/9. Five of them had positive consanguinity; one was homozygous for EIF2AK3 missense mutation, resulting in Wolcott Rallison syndrome and the other harbored a novel homozygous GCK mutation. The latter's sister was heterozygous for the same mutation confirming a genetic diagnosis of maturity-onset diabetes of the young. The 3rd patient was heterozygous for a novel INS missense mutation which is likely to affect insulin protein folding and was also heterozygous for a novel ABCC8 missense variant; possibly a benign polymorphism. The 4<sup>th</sup> case had heterozygous KCNJ11 missense mutation and she was successfully shifted from insulin to sulphonylurea

therapy. The 5<sup>th</sup> case was heterozygous for ABCC8 mutation and achieved good glycemic control on sulphonylurea therapy. The last case had homozygous mutation for SLC19A2 responsible for thiamine responsive megaloblastic anemia.

**Conclusions:** In our cohort, genetic testing has significant implications for clinical management of PNDM.

P2-1604

#### ASSOCIATION OF HYPOCALCEMIA WITH CONGENITAL HEART DISEASE IN 22Q11.2 DELETION SYNDROME

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**Objectives:** Hypocalcemia is one of the cardinal features of 22q11.2 deletion syndrome (22q11.2 DS). Hypocalcemia and other features of 22q11.2 deletion syndrome including congenital heart disease (CHD), immunodeficiency, and palatal anomalies, are primarily ascribed to problems with morphogenesis and function of the pharyngeal arch system derivatives including craniofacial structures, the thymus and parathyroid glands, the aortic arch, and the cardiac outflow tract. We previously reported hypocalcemia and CHD (particularly conotruncal anomalies) in 50% and 74% of patients with 22q11.2DS respectively. In light of the aforementioned embryology, we hypothesized that hypocalcemia would be identified more frequently in those patients with 22q11.2DS and CHD.

**Methods:** We conducted a retrospective IRB approved chart review on 1300 subjects with 22q11.2DS evaluated via the 22q11 and You Center at the Children's Hospital of Philadelphia. 22q11.2 deletions were confirmed clinically using FISH, CGH, SNP microarray, or MLPA. Fisher's exact test measured differences between the groups.

**Results:** 852 patients had both formal cardiac evaluations and calcium levels available for review. Of these, 466 (54.6%) had a diagnosis of hypocalcemia and 550 (64.5%) had CHD. Of those with CHD, 62% had hypocalcemia, while only 38% without CHD had hypocalcemia. Thus, we established the frequency of hypocalcemia to be greater in patients with 22q11.2DS and CHD as compared to those sans CHD ( $p,0.001$ ). We also analyzed age of onset of hypocalcemia in these two groups and found 69% of the group with CHD had neonatal/infantile hypocalcemia vs. 14% in the non-CHD group.

**Conclusions:** In our large cohort of subjects with 22q11.2DS with both cardiac and calcium data, hypocalcemia was more often present in those patients with CHD and was more likely to be diagnosed during infancy. This important finding may reflect an embryological association, ascertainment bias in identifying younger patients in association with CHD during neonatal hospitalization, a resultant finding as an associated physiologic stressor, or a combination of these factors. Nonetheless, early diagnosis of 22q11.2DS, in particular as a

cause of CHD is vital in identification and early treatment of hypocalcemia.

P2-1605

#### **ETHICAL ISSUES RAISED BY OFFERING OVARIAN TISSUE CRYOPRESERVATION TO GIRLS WITH TURNER SYNDROME**

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**Objectives:** Ovarian tissue cryopreservation (OTC) has been well described in girls awaiting gonadotoxic cancer treatments. Auto transplantation of cryopreserved ovarian tissue in cancer survivors has resulted in restoration of ovarian function and more than 100 pregnancies. This has led to a new debate to expand OTC as a fertility preservation option to girls with Turner syndrome (TS). Although OTC has been experimentally performed in these patients, the promise of fertility preservation is at present hypothetical.

**Methods:** A literature search was undertaken to identify the ethical issues associated with OTC in girls with TS. All arguments identified were divided into four subcategories based on basic ethical principles (autonomy, beneficence, non-maleficence, and justice). A multidisciplinary expert panel (including patients and parents) rated and prioritized all arguments extracted from the literature. Group consensus was reached by a two-round ethical Delphi method including one questionnaire survey and one consensus meeting.

**Results:** OTC in girls with TS raises a number of ethical considerations. The primary objective of OTC remains to promote the autonomy of patients by giving them the hope of having genetic concordant children in the future, and thus improve their psychosocial well-being. However, patients younger than 16 do not have the legal capacity to make their own decision, requiring an approved consent from both parents. Furthermore, besides the potential risks associated with the surgical retrieval, it is important to be aware that, at present, the promise of fertility preservation in girls with TS is still hypothetical and may produce false hope. Still, we think that it is defensible to offer OTC to patients with TS who are demanding this fertility preservation option, provided that these girls (and their parents) are well-informed about all aspects of the experimental procedure.

**Conclusions:** An overview of ethical issues raised by offering OTC as a fertility preservation option to girls with TS with focus on basic ethical principles. This ethical analysis forms a basis for further debates and may be helpful for the development of research protocols to collect more data on the possible benefits and harms of OTC in girls with TS.

P2-1606

#### **COGNITIVE AND BEHAVIORAL PHENOTYPE OF CHILDREN WITH PSEUDOHYPOPARATHYROIDISM**

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**Objectives:** Pseudohypoparathyroidism (PHP) is a rare genetic disorder associated with multi-hormone resistance, obesity and cognitive impairment. We undertook the first systematic evaluation of cognitive function, executive function and behavior in children with PHP.

**Methods:** Participants 6-18 years old with PHP, unaffected siblings and obese controls completed a series of neurocognitive assessments. Demographic data and relevant patient history were obtained. Continuous variables were analyzed by one way ANOVA followed by the Student's t-test (obese controls) or paired t-test (siblings).

**Results:** We enrolled 19 patients with PHP, 9 siblings and 14 obese controls. All groups were similar in age, race, gender, parent education and family income. The PHP group had a mean IQ of  $86.5 \pm 16.0$  (range 60–116); 21% had an IQ <70. The PHP group had significantly lower IQs than obese controls (mean differences: composite IQ -16.7, 95%CI -27.0 to -6.3,  $p < 0.01$ ; verbal IQ -16.0, 95% CI -23.7 to -8.4,  $p < 0.001$ ; nonverbal IQ -12.8, 95%CI -24.9 to -0.78,  $p = 0.04$ ) and their unaffected siblings (composite IQ -22.2, 95%CI -33.0 to -11.4,  $p < 0.01$ ; verbal IQ -17, 95%CI -24.9 to -9.2,  $p < 0.01$ ; nonverbal IQ -21.1, 95%CI -35.8 to -6.5,  $p = 0.01$ ). Education history in the PHP group was significant for repeating a grade (41%), special education services (88%), occupational therapy (35%), physical therapy (47%), and speech therapy (35 %). In contrast, no siblings and one obese control (7%) repeated a grade and none received additional services. The PHP group had lower adaptive behavior composite scores (mean difference vs. siblings: -22.6, 95%CI -9.6 to -35.7,  $p < 0.01$ ). The PHP group had significantly more affective, anxiety, and ADHD problems on the Child Behavior Checklist. The PHP group had significantly poorer executive function skills as measured by the Delis-Kaplan Executive Function System and parent report; the greatest deficits were in working memory and initiating behaviors.

**Conclusions:** In summary, children with PHP have significant deficits in cognition, adaptive behavior and executive function, as well as behavior problems. Children with PHP typically require additional education services and should receive evaluation by early intervention specialists.

# **PUBERTAL DEVELOPMENT AND GONADAL FUNCTION IN PATIENTS WITH SILVER-RUSSELL SYNDROME: A LONGITUDINAL STUDY**

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**Objectives:** Patients with Silver-Russell syndrome (SRS) are born small for gestational age (SGA), show postnatal growth failure and have an increased risk for genital anomalies. Whether SRS patients experience reproductive issues has never been evaluated. We, therefore, assessed pubertal progression and parameters of gonadal function in SRS patients.

**Methods:** In 31 genetically tested SRS patients (15 males; 48.3% 11p15 LOM; 22.5% mUPD7; 29.0% clinical diagnosis) and 117 patients born SGA without SRS (non-SRS; 65 males) participating in a large Dutch growth hormone trial, we assessed onset and progression of puberty. Furthermore we longitudinally measured parameters of gonadal function (serum levels of FSH, LH, AMH, inhibin B and testosterone) from childhood (age 6 yrs) to young adulthood (age 16 yrs) in both groups and compared these to healthy controls. Only samples that were drawn before start of oral contraceptives were used.

**Results:** Mean age at onset of puberty was similar in SRS and non-SRS (11.5 yrs vs. 11.6 yrs in males ( $p=0.55$ ) and 10.5 yrs vs. 10.7 yrs in females ( $p=0.39$ )). Duration of puberty to attainment of Tanner stage 5 was similar in SRS and non-SRS. There was 1 SRS female with primary amenorrhea due to Müllerian agenesis. Mean levels of LH, FSH, inhibin B, AMH and testosterone were similar in SRS and non-SRS. Four of 15 SRS males had a postpubertal inhibin B level P95, suggesting Sertoli cell dysfunction. One of these males, with a history of cryptorchidism, hypospadias and orchidopexy, had also a testosterone <P10, LH >P95, and AMH

**Conclusions:** Our study indicates that SRS patients have a similar age at onset of puberty and pubertal progression as non-SRS subjects born SGA. Although gonadal function was on average similar in SRS, non-SRS and healthy references, disturbances in Sertoli cell function are more common in SRS males. The primordial follicle pool in SRS females is similar as in non-SRS SGA subjects and healthy controls.

# **AUTOIMMUNE DISEASES IN TURNER SYNDROME: THE ROLE OF XP DELETIONS AND FOXP3 HAPLOINSUFFICIENCY**

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Marketa Pavlikova, MS/MA, Faculty of Mathematics and Physics, Charles University in Prague, Prague, Czech Republic; Jan Lebl, MD, Motol University Hospital in Prague, Prague, Czech Republic

**Objectives:** Individuals with Turner syndrome (TS) have a higher risk to develop autoimmune diseases (AID) such as autoimmune thyroid disease (AITD) and celiac disease. The reason for this phenomenon is still unknown. Previous studies tracking associations between distinct karyotypes and AID in TS brought inconsistent results.

We aimed to clarify the role of the karyotype for AID. Furthermore, we investigated whether common therapies for females with TS like growth hormone and sexual hormones impact the occurrence of AID.

**Methods:** We analyzed retrospective data on clinical course, AID, karyotype and therapy in a large cohort of 286 Czech females with TS (current age 2.8-43.4 years, median 18.7). Karyotypes were sorted according usual classifications and a novel *FOXP3* classification. We tested the influence of karyotypes and medications on the occurrence of AID.

**Results:** The prevalence of AITD (25.5%) and celiac disease (8.7%) in the whole cohort was similar to previous studies. Other AID occurred in single cases only. The prevalence of AITD was higher in females with an isochromosome Xq (46,XiXq, 41.0%,  $p=0.01$ ) or a Xp deletion (46,XdelXp, 40.0%,  $p=0.01$ ). The higher prevalence of celiac disease in 46,XiXq (18.4%) and 46,XdelXp (10.0%) was not significant ( $p=0.35$ ). Both karyotype variants lack the short arm of the X chromosome where the *FOXP3* gene is located. As *FOXP3* controls regulatory T cells, its haploinsufficiency may facilitate the development of AITD (and AID in general) in TS. A novel karyotype classification reflecting the number of *FOXP3* copies showed a tendency to a higher occurrence of AITD (29.2%) in subjects with a single copy of *FOXP3* (including 45,X; 46,XiXq; 46,XdelXp; 46,Xmar; 46,XY-material;  $p=0.36$ ).

Concerning the impact of therapy, we showed no link between the mean age at initiation of growth hormone and/or sexual hormone administration and the occurrence of AID.

**Conclusions:** Absence of the short arm of the X chromosome is correlated with a significantly higher occurrence of AITD in females with TS. Haploinsufficiency of *FOXP3* (which is located on the short arm of the X chromosome) may contribute to the development of AITD. Therapy with growth hormone and sexual hormones seems not to increase the risk of AID in TS.

# **NKX2-1 GENE DEFECTS IN A PEDIATRIC COHORT WITH SUSPECTED BRAIN-LUNG-THYROID SYNDROME.**

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Spain; Amanda Herranz, MS/MA, Thyroid Molecular Laboratory, Institute for Medical and Molecular Genetics (INGEMM), La Paz University Hospital, Madrid, Spain; Daniel Natera-De Benito, MD, Pediatric Neurology, Fuenlabrada University Hospital, Madrid, Spain; Maria Gallego, MD, Pediatric Endocrinology Department, Doce de Octubre University Hospital, Madrid, Spain; Maria Palomares, PhD; Julian Nevado, PhD, Functional and Structural Genomic, Institute for Medical and Molecular Genetics (INGEMM), La Paz University Hospital, Madrid, Spain; Jose C. Moreno, PhD, Thyroid Molecular Laboratory, Institute for Medical and Molecular Genetics (INGEMM), La Paz University Hospital, Madrid, Spain

**Objectives:** To assess the molecular basis of clinical phenotypes consistent with the Brain-Lung-Thyroid syndrome (BLTS).

**Methods:** A cohort of 15 patients (80% male), with mean age of  $7.9 \pm 6.5$  years at clinical suspicion of BLTS. Nine (60%) had the complete triad: neurological signs (most frequently chorea and/or developmental delay), respiratory problems (neonatal respiratory distress, bronchiolitis and other recurrent lung infections) and congenital or primary hypothyroidism. Three patients (20%) presented neurological signs and hypothyroidism, one patient (6.6%) neurological and respiratory problems, 1 only hypothyroidism and respiratory features and finally one patient with benign hereditary chorea. PCR and Sanger sequencing of the whole coding region of *NKX2-1* was performed in all patients, MLPA was performed in 10. One patient was diagnosed by Comparative Genomic Hybridization (CGH)-array and another by genome-wide SNP-array.

**Results:** We identified *NKX2-1* defects in 4 patients (26 %): a 1 bp-deletion in exon 1 (c.224insG) causing a frameshift and early truncation of the protein (p.V75fsX408) in a 14 y.o. boy with BLTS and severe congenital lung emphysema; a missense mutation in exon 2 (p.N211S) in a 8 y.o. boy with the typical triad whose mother, uncle and cousin (but none of the grandparents) carried the same mutation, suggesting germinal mosaicism in the pedigree; an intragenic 253 bp-deletion located in exon 2 in a 17 y.o. boy with BLTS and finally a 3.44 Mb interstitial deletion including the entire *NKX2-1* and 19 additional genes in a 10 y.o. girl with classical BLTS associated with joint hyperlaxity and humoral immunodeficiency (hypogammaglobulinemia).

**Conclusions:** Pediatric BLTS is a challenging and frequently delayed diagnosis, given the variability and subsequent occurrence of features. The genetic background of BLTS seems heterogeneous since defects in *NKX2-1* are present in only 25% of patients using all available methodologies. Complex phenotype additional to BLTS should suggest large deletions in Chr. 14q including *NKX2-1*.

P2-1610

## PREVALENCE AND RISK FACTORS OF DIABETES MELLITUS IN KOREAN PRADER-WILLI SYNDROME

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**Objectives:** Prader-Willi syndrome (PWS) is often related to severe obesity and type 2 diabetes mellitus (DM) which can lead to further morbidity and mortality. However a study about prevalence of DM and other variables relevant to DM in Korean PWS have not been reported yet. This study investigated the prevalence, risk factors and long-term complications of DM in Korean PWS.

**Methods:** Of all 211 patients diagnosed with PWS at Samsung Medical Center from 1994 to 2016, we performed a retrospective cohort study of 84 PWS patients aged 10.3-35.8 years because the youngest patient with DM was 10.1 years. We estimated the occurrence of DM according to age (10-18 years versus >18 years), gender, body mass index (BMI), genotypes, growth hormone (GH) therapy, homeostasis model of assessment-insulin resistance (HOMA-IR) and presence of dyslipidemia or hypogonadism or central precocious puberty (CPP).

**Results:** Of all 211 PWS patients, Type 2 DM was found in 29 patients (13.7%). The mean age of DM onset was  $15.9 \pm 3.6$  years. Adult group (>18 years), obesity (BMI cut-off point >30 in adults, >2 SDS in children and adolescents), HOMA-IR, presence of dyslipidemia or hypogonadism or CPP were associated with occurrence of DM in univariate analysis. GH therapy was not related to DM development ( $p=0.141$ ). However in multivariate logistic regression analysis, only obesity ( $p=0.001$ ) and HOMA-IR ( $p<0.001$ ) were significant predictive factors for DM development in PWS.

Of PWS with DM subjects, at least one microvascular complication was found in 7 patients, and non-proliferative diabetic retinopathy was the most common complication (6/7). Older age and HOMA-IR were positively correlated with occurrence of diabetic microvascular complications ( $p<0.05$ , Spearman correlation coefficient 0.393 and 0.434, respectively).

**Conclusions:** The prevalence of diabetes in Korean PWS was similar to results of other previous studies. Moreover severe obesity and HOMA-IR were strong predictive factors for development of type 2 DM in PWS. From these results, we especially suggest that regular monitoring of glucose homeostasis parameters is important to prevent the progression of diabetes and diabetic microvascular complications.

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Table 1. Baseline characteristics of the patients with PWS.

	DM, n (%)	Non-DM, n (%)	Total, n (%)	P-value <sup>a</sup>
	29 (34.5)	55 (65.5)	84 (100)	
Age (years) (range)	20.4±5.7 (12.7–35.8)	15.8±4.1 (10.3–31.8)	17.4±5.1 (10.3–35.8)	<.001
Age at diagnosis with DM	15.9±3.6 (10.1–27.0)	–	–	–
Age at diagnosis with PWS	6.9±7.2	4.7±5.0	5.5±5.9	0.151
Gender (male), n (%)	22 (75.9)	30 (54.5)	52 (61.9)	0.057
Genotype (deletion), n (%)	21 (72.4)	38 (69.1)	59 (70.2)	0.757
BMI, kg/m <sup>2</sup> (SD)	35.7±9.2 (2.8±1.0)	28.3±8.9 (1.7±1.3)	30.8±9.6 (2.1±1.3)	<.001
Obesity <sup>b</sup> , n (%)	23 (79.3)	22 (40)	57 (67.9)	0.001
HOMA-IR	6.3±3.5	3.4±3.8	4.4±3.9	0.001
HbA1C, % (mmol/mol)	8.4±2.3	5.6±0.3	6.6±1.9	<.001
Basal insulin (μU/mL)	45.7±31.1	25.3±23.0	32.5±27.7	0.001
Basal C-peptide (ng/mL)	7.0±2.8	4.8±2.9	5.7±3.0	0.004
Age at GHT start (years)	7.0±3.8	6.7±4.3	6.8±4.1	0.795

<sup>a</sup> Mann-Whitney U-test; <sup>b</sup> BMI ≥ 30 kg/m<sup>2</sup>.

overtime were found. No new cases of TM were diagnosed. TM and PPP were not always related. 82% of adolescent and young adult patients presented, apparently, a normal hypothalamus-hypophysis-testicles functionality with normal values of FSH, LH and Testosterone. In 18% , testicular autonomy persisted even during post-pubertal period; oligospermia was detected only in one patient. No new testicular lesions were demonstrated by ultrasound evaluation, except two cases of I and II degree varicocele and two cases of epididymis' cysts.

**Conclusions:** Gonadal diseases are typical in MAS males and they are frequently represented by TM (63%). The available evidences suggest a lower risk for TM to evolve in malignancy, thereby a conservative follow-up (by ultrasound) is recommended. Gonadal functionality, during post-pubertal epoch, does not seem to be compromised among the majority of MAS males, although testicular autonomy may persist. However, further studies are needed to establish reproductive function in these subjects.

P2-1612

## LONGITUDINAL EVALUATION OF TESTICULAR MORPHOLOGY AND FUNCTION IN MALE SUBJECTS AFFECTED FROM MCCUNE-ALBRIGHT SYNDROME

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**Objectives:** Knowledge about testicular function in males affected from McCune-Albright syndrome (MAS) is limited, because of the rarity of this syndrome in male. In a previous study, we demonstrated for the first time, an high incidence (63%) of testicular microlithiasis (TM) in males with MAS, even in absence of peripheral precocious puberty (PPP). Clinical meaning of TM currently remain under discussion.

### Objectives:

To establish what the evolution in time will be of hypothalamus-hypophysis-testicles functionality and of TM. We also evaluated the possible association with new testicular lesions, ultrasonographically detectable, in MAS males.

**Methods:** We recruited 11 MAS patients (diagnosis confirmed by specific genetic tests), already evaluated in the previous collaborative study, and they underwent clinical, laboratory and ultrasound evaluation after almost 10 years from the first assessment.

**Results:** 55% of patients presented a PPP history. TM was detected in 63% of patients and no ultrasound changes overtime were found. No new cases of TM were diagnosed. TM and PPP were not always related. 82% of adolescent and young adult patients presented, apparently, a normal

P2-1611

## LONGITUDINAL EVALUATION OF TESTICULAR MORPHOLOGY AND FUNCTION IN MALE SUBJECTS AFFECTED FROM MCCUNE-ALBRIGHT SYNDROME.

Malgorzata Wasniewska, PhD, University of Messina, Messina, Italy; Patrizia Matarazzo, MD, Regina Margherita Children's Hospital - Health and Science , Turin, Italy; Domenico Corica, MD, University of Messina, MESSINA, Italy; Maria Cristina Vigone, MD, IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy; Maria Francesca Messina, MD, University of Messina, MESSINA, Italy; Luisa De Sanctis, PhD, Regina Margherita Children's Hospital – Università di Torino, Turin, Italy; Filippo De Luca, PhD, University of Messina, Messina, Italy; Daniele Tessaris, PhD, Regina Margherita Children's Hospital - Health and Science , Turin, Italy

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**Objectives:** To establish what the evolution in time will be of hypothalamus-hypophysis-testicles functionality and of TM. We also evaluated the possible association with new testicular lesions, ultrasonographically detectable, in MAS males.

**Methods:** We recruited 11 MAS patients (diagnosis confirmed by specific genetic tests), already evaluated in the previous collaborative study, and they underwent clinical, laboratory and ultrasound evaluation after almost 10 years from the first assessment.

**Results:** 55% of patients presented a PPP history. TM was detected in 63% of patients and no ultrasound changes

hypothalamus-hypophysis-testicles functionality with normal values of FSH, LH and Testosterone. In 18% , testicular autonomy persisted even during post-pubertal period; oligospermia was detected only in one patient. No new testicular lesions were demonstrated by ultrasound evaluation, except two cases of I and II degree varicocele and two cases of epididymis' cysts.

**Conclusions:** Gonadal diseases are typical in MAS males and they are frequently represented by TM (63%). The available evidences suggest a lower risk for TM to evolve in malignancy, thereby a conservative follow-up (by ultrasound) is recommended. Gonadal functionality, during post-pubertal epoch, does not seem to be compromised among the majority of MAS males, although testicular autonomy may persist. However, further studies are needed to establish reproductive function in these subjects.

P2-1613

#### PRIMARY OVARIAN INSUFFICIENCY IN TWO GIRLS WITH RETT SYNDROME

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**Objectives:** Rett syndrome (RTT) is a progressive neurodevelopmental disorder, prevalent in female. Mutation of *Methyl-CpG-binding protein 2* (MeCP2) gene, localized in the long arm of chromosome X (Xq28), is implicated in about 95% of classic RTT. There are no studies available about gonadal function in these patients.

**Methods:** We report the cases of two girls with RTT (*de novo* mutation of MeCP2) who came to our attention for secondary amenorrhea at the age of 19 (patient 1) e 11.6 (patient 2) years of age. Both presented spontaneous pubertal development with menarche at the age of 11 and 10.3, respectively. Furthermore, they were both obese (BMI +2.4DS) and clinical hyperandrogenemia was reported in patient 1.

**Results:** We first hypothesized as diagnosis menstrual irregularities in obese subjects, therefore we evaluated the hypothalamus-hypophysis-gonads axis functionality. Basal gonadotropin resulted slightly upper than normal values, estradiol was lower than normal range, adrenal steroids, prolactin, thyroid function e serology for coeliac disease resulted normal. Karyotype was normal (46,XX) in both. Pelvic ultrasound was normal for age in both patients. LHRH test highlighted a pronounced increase of FSH and of LH values in particular (LH peaks 169.95 mUI/ml in patient 1 and 84.36 mUI/ml in patient 2).

**Conclusions:** Based on clinical and laboratory observations we diagnosed hypergonadotropic hypogonadism in both patients. Moreover, we supposed in these patients a primary ovarian insufficiency (POI). FMR1 (fragile X mental retardation 1) and FMR2 genes, often involved in POI with genetic origin, are localized in the long arm of chromosome X (Xq27.3 and Xq28, respectively) near to MeCP2 gene, and

their mutations might determine POI in RTT patients. For this reason, we carried out a genetic survey to search FMR1 pre-mutation and/or FMR2 deletions.

Meanwhile our patients started a diet and patient 1 also started an estro-progestinic therapy.

P2-1614

#### HARLEQUIN SYNDROME AND TRISOMY 21: NOTHING TO SWEAT ABOUT

*Kathryn Eckert, MD, University of Nevada, Reno School of Medicine, Reno, NV, United States; Alyssa Eckert, BS/BA, University of Nevada, Reno, Reno, NV, United States; Gerard Hershewe, DO; Josh Gratwohl, BS/BA, University of Nevada, Reno School of Medicine, Reno, NV, United States*

**Objectives:** A 5 year old female with trisomy 21 presented with hemifacial pallor and anhidrosis characteristic of Harlequin Syndrome. To our knowledge, no patient with trisomy 21 and Harlequin Syndrome has been described.

**Methods:** A five year old girl with trisomy 21 presented to the pediatric endocrinology clinic for growth evaluation. It was noted at birth that she had features of trisomy 21, confirmed by chromosome analysis. She had a ventricular septal defect and patent ductus arteriosus, both of which were surgically repaired within the first four months of life. She has had poor weight gain and is G-tube dependent.

At the age of two, she was noted to have hemifacial flushing and hyperhidrosis on her right side and pallor and anhidrosis on the affected left side. Evaluation has included a spinal MRI, which did not reveal any thoracic or cervical lesions, and an MRI of the brain with and without contrast revealed elevation of the superior lateral angles of both orbits giving the appearance of a "Harlequin mask". MRI brain was otherwise normal. Vascular flow voids in the vertebrobasilar and carotid arteries, circle of Willis, and dural venous sinuses were normal. Ophthalmological examination ruled out a concomitant Horner's syndrome.

**Results:** The patient's mother provided photographs documenting hemifacial flushing and hyperhidrosis on the right side and pallor and anhidrosis on the left side, classic for Harlequin syndrome but without obvious etiology to date.

**Conclusions:** Harlequin Syndrome is a rare disorder, with fewer than 100 reported cases in the literature. Many cases occur due to damage to the sympathetic nervous system, although 6% of cases are believed to be congenital. Patients with Harlequin Syndrome may also present with Horner's, Adie's, or Ross' Syndrome. However, there has been one reported case of Harlequin Syndrome without any concomitant disorders. Further testing will include MR Angiogram, thermography, and frontal and lateral skull films. Typically, no treatment is required for Harlequin Syndrome. The Harlequin "mask" is not known to be related to classic Harlequin symptoms but deserves evaluation to rule out coronal suture synostosis.



### RENAL AGENESIS, MÜLLERIAN AGENESIS, AND HYPOMAGNESEMIA: A CASE REPORT OF A 17Q12 DELETION ENCOMPASSING THE HNF1B GENE

Kayla Flood, MD, University of Saskatchewan, Saskatoon, SK, Canada; Munier Nour, MD; Anke Banks, MD; Mark Inman, MD, University of Saskatchewan, Saskatoon, SK, Canada

**Objectives:** We present a 16-year-old female with primary amenorrhea, hypomagnesemia, and a solitary kidney. In addition, we review the literature on phenotypes associated with 17q12 deletion syndrome, as it applies to the investigation of patients presenting with renal and endocrine disease.

**Methods:** Our patient presented at one month of age with a urinary tract infection leading to an incidental finding of a solitary kidney. At 15 years of age, she was referred to nephrology whose assessment revealed elevated serum creatinine, persistent proteinuria, and a non-hypertrophied left solitary kidney on renal ultrasound. Further laboratory investigations demonstrated hypomagnesemia and renal magnesium wasting. She was noted to have primary amenorrhea, despite normal pubertal development, including thelarche and adrenarche. A pelvic ultrasound revealed normal adnexal structures but an absent uterus. A pelvic MRI confirmed the absence of a uterus and the upper one third of the vagina consistent with Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome.

**Results:** Detailed endocrine evaluation revealed 46, XX karyotype with appropriate gonadotropin, estradiol, and testosterone concentrations. She had normal blood glucose regulation. Molecular genetic sequencing studies failed to identify the expected sequence variant in the *Hepatocyte Nuclear Factor 1B* (*HNF1B*) gene. However, array comparative genomic hybridization (CGH) analysis demonstrated a heterozygous 1.4Mb deletion in chromosome 17q12 region corresponding to the loss of the *HNF1B*, *LHX1* and *PIGW* genes.

**Conclusions:** Although *HNF1B* mutations are most commonly thought of as a candidate gene for monogenic diabetes and associated with renal cysts, our patient demonstrates a broader phenotypic presentation stemming from the complete loss of *HNF1B*. The findings of 17q12 deletion explain the constellation of clinical findings seen in our patient with MRKH syndrome, renal agenesis, and hypomagnesemia. Therefore, in the presence of clinical suspicion, analysis of the *HNF1B* gene by both molecular gene sequencing and array CGH may be required to confirm the diagnosis.

P2-1616

### A UNIQUE PRESENTATION OF IPEX SYNDROME

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Stephen Kingsmore, MD, Rady Children's Hospital, San Diego, CA, United States; Ron S Newfield, MD, University of California in San Diego and Rady Children's Hospital, San Diego, CA, United States

**Objectives:** IPEX syndrome (Immune dysregulation, Polyendocrinopathy, X-linked) is a rare disorder associated with mutations within *FOXP3*, a key transcription factor for T regulatory cells. IPEX is characterized by severe deficiency in T regulatory cells, which leads to multi-organ autoimmunity. Enteropathy with or without type 1 diabetes typically occurs early in disease. Later, most individuals also develop autoimmune thyroid disease, hematologic dysfunction, dermatitis, and failure to thrive. IPEX has a poor prognosis with most affected males dying by age two years. Bone marrow transplant (BMT) is the most successful treatment, with better outcomes if performed early.

**Methods:**

**Results:** We describe a 4 month old male Hispanic infant who presented with diabetes mellitus without ketoacidosis. Insulin antibody was > 50 U/ml (normal < 0.4 U/ml). GAD and ICA512 antibodies were negative. Initial hemoglobin A1c was 7.2% (normal <6.5%). He was also found to have thyroid peroxidase (TPO) antibodies (81 IU/ml, normal < 9), but normal thyroid function. His mother did not have TPO antibodies. One month after diagnosis, his glucose was 128 mg/dL and c-peptide was low (0.59 ng/ml, normal 0.8-3.1). Rapid, trio, whole genome sequencing (WGS) identified a maternally inherited, hemizygous, pathogenic, canonical splice site variant (c.-23+1G>T) in *FOXP3*, which was clinically confirmed by Sanger sequencing. This variant has been previously described to be causative for IPEX. His high IgE (350 kU/L, normal 0-8) was consistent with an IPEX diagnosis. While young, our patient is atypical in that he is mildly obese and has not developed enteropathy, dermatitis, or blood disorders.

**Conclusions:** This case describes an early and atypical presentation of IPEX syndrome by rapid WGS. IPEX should be considered in the differential diagnosis for autoimmune mediated diabetes of onset

P2-1617

### DIAZOXIDE-RESPONSIVE HYPERINSULINISM IN AN INFANT WITH SOTOS SYNDROME

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**Objectives:** Overgrowth syndromes such as Sotos Syndrome are associated with dysregulated insulin secretion in infancy. Although a transient finding, the underlying mechanism of insulin secretion is unclear. We describe an infant with physical features of Sotos Syndrome, a confirmed NSD1 mutation and diazoxide-responsive hyperinsulinemic hypoglycemia.

**Methods:** Chart review was performed.

**Results:** A full-term female infant, appropriate for gestational age, was born via C-section. Immediately after birth, the infant was tachypneic and serum glucose was 10 mg/dL. Despite a rapid dextrose bolus, serum glucose remained 17 mg/dL. Intravenous dextrose infusion (GIR 8 mg/kg/min) was started and euglycemia was achieved. Physical features were notable for macrocephaly with frontal bossing, hepatomegaly and poor feeding. Neuroimaging revealed lissencephaly and scattered white matter injury with periventricular calcifications. These findings were suspicious for infectious etiology, however definitive testing was negative and hypoglycemia persisted. Critical sample was obtained with an inappropriately normal insulin level of 3.6 mIU/mL (2-13 mIU/mL) in the setting of a serum glucose of 53 mg/dL. Microarray analysis revealed a 5q35.2-35.3 deletion, which included the NSD1 gene, consistent with Sotos syndrome. At 3 weeks of life, she required an intravenous GIR of 11 mg/kg/min and full enteral nutrition to maintain euglycemia. Diazoxide therapy was initiated at 10 mg/kg/day. After 3 days of diazoxide therapy, intravenous glucose infusion was completely discontinued.

**Conclusions:** Sotos Syndrome may present as hyperinsulinemic hypoglycemia, manifesting shortly after birth. Hyperinsulinism in Sotos Syndrome may be under-recognized due to other manifestations of the disorder. Therefore, infants with physical features of Sotos Syndrome and neonatal hypoglycemia should be screened for hyperinsulinism as untreated hypoglycemia can adversely affect brain development and have long-term neurologic sequelae.

This case also suggests that the haploinsufficiency of NSD1 may affect the potassium-ATP channel function in pancreatic beta cells, making hyperinsulinism in Sotos Syndrome diazoxide-responsive. We conclude that diazoxide should be considered as a treatment in Sotos Syndrome until transient hyperinsulinism resolves.

P2-1618

#### **A NOVEL FRAMESHIFT MUTATION IN ESCO2 GENE CAUSE ROBERTS SYNDROME: CASE PRESENTATION**

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**Objectives:** Roberts syndrome (OMIM #268300) is a rare autosomal recessive disorder characterized primarily by symmetric limb malformations, craniofacial findings, prenatal and postnatal growth retardation. Our aim is to report the molecular and clinical characteristics of a Turkish family with Roberts syndrome who had a novel homozygous frameshift mutation in the *ESCO2* gene.

#### **Methods: CASE REPORT**

An eight days old boy presented to our clinic, with feeding difficulties, lack of movement and multiple anomalies. He was 27-year-old mother's first pregnancy from 39 weeks gestation, born with 2020 gram. On physical examination, his

body weight was 2590 gram (<3p), height was 41 cm (<3p), and head circumference was 32 cm (<3p). On examination of the head and neck, there was a prominent frontal bone, open and flat forehead, microcephaly, sparse hair, hypertelorism, shallow orbits, exophthalmia, highly arched palate, malar hypoplasia, nasal hypoplasia, depressed nasal bridge, low and and rear-positioned ears, malformed helices, micrognathia, midfacial capillary hemangioma and short neck. On examination of the skeletal system, there were bilateral symmetric hypomelia, flexion contracture in all extremities, bilateral pesquinovarus. On upper extremity X-Ray, the radius and ulna were aplasic bilaterally, the humeruses were normal bilaterally, and there were not metacarpal bones in the right hand and in the left hand. On lower X-Ray, the femurs were short bilaterally, the fibulas were aplastic bilaterally, there were not bilaterally metatarsal bones in the foot, and there was midline fracture of the left femur.

**Results:** With these clinical findings, the case was diagnosed as Roberts syndrome. In the patient, a homozygous 1-base insertion (c.877\_878insA) leading to a frameshift mutation (p.R293Kfs\*8) was identified a novel mutation in the *ESCO2* gene. Parents were heterozygous, presenting one normal variant and the c.877\_878insA mutation of *ESCO2* gene.

**Conclusions:** RBS is a syndrome with multiple anomalies and a fatal course. It is important that families should be informed about prenatal diagnosis and preimplantation genetic diagnosis. In this case, the previously no described *ESCO2* gene a novel a homozygous frameshift mutation was detected.

P2-1619

#### **PARTIAL GROWTH HORMONE DEFICIENCY IN A SUBJECT WITH 18P MICRODELETION SYNDROME - CASE REPORT**

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**Background:** Subtelomeric deletion of short arm of chromosome 18 is a rare chromosomal disorder with estimated prevalence of 1 in every 50 000 live births. Its phenotypic variability makes it difficult to recognize. Short stature has been associated with 18p- syndrome. Only 23% of 18p- subjects have isolated growth hormone deficiency (GHD) and some of them have started growth hormone treatment. The beneficial effect of GH treatment is currently under active investigation.

**Methods:** Microdeletion of 18p- was confirmed via MLPA.

**Results: Case presentation:** A 6-year-old female was referred for short stature and dysmorphic features. She is a product of non-consanguineous marriage of healthy parents with normal stature. Subject was born in 39 gestational week with low birth weight of 1980 g and length of 45 cm. At age of 1 year her weight was 4850 g. She has communication difficulties with developmental delay. At first evaluation of 6 1/12 height SDS was -5.45 and weight SDS -3.11. She was noted to have

dysmorphic features including microcephaly (SDS -3.11), macrostomia, short philtrum, dysplastic ears with lateral protrusion, bilateral fifth finger clinodactyly. Examinations revealed mitral valve prolapse with mild mitral insufficiency, incomplete rotation of right kidney and disharmonic bone age (BA) with wrist BA of 4 6/12 and radius and ulna's BA of 6 6/12. Standard karyotyping found normal female karyotype 46 XX. MLPA screening for microdeletions, subtelomeric deletions and duplications revealed the presence of subtelomeric microdeletion 18p-. Low serum IGF-1 of 51.5 ng/ml was detected with normal IGFBP3 and thyroid functional tests. Result of GH provocation test with arginine showed basal level of 1.07 ng/ml and peak level of 8.84 ng/ml, and stimulation test with physical exercise- peak of 0.538 ng/ml. Due to partial GHD treatment with GH has been started.

**Conclusions:** Subtelomeric microdeletion of 18p- is a rare syndrome. We highlight the importance of an evaluation for growth hormone deficiency in patients with subtelomeric 18p- syndrome as the replacement therapy may improve their quality of life.

P2-1620

#### CLINICAL FEATURES OF TWO JAPANESE PATIENTS WITH MICRODUPLICATIONS OF 5Q35.2-Q35.3 ENCOMPASSING NSD1

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**Objectives:** Loss-of-function mutations or microdeletions of *NSD1* are known to cause Sotos syndrome. Although microduplications encompassing *NSD1* have been proposed in a small number of patients with microcephaly, short stature and developmental delay, the phenotypic consequences have not been fully characterized. We encountered two Japanese females with small-for-gestational age (SGA), short stature and microcephaly. The clinical and genetic features were assessed.

**Methods:** Patient 1 is now 4 years old Japanese girl. She was born at 37 weeks of gestation and her birth weight, length and occipitofrontal circumference (OFC) was 2,086 g (-1.9 SD), 42.5 cm (-2.2 SD) and 30.0 cm (-2.0 SD), respectively. At 3 years of age, she showed growth retardation, her height and OFC was 84.5 cm (-2.4 SD) and 43.0cm (-3.4 SD). Growth hormone (GH) provocation test showed normal response. GH

therapy was initiated for SGA short stature. Her developmental milestones have been normal.

Patient 2 is now 6 years old Japanese girl. She was born at 38 weeks of gestational age with no complications. Her height, weight and head circumference were 44.0 cm (-1.9SD), 2,374 g (-1.3SD) and 30.5 cm (-1.7SD) at birth. At 2 years of age, she was referred to our hospital due to short stature. Provocation test using L-arginine and insulin revealed hypersecretion of GH (basal/peak value of GH was 4.20/58.5 ng/ml and 8.30/24.3 ng/ml respectively. She had neither distinctive facial features nor developmental delay.

To detect copy number alterations, we performed array comparative genomic hybridization using DNA from peripheral blood samples.

**Results:** Copy number analysis revealed 1.96 Mb and 1.42 Mb microduplications in 5q35 including *NSD1* gene. The same microduplications were not identified in the parents of each patient. Our patients manifested pre- and postnatal growth failure and microcephaly as previously reported. On the other hand, none of our patients showed developmental delay, which are characteristic findings in *NSD1* microduplication.

**Conclusions:** We report two Japanese female with microduplication of 5q35.2-q35.3 encompassing *NSD1*. Our cases suggest the wide phenotypic spectrum of *NSD1* microduplication.

#### POSTER SESSION 2

**Friday, September 15, 2017, 11:30am-12:30pm**

#### P2 - Thyroid

**P2-1700 – P2-1734**

P2-1700

#### ATA GUIDELINES ON PEDIATRIC DIFFERENTIATED THYROID CARCINOMA WOULD REDUCE THE NEED FOR RADIOIODINE ABLATION IN LOW RISK DISEASE

*Nisha Bhavani, MD; Kingini Bhadrar, MD; Vasantha Nair, MD; Usha V Menon, MD; Praveen V Pavithran, MD; Arun S Menon, MD; Nithya Abraham, MD; Annie Pulikkal, MD; Harish Kumar, MD, AMRITA UNIVERSITY, KOCHI, India*

**Objectives:** Until the American Thyroid Association(ATA) guidelines on management of differentiated thyroid carcinoma (DTC) in children became available in 2015, all children with DTC were being treated like adults. Here we aim to validate the current pediatric ATA guidelines in a large cohort of pediatric DTC patients.

**Methods:** A retrospective study of patients less than 18 years of age at diagnosis of DTC being followed up in a single centre was done. 38 children were included. Mean age at diagnosis was 14 years and mean duration of follow up was 36 months ( range 6-110 months). According to the pediatric ATA guidelines, 13 had low risk,18 had intermediate risk and 7 had high risk disease. The guidelines were validated for preoperative staging, extent of thyroidectomy, use of radioiodine ablation, use of whole body iodine(WBI) scans for follow up and prognostic factors.

**Results:** For preoperative staging, ultrasound and FNAC of the thyroid nodule were done but cytological analysis of the lymphnodes and preoperative advanced cervical imaging was not done. All except six patients underwent total thyroidectomy. Central neck dissection was done in 5 and lateral neck dissection in 18 patients depending on the preoperative ultrasound and intraoperative neck findings. All children had cervical lymphnode metastasis at diagnosis. All children except two who did not have a positive diagnostic WBI scan postoperatively underwent high dose radioiodine ablation. Had the present guidelines been applied, 13 patients with low risk disease would not have received the radioiodine ablation. Repeat radioiodine therapy was given to 8 children of which present guidelines would have avoided it in 3 patients with intermediate risk disease. Diagnostic WBI scan was used only sparingly on follow up when there was evidence of persistent disease not visible on ultrasound. Patients with low risk disease had a good outcome with 8 out of 13 having no evidence of disease and remaining five having declining thyroglobulin antibody levels on follow up. No single prognostic factor could be identified which could predict the response at last visit.

**Conclusions:** The ATA guidelines on pediatric DTC is applicable in this cohort of patients. Practicing these guidelines would have changed the management of children with low risk DTC.

P2-1701

#### **A RETROSPECTIVE THYROID CANCER REVIEW OF 52 PEDIATRIC CASES BASED ON HOSPITAL REGISTRY OF THYROID OCCUPIED LESION**

*Jiali Wang, BS/BA, Capital Medical University, Beijing, China*

**Objectives:** To describe the clinical characteristics and prognosis of pediatric thyroid cancer based on the hospitalized thyroid occupied lesion.

**Methods:** Ruled in thyroid occupied lesion from register system of Beijing Children's Hospital, Capital Medical University between July 2006 and November 2016 by key word of thyroid according to the main diagnosis, summary the clinical characteristics and follow up their prognosis.

**Results:** The total number of thyroid occupied lesions hospitalized and treated in our hospital is increasing in last 10 years, they were 26 thyroid abscess and 119 thyroid nodules, it accounts for 9.76% (145/1487) of all children with thyroid disease hospitalized in our hospital. 100 patients with thyroid nodules receiving thyroid surgery and 52 of them were identified as malignant from pathology databases. Ultrasonic diagnoses include 34 malignant, 48 benign, 17 suspicious and 1 without ultrasound result. 52 patients with thyroid cancer with normal thyroid function include 18 boys and 34 girls and their average age is 10 years old. Neck mass was the chief complaint in 50 of 52 patients, it is always unilateral (10/52) and solid (34/52). US features such as hypoechogenicity (40/51), calcification (31/51), irregular margins (29/51), and lymph nodes metastases (36/51) are more common in malignant lesions. FNA was performed in 6 patients, 5

considered malignant and 1 benign, which is consistent with the result of ultrasound. The near term complications of surgery include hypothyroidism (51/52), hypocalcemia (21/52), hoarse (9/52), pressure symptom (2/52), and deglutition barrier (1/52). 39 patients received long term follow-up 0.25~7.35 years, 5 patients had permanent hoarse, 38 had hypothyroidism and 4 relapsed.

**Conclusions:** Cases of TC are increasing yearly and common in girls than boys. The neck masses are the main chief-complaint and more common on the left, hard, and accompanied by lymph node metastases. The accurate rate of ultrasound for the diagnosis of TC is high. The prognosis of pediatric thyroid cancer is better than adult patients and has a low rate of recurrence.

P2-1702

#### **HIGH FREQUENCY OF IN SITU THYROID IN TWINS WITH CONGENITAL HYPOTHYROIDISM: THE IMPORTANCE OF RE-EVALUATION OF THE DIAGNOSIS**

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**Objectives:** Recent studies reported a high incidence of congenital hypothyroidism (CH) with eutopic thyroid (GIS) in twins. The aims were: 1) to determine the evolution of thyroid function in CH twins; 2) to evaluate the genetic background using Next Generation Sequencing (NGS); 3) to assess the growth and neurodevelopment of the affected twin in comparison with the healthy co-twin (29 couples) at a pre-scholar age.

**Methods:** 48 probands and 53 co-twins (total 101 subjects) born from 43 couples and 5 triplets were recruited. All patients were detected by newborn screening for CH and were followed-up (2-24 years). We assessed thyroid function (TSH, FT4, thyroid auto-immunity) and performed thyroid US-scan. The auxological follow-up consisted of half-yearly examinations.

**Results:** 70% were dizygotic (DZ), 30% were monozygotic (MZ). 40% were born after in vitro fertilization and 76% of the twins were born preterm (GA<37). 58/101 patients were affected by CH. First neonatal screening (3-5 days of life) resulted negative in 24/58 twins, they were identified at re-screening (14-21 days). Between these missed patients, 8/24 patients were affected by permanent CH (GIS=7; ectopy =1). TSH at first screening resulted significantly reduced in MZ twins as compared to DZ twins (P 0.04). Among the CH twins

85% showed an in situ thyroid, and 15% thyroid dysgenesis (TD) (5% athyreosis, 7% ectopy, 3% hemiagenesis). At the age of 3 years twins affected by GIS-CH underwent re-evaluation: permanent CH was confirmed in 34% of subjects requiring treatment re-introduction. The remaining 56% showed transient CH. 10% showed persistent hyperthyrotropinemia (TSH 5-10mU/L). Preterm twins affected by severe prematurity were prevalent in the group affected by transient CH (P 0.08). CH cases with GIS showed a wild-type profile at NGS in 50% of cases and the remaining 50% displayed variants in genes implicated in dysmorphogenesis. The assessment of growth showed a lower weight (P 0.004) and height (P 0.002) in CH twins compared to their co-twins and compared to their target height (P 0.01). IQ was normal in both groups.

**Conclusions:** CH with GIS is the most common aetiology in twins. CH in twins is characterized by a high incidence of transient forms. Re-screening in twins should be considered a valid approach to identify hypothyroid twins.

P2-1703

#### PREVALENCE AND NATURE OF THYROMEGALY IN CROATIAN SCHOOLCHILDREN 17 YEARS AFTER INCREASE IN SALT IODIZATION

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**Objectives:** To assess prevalence and nature of thyromegaly in Croatian schoolchildren 17 years after increase in salt iodization with 25 mg KI/kg introduced in 1996. Results are compared with results of study conducted in 1993., when salt was iodized with 10 mg KI/kg and median urinary iodine concentration (UIC) was 50 µg/L. Study used the same methods as current, and comprised 5461 Croatian schoolchildren of same ages and sex distribution.

**Methods:** Study conducted through 2013. covered 3594 children (1777 girls and 1817 boys) aged 10-18 years and same examiner determined thyroid size by palpation. In all goitrous children TSH, T4, T3, TPO and Tg antibodies were measured and thyroid ultrasound was performed. Median UIC was 147 µg/L.

**Results:** Thyromegaly was found in 32 children (0.89% v.s. 2.8% in 1996.  $p < 0.00001$ ), simple goiter (SG) in 16 children (14 girls and 2 boys) (0.4% v.s. 2.3% in 1996.,  $p < 0.00001$ ), autoimmune thyroiditis (AT) in 12 children (11 girls and 1 boy) (0.33% v.s. 0.34% in 1996., n.s.). Benign thyroid nodules were identified in two children: toxic adenoma and cyst (in 1996. two adenoma and one cyst). No cases of Graves disease was found (in 1996. three patients). Subclinical hypothyroidism was found in one and overt in two AT children (in 1996. three overt, two subclinical hypothyroidism). Female/male ratio for SG patients was 7 (9.5 in 1996.) and in AT patients 11 (8.5 in 1996.). No

correlation between prevalence of thyromegaly and age was found.

**Conclusions:** The change from mildly deficient to sufficient iodine supply in Croatian schoolchildren was associated with significant decline in the prevalence of SG, while prevalence of AT remained unchanged.

P2-1704

#### LOW THYROXINE, NOT TRIIODOTHYRONINE, IS THE PREDOMINANT FEATURE IN MALNOURISHED CHILDREN LESS THAN 24 MONTHS OLD

*Takashi Hamajima, MD; Masako Izawa, PhD; Yuichi Nishikado, MD; Naoko Nishimura, MD, Aichi children's health and medical center, Obu, Japan*

**Objectives:** To evaluate the thyroid function in malnourished children less than 24 months old.

**Methods:** From 2004 to 2016, we examined the thyroid functions of the children (between 6 and 24 months old) at their initial visit, who visited our department due to failure to thrive (group 1). All the patients in group 1 were ascertained to be able to recover their thyroid hormone levels into reference ranges without thyroxine replacement therapy at their follow-up visits. As a control, we compared the thyroid functions of the same age group patients who had premature thelarche or micropenis (group 2). Additionally, we evaluated the thyroid functions in patients with eating disorder (group 3) and non-endocrine short stature (group 4), both groups ages are between 9 and 15 years old. Furthermore, the patients in group 1 were classified into three groups by BMI SD score: between 0 and -1 SD (group A), between -1 and -2 SD (group B), and less than -2SD (group C), and we compared free thyroxine (FT4) and free triiodothyronine (FT3) levels among each group.

**Results:** The number of subjects in each group was 38, 32, 29, and 140, in group 1, 2, 3, and 4, respectively. The levels of FT4 was  $1.05 \pm 0.26$ ,  $1.20 \pm 0.17$ ,  $0.84 \pm 0.23$ , and  $1.07 \pm 0.16$  ng/dl, in group 1, 2, 3, and 4, respectively. The levels of FT3 was  $4.11 \pm 0.80$ ,  $4.45 \pm 0.56$ ,  $1.64 \pm 0.52$ , and  $3.94 \pm 0.43$  pg/ml, in group 1, 2, 3, and 4, respectively. Comparing FT4 and FT3 between group 1 and 2, only FT4 levels were significantly lower in group 1 ( $p = .02$ ). On the other hand, between group 3 and 4, both FT4 and FT3 were significantly lower in group 3 ( $p < .001$ ). In group 1, the levels of FT4 was  $1.15 \pm 0.29$ ,  $1.09 \pm 0.22$ , and  $0.86 \pm 0.24$  ng/dl, in group A, B, and C, respectively. The levels of FT3 was  $4.36 \pm 0.97$ ,  $4.23 \pm 0.69$ , and  $3.60 \pm 0.77$  pg/ml, in group A, B, and C, respectively. FT4 levels were significantly lower in group C compared to group A and B ( $p < .05$ ), whereas there were no significant differences in FT3 among each group.

**Conclusions:** In malnourishment condition, low T3 is said to be the specific thyroid dysfunction which is known as "low T3 syndrome" or "euthyroid sick syndrome". However, our results suggest that low T4, not T3, was the predominant feature in malnourished children less than 24 months old.

# LEVOTHYROXINE DOSES OF LESS THAN 2.3 µG/KG/DAY AT AGE 1 YEAR AND 1.4 µG/KG/DAY AT AGE 3 YEARS MAY PREDICT TRANSIENT CONGENITAL HYPOTHYROIDISM

*Shinji Higuchi, MD; Yukihiro Hasegawa, PhD, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan*

**Objectives:** Congenital hypothyroidism (CH) could be divided into two types, permanent CH (P-CH) and transient CH (T-CH). At least three reports revealed significant differences in levothyroxine (LT4) dose between the two types during childhood. However, no cutoff LT4 dose has been established yet to differentiate between the two types. The purpose of this study was to propose cutoff LT4 doses at ages 1 and 3 years.

**Methods:** This study was a single-institution retrospective study. Of 93 neonatal screening-positive patients, 34 were eligible and included in the study after the exclusion of Down syndrome and so on. The 34 subjects had been treated with LT4 for CH based on their screening results for TSH and fT4. The subjects' long-term need for LT4 treatment was assessed by their charts between March 2010 and March 2016, and the subjects were classified as having P-CH (n=19) and T-CH (n=15). The patients with P-CH were divided into three subgroups: 1) patients who required an increase in LT4 dose after initiation of LT4 (n=12), 2) patients with increased TSH level (>5 µIU/mL) during a dose reduction (n=6), and 3) patients with high TSH peaks (>40 µIU/mL) at the TRH stimulation test after interruption of LT4 (n=1). In patients with T-CH, LT4 readministration was not introduced during the follow-up of ≥1 year after discontinuance of LT4 treatment. The LT4 doses at ages 1 and 3 years were compared between the two groups, and receiver-operating characteristic analysis for the groups was performed to set the cutoff doses of LT4 at those ages.

**Results:** A significant difference was found between the two groups at ages 1 year (2.6±1.5 and 1.0±0.5 µg/kg/day for P-CH and T-CH,  $p=0.0003$ ) and 3 years (2.9±0.9 and 1.9±0.5 µg/kg/day,  $p=0.0004$ ). When the cutoff LT4 doses at 1 and 3 years were set as 2.25 and 1.35 µg/kg/day, respectively, the sensitivity and specificity were 80% and 80%, and 79% and 84%, respectively. In the T-CH group, 3 patients were false-positive for P-CH both at ages 1 and 3 years; in all the three patients, the initial doses were as high as 10 µg/kg/day.

**Conclusions:** Our study suggests that when LT4 doses are <2.3 and 1.4 µg/kg/day at ages 1 and 3 years, respectively, a diagnosis of T-CH should be suspected.

# NATIONAL UK GUIDELINES FOR THE INVESTIGATION, TREATMENT AND LONG-TERM FOLLOW-UP OF PAEDIATRIC DIFFERENTIATED THYROID CARCINOMA

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*Trust, London, United Kingdom; Tim Beale, MBBS; Mark Gaze, MD; Sabine Pomplun, MBBS, UCLH NHS Foundation Trust, London, United Kingdom; Shonali Natu, MBBS, North Tees and Hartlepool NHS Foundation Trust, London, United Kingdom; Sarah Freeston, MS/MA, UCLH Medical School, London, United Kingdom; Sophie Wilne, MBBS, Nottingham University Hospitals' NHS Trust, London, United Kingdom*

**Objectives:** Although rare, the incidence of differentiated thyroid cancer (DTC) in childhood is increasing and despite low mortality rates, children and young people <19 years (CYP) with DTC are at risk of long-term morbidity. A paucity of RCTs in the field has led to a lack of consensus on how these CYP should be best managed. We intend to provide management guidelines for all paediatricians and paediatric endocrine, oncological, surgical, genetic and radiological specialists caring for children and young people under 19 years of age (CYP) with suspected or confirmed DTC, thereby improving long term outcomes.

**Methods:** Clinical questions were formulated based on a PICO (Population, Intervention, Comparison, Outcome) format by a multidisciplinary Guideline Development Group to guide systematic searches via the Ovid MEDLINE (Jan 1990–Nov 2016) and Cochrane Library (2016, Issue 12) TRIP and EMBASE electronic registries, identifying 250 separate research articles. Publications underwent a three-tier filtering process and 164 were reviewed using the GRADE approach. Where recommendations could not be made, a two-stage international Delphi consensus process was conducted.

**Results:** 64 clinical questions were identified, leading to 42 recommendations based largely on low to very low quality evidence. 23 further recommendations achieved >70% agreement via the Delphi consensus process. Important recommendations include: that all CYP with DTC be managed in an age-appropriate tertiary centre linked to a paediatric oncology centre with care co-ordinated by a clinician with expertise in DTC; to proceed to diagnostic surgery in cases of inconclusive cytology results; and recommendations on risk stratification at diagnosis. Recommendations on extent of surgery and lymph node dissection, timing and use of radioiodine therapy, and long-term follow-up are also detailed.

**Conclusions:** These National Institute of Health and Care Excellence (NICE) and Royal College of Paediatrics and Child Health (RCPCH)-endorsed guidelines provide the first UK evidence- and consensus-based national recommendations for the management of paediatric DTC. Through its implementation, we hope to achieve better consistency in the quality of care of such patients and improve long-term quality of survival.

# NEWBORN SCREENING IN THE US CAN MISS PERSISTENT MILD HYPOTHYROIDISM

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**Objectives:** The aim of this study was to determine if Thyroid Stimulating Hormone (TSH) thresholds on repeat Newborn Screen (NBS) are age-adjusted to account for the expected reduction in TSH concentrations with each day of life.

**Methods:** All NBS centers in the USA were contacted and asked to provide information on their NBS protocols, TSH thresholds and whether these were age-adjusted.

**Results:** Of the 51 NBS centers, 50 (98%) accept NBS tests until at least 1 month of life. In 28 centers, repeat NBS are requested for mild elevation in TSH up to a median of 50uIU/ml [IQR 50-60]. Of these, 16 do not adjust TSH thresholds for analysis of the second test. Similarly, 8 of the 14 centers that perform routine second NBS in all infants do not adjust TSH thresholds for the second NBS.

**Conclusions:** We have demonstrated significant variation in NBS practices for screening for CH in the US. Many centers do not adjust the TSH threshold beyond the first 2 days of life and continue to offer repeat NBS outside of this time-frame. This approach will miss CH in infants with persistent mild TSH elevations. We recommend that all centers review their practice and provide age-adjusted TSH thresholds, and consider developing a consistent national approach.

P2-1708

#### THYROID FUNCTION AND OBESITY IN KOREAN CHILDREN AND ADOLESCENTS: KOREAN NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY VI (2013-2015)

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**Objectives:** Obesity in children and adolescents is increasing worldwide. Recently, high serum thyroid-stimulating hormone (TSH) was reported in obese youth. However, there is lack of data between obesity and TSH in Korean children and adolescents. The aim of the present study is to evaluate thyroid function and its association with obesity and metabolic profiles in Korean youth.

**Methods:** Data from the Korean National Health and Nutrition Examination Survey VI (2013-2015) were used, which is the nationally representative cross-sectional data. In total, 1,074 subjects (boys 562, 51.5%) aged 10-19 years with available free T4, TSH and anti-TPO antibody were included. Subclinical hypothyroidism was defined as elevated TSH (TSH >4.2 IU/L) with normal free T4. Study participants were categorized into two groups; normal weight (group 1) and overweight and obese group (group 2). Anthropometric and

metabolic profiles including abdominal obesity, hypertension, elevated fasting glucose, elevated triglyceride and low high-density lipoprotein cholesterol were compared between two groups. Logistic regression analysis was performed to association between thyroid function and metabolic profiles.

**Results:** The prevalence of overweight and obesity was 30.8% (boys 33.7% and girls 27.7%). The prevalence of metabolic syndrome 1.9%. Free T4, TSH and anti-TPO Ab was not significantly different between group 1 and 2. Subclinical hypothyroidism was 14.5% in the group 1 and 20.0% in the group 2 (p=0.052). In logistic regression analysis adjusted for age and sex, TSH was an independent predictor of overweight and obesity (OR 1.12, 95% CI 1.01-1.23; p=0.018). Total cholesterol was an independent predictor of subclinical hypothyroidism (OR 4.1, 95% CI 1.3-12.4; p=0.013). Marginal significance was observed in TSH for predicting metabolic syndrome (OR 1.19, 95% CI 0.98-0.43; p=0.072) and in BMI z-score for predicting subclinical hypothyroidism (OR 1.16, 95% CI 0.98-1.37; p=0.085)

**Conclusions:** This study demonstrated that subclinical hypothyroidism was more common in overweight and obese Korean youth with a marginal significance. Elevated TSH was associated with increased body fat. Subclinical hypothyroid showed a positive correlation with BMI z-score.

P2-1709

#### TRAB MEASUREMENT ACROSS GENERATIONS. GOOD AGREEMENT BETWEEN THREE METHODS - OF 1ST, 2ND AND 3RDGENERATION - FOR THE DETECTION OF AUTOANTIBODIES TO THE THYROTROPHIN RECEPTOR.

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**Introduction:** Graves' disease (GD) is the most common cause of hyperthyroidism (HT) in children, caused by autoantibodies that bind to the thyrotrophin receptor and stimulate the signal transduction cascade. Measurement of TRABs is used to confirm the diagnosis of GD. Currently, traditional RIA methods (1<sup>st</sup>) are being replaced by ELISA (2<sup>nd</sup>) and automated methods (3<sup>rd</sup>-generation).

**Aim:** To evaluate agreement between methods across generations to measure TRABs in samples of patients with autoimmune and non-autoimmune thyroid disease.



**Methods: Subjects and methods:** 98 serum samples from 98 patients aged (X±SD) 9.7±5.27 years were included in the study. Patient diagnoses were: HT (n=40); hypothyroidism secondary to chronic lymphocytic thyroiditis (n=10); non-autoimmune hypothyroidism (n=25), and autoimmune disease with normal thyroid function (n=23).

TRAbs were assessed by three commercial methods: 1<sup>st</sup>-generation TBII assay RSR (RSR) cut-off point <10%; 2<sup>nd</sup>-generation TBII assay Elisa RSR (ELISA) cut-off point rd-generation anti-TSHR assay using the Cobas EQL Roche (ECLIA) cut-off point

**Results:** The methods showed a positive correlation with deviation from linearity (p <0.01). Overall, K was good between methods RIA vs. ELISA (K=0.72); RIA vs. ECLIA (K=0.70) and ELISA vs. ECLIA (K=0.79) with no significant difference. In all diagnosis-related groups, K was good to very good; disagreement was greatest in the HT group being good in ELISA vs. ECLIA (K=0.78) and RIA vs. ECLIA (K=0.61), and moderate RIA vs. ELISA (K=0.56) with no significant difference. In samples with discordant results TRAb levels were near the cut-off point.

**Conclusions:** In spite of different characteristics of the methods, good agreement was found. Disagreement was greatest in the HT group. In samples with discordant results TRAb levels were near the cut-off point. The methodological shift to a 2<sup>nd</sup> or 3<sup>rd</sup>-generation method seems to be reliable for the diagnosis of GD. It is suggested that patient follow-up should be done with the same method.

P2-1710

#### UPDATED OUTCOMES OF CHILDREN WITH HEREDITARY MEDULLARY THYROID CARCINOMA (MTC) TREATED WITH VANDETANIB

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**Objectives:** Medullary thyroid carcinoma (MTC) is a manifestation of multiple endocrine neoplasia type 2 (MEN2) syndromes caused by germline, activating mutations in the RET proto-oncogene. Vandetanib, a VEGF and EGF receptor inhibitor, blocks RET tyrosine kinase activity and is approved for treatment of unresectable, advanced, or metastatic MTC. Beginning in July 2007, we conducted a phase I/II trial of vandetanib for children and adolescents with MTC to define a

recommended dose and assess antitumor activity. Our results through 7/2011 were previously published showing that Vandetanib is well tolerated and active in children with advanced or metastatic hereditary MTC<sup>1</sup>. We now report our outcomes as of 1/2017.

**Methods:** Tumor burden was evaluated using Response Evaluation Criteria In Solid Tumors (RECISTv.1.0) in order to define when patients had partial response, stable disease, or progression of disease. Tumor markers carcinoembryonic antigen (CEA), and calcitonin (CT) were measured, and toxicities were monitored.

**Results:** 17 patients (8 male, median age 13 years, range 9-17) were enrolled. 16 had a RET p.M918T germline mutation. The duration of vandetanib treatment was 5.6 years (0.1-9.2+) with treatment ongoing in 8 patients. Best response was partial response (PR) in 10, stable disease (SD) in 6, and progressive disease (PD) in 1 pt. Time to achieve PR (n=10) was 0.6 years (0.4-2.4). Time to best response (n=16) was 1.5 years (0-4.1). Duration of response was 5.1 years (1.3-8.6+) in patients with PR and 4.8 years (0.6-7.3+) in patients with SD. Seven patients had PD after initial PR/SD and subsequently received sunitinib, sorafenib, and/or cabozantinib. Disease progression was increase in target (n=2), non-target/new lesions (n=5), or CT/CEA (n=1). Six patients died from disease, 2.1 years (0.4-4.3) after stopping vandetanib. Progression free survival (PFS) was 6.2 years (95% CI 3.3-na) and overall survival (OS) was 8.0 years (95% CI 6.4-na). No patients came off treatment for toxicity, although dose reductions occurred in 8 patients.

**Conclusions:** Many children with hereditary MTC sustained PR/SD on vandetanib. However, half ultimately developed PD and 6/17 (35%) have died from disease despite treatment with other targeted therapies.

P2-1711

#### THYROID DISORDERS AND GROWTH DISTURBANCES AFTER HSCT PROCEDURE IN CHILDREN WITH NON-ONCOLOGICAL DISEASES

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**Objectives:** Hematopoietic stem cell transplantation (HSCT) is a life-saving treatment for children with certain inborn diseases (such as severe immunodeficiencies, inborn errors of metabolism, bone marrow aplasia) and acquired bone marrow insufficiency. However, the HSCT procedure is associated with many long-term complications, such as growth disturbances and thyroid dysfunctions.

**Objective:** Evaluation of the growth pattern and thyroid function in patients treated with HSCT for inborn diseases or bone marrow aplasia.

**Methods: Patients:** A group of 31 patients who received HSCT treatment for non-oncological diseases in the Dept. of Pediatric Hematology in Lublin from 2005 to 2016. Patients were divided into 3 groups: patients who underwent HSCT

before the age of 3 years, between 3-10 yrs, and patients older than 10 years.

**Methods:** Retrospective analysis of patients' medical data. Eight parameters: height, weight and BMI percentile and TSH, fT3, fT4, TPO Ab, Tg Ab levels were compared in 3 groups of patients in 3 time periods: before the HSCT, 12 and 24 months after the HSCT. The levels of TSH, fT3, fT4 and anti-thyroid Ab were also determined in the control group of 66 healthy children and young adults.

**Results:** L-thyroxine substitution was started in 4 patients due to abnormal laboratory results. There was a significant decrease in the fT3 levels and an increase in TPO Ab in the oldest age group. The prevalence of hypothyroidism in the group of patients treated with the HSCT was higher than in the control group (12,9% vs 6,1%). There was no significant difference in the percentiles of height, weight, and BMI between the 3 groups of patients in 2-year follow-up. Before the HSCT treatment, 9 patients had growth deficiency- in the group aged <3yrs-3 patients, 3-10 yrs-4, and >10 yrs-2. During the follow-up period of 2 years height deficiency was still observed in 2 patients in the youngest group and in 4 patients in the middle group. Both patients from the oldest group were diagnosed with somatotrophic pituitary gland insufficiency and treated with rh GH.

**Conclusions:** Thyroid dysfunctions are more prevalent in patients who have received HSCT treatment than in the control group. Growth disturbances were observed mainly in patients who underwent the HSCT between the 3rd and 10th year of age.

P2-1712

#### OUTCOME OF THE NATIONAL NEWBORN BLOODSPOT SCREENING PROGRAMME FOR CONGENITAL HYPOTHYROIDISM IN THE REPUBLIC OF IRELAND

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**Objectives:** To assess the management and outcome of patients with congenital hypothyroidism diagnosed in the Republic of Ireland since screening began in 1979.

**Methods:** The newborn screening records of all patients diagnosed with congenital hypothyroidism were reviewed. Screen positive infants had a bloodspot TSH value of >15mIU/L on day 3-5 of life, values of 8-15 mIU/L required a repeat bloodspot screening card. Data on gender, birth weight, day of life screened, bloodspot TSH value, liquid TFTs result, diagnosis, day of initiation of thyroxine and thyroxine dose was collected.

**Results:** One thousand and forty seven of 2,361,281 patients screened were diagnosed with congenital hypothyroidism in the Republic of Ireland between July 1979 and December 2016 (652 female, 395 male). The incidence rate increased from 1:3500 in 1979 to 1:1500 in 2016 although screening TSH cut off was unchanged. Ninety-four patients (9%) were

premature. Four hundred and seventy-two patients had thyroid dysgenesis (266 ectopy, 169 athyreosis, 36 hypoplasia) and 361 had a normal gland in situ of which 32 patients had trisomy 21. Five patients had congenital hypothyroidism secondary to maternal antibodies and 20 patients post iodine exposure perioperatively. Retrospective sub classification was not possible for all infants diagnosed in 1979-1981 as scans were not always performed.

Levothyroxine treatment was initiated at a median age of 10 days with a mean dose of 11ug/L.

**Conclusions:** NNBS for CHT in Ireland compares favourably with international recommendations. Screening TSH cut-off (8mIU/L) did not change during the study period. As has been reported elsewhere, the incidence of CHT increased in Ireland over the study period. The increase was mainly represented by an increase in cases of gland in situ CHT.

P2-1713

#### A QUARTER-OF-CENTURY OF THE CONGENITAL HYPOTHYROIDISM (CH) SCREENING PROGRAM OF THE STATE OF PARANA (SOUTHERN BRAZIL): PREVALENCE AND ETIOLOGY.

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**Objectives:** Since the implementation of congenital hypothyroidism (CH) newborn screening around the world, an incidence rise and improvement of prognosis has been observed. Changes in screening strategies and further investigation intend to optimize diagnosis and elucidate etiology. The aim of this study was to determine the prevalence of CH and to identify the etiology of the disease of our screening program.

**Methods:** A retrospective cohort analysis was performed from 1991-2016. Screening has been conducted by the Ecumenical Foundation for the Protection of the Handicapped at Curitiba, State of Paraná, Brazil using TSH (Delphia), measured in dry blood spots collected 48h after birth, followed by confirmatory serum thyroid function tests (neonatal and after 3 years old) complemented with thyroid scan and ultrasound. TSH cutoff was: 20mIU/L (1991-1996), 15mIU/L (1996-2003) and 10mIU/L after. Prematures retesting was introduced in 2010. Patients were referred to the Pediatric Endocrinology Unit, Department of Pediatrics, Federal University of Paraná.

**Results:** A total of 4,142,120 newborns were screened, 1,170 cases were detected and the files of 1,152 patients were evaluated. Prevalence of CH was 1:3,269, changing from: 1:4,510 in the first period to 1:2,296 in the last 5 years, with a female to male ratio of 1.5:1, with an important predominance of female in dysgenetic gland. In 1152 cases with CH, 954 were diagnosed with permanent CH (82.8%) and 198 with transient hypothyroidism (17.1%). Etiology of CH still remains unknown in 428 patients. Among 526 patients with complete investigation, 168 (32%) had a normal or enlarged size gland and were considered to have dysmorphogenesis, while 357 had a dysgenetic gland (42% ectopic gland; 22% agenesis and 3.6% hypoplasia). Patients with agenesis had lower values of T<sub>4</sub> and higher values of TSH in the neonatal period and after three years of age. One patient was detected with thyroid hormone resistance syndrome, and a TR-beta mutation was detected. Consanguineous marriage was reported in 2.8% of the whole group, and 8% in patients with dysmorphogenesis.

**Conclusions:** The incidence of CH has increased with the changes in testing strategy. A female preponderance was observed. Thyroid ectopy was the most common cause in agreement with the literature.

P2-1714

#### NOVEL HOMOZYGOUS SODIUM/IODIDE SYMPORTER (NIS) GENE VARIANTS OF UNKNOWN CLINICAL SIGNIFICANCE ASSOCIATED WITH DYSHORMONOGENETIC CONGENITAL HYPOTHYROIDISM

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**Objectives:** Iodide transport defect (ITD) is an autosomal recessive disorder whose hallmark is the inability of the thyroid follicular cell to actively accumulate iodide. ITD is an uncommon cause of dysmorphogenetic congenital hypothyroidism that results from inactivating mutations in the sodium iodide symporter (NIS)-coding gene. Clinical manifestations include low to absent thyroid iodide accumulation and, if untreated, variable degrees of hypothyroidism, goiter, and even mental retardation. The objective of this work was to investigate the presence of inactivating mutations in NIS-coding gene in two unrelated pediatric patients with a clinical ITD phenotype.

**Methods:** The genomic DNA encoding all fifteen NIS-coding gene exons were PCR-amplified and further subjected to Sanger sequencing. Moreover, bioinformatics analysis of the newly identified NIS variants was performed using Alamut software.

**Results:** We identify two homozygous variants in the DNA sequence encoding NIS in two unrelated pediatric patients with dysmorphogenetic congenital hypothyroidism. The patients were homozygous for the variants c.1673A>C in exon

11 and c.1973C>T in exon 13, respectively. Significantly, both variants were silent, not observed in the genome of 50 healthy controls, and therefore classified as variants of unknown clinical significance.

Bioinformatics analysis revealed that both variants are potentially deleterious for normal NIS mRNA splicing to maintain the open reading frame. The variant c.1673A>C would result in the disruption of a splicing enhancer located in exon 11—retention of intron 11—originating the putative mutant p.P443fsX86 NIS, whereas c.1973C>T would result in a novel splicing silencer in exon 13—retention of intron 13—originating the putative mutant T550fsX3 NIS. Future experiments using functional in vivo mini-gene splicing assays are required to fully characterize splicing defects.

**Conclusions:** In conclusion, we identified two novel NIS variants of unknown clinical significance associated with dysmorphogenetic congenital hypothyroidism. These variants lead to potential mis-splicing defects causing structural changes in NIS molecules that impair its normal biogenesis and function.

P2-1715

#### INCIDENCE RATE OF CONGENITAL HYPOTHYROIDISM IN NOTRE DAME DE SECOURS UNIVERSITY HOSPITAL - BYBLOS - LEBANON

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**Objectives:** Congenital hypothyroidism (CH), occurring approximately 1/2000 to 1/4000 newborns, is one of the most common preventable causes of mental retardation. The aim of the study is to determine the incidence of CH in our hospital and some characteristic factors of the disease (sex, preterm delivery, length and weight at birth, head circumference, maternal age, and consanguinity).

**Methods:** A total of 8364 newborns were screened by measuring newborn TSH, over a period extending between January 2009 and December 2015. The applied technique is based on measuring venous blood TSH which is different from using blood spots. The sample included every newborn having a TSH level at birth >20mIU/L. Since birth, the newborns' detailed medical records were followed upon and analyzed using SPSS 22.

**Results:** Out of 8364 screening tests done, the number of newborns having TSH>20mIU/L was 669. When TSH was repeated, 636 patients presented a normal level while 33 children were diagnosed with congenital hypothyroidism (15 boys and 18 girls), giving an incidence of 33: 8364 (1: 253) which is uncommonly high. As for the characteristics, we noted a significant association between CH and the age of the mother (p-value 0.03), newborn weight (p-value 0.04), and gestational age (p-value 0.01). The other variables studied (sex, length at birth, head circumference, consanguinity of the parents), were not associated with CH. It is important to

mention that 36 mothers out of 631 gave birth to 74 children having all TSH>20mIU/L at birth. Therefore, giving birth to a child with TSH>20mIU/L may affect the probability for the same mother to have another offspring with TSH>20mIU/L (to be studied in further researches).

**Conclusions:** The incidence of congenital hypothyroidism is about 1/253 in NDS Hospital-Byblos. The risk of having a baby with CH increases with increasing maternal age. Whereas, the risk of the disease decreases when the weight of the newborn increases [OR=0.8 (0.6-0.9)] and decreases when the gestational age is  $\geq 37$  weeks [OR=0.3 (0.1-0.7)]. The use of venous TSH gives a rapid result, thus allowing faster treatment initiation.

P2-1716

#### CHANGES IN DISEASE STRATIFICATION AFTER 2 YEARS OF FOLLOW UP IN A PEDIATRIC COHORT WITH DIFFERENTIATED THYROID CANCER (DTC)

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**Background:** Childhood onset DTC has a more aggressive presentation but no overall increase in mortality compared to adults.

**Objective:** to describe the initial postoperative ATA risk classification of a cohort of pediatric patients with DTC treated uniformly and to evaluate the response to initial therapy at 2 years based on the modified ATA dynamic risk stratification (DRS) for adults.

**Patients and Methods:** retrospective study of 17 patients diagnosed with papillary DTC between 2008 and 2015 treated initially with total thyroidectomy and radioactive thyroid ablation. Median age at diagnosis was 13,8 years (range 5,2-18) and 11/17 were pubertal. Initial pediatric ATA risk was classified in low, intermediate and high risk according to TNM, thyroglobulin (TG) and images. Clinical outcome at 2 years was assessed by DRS into 4 categories: excellent response (non evidence of disease [NED]), indeterminate response, biochemical incomplete response and structural incomplete response according to stimulated TG and imaging findings.

**Results:** postoperative ATA risk classification showed 18 %, 18 % and 64% patients with low, intermediate and high risk. DRS at 2 years revealed 47%, 18%, 6% and 29% of patients with excellent, indeterminate, biochemical incomplete and

structural incomplete response respectively. At 2 years all low risk patients remained NED while 33% of the intermediate and 36% of the high risk group achieved NED status. Only 1 pubertal patient of the intermediate risk group presented at 2 years a cervical relapse.

**Conclusions:** Our data confirm the aggressiveness of pediatric DTC at presentation assessed by the pediatric ATA risk classification. At 2 years of follow-up clinical outcome by DRS showed a marked change in the cohort risk composition compared to admission. Although preliminary, our results suggest that DRS is a good and useful response to therapy classification in the surveillance of pediatric DTC patients allowing a more accurate treatment decision according to changes in biochemical and structural findings.

P2-1717

#### NEUROCOGNITIVE FUNCTION IN ADOLESCENTS WITH HYPERTHYROIDISM

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**Objectives:** Many adolescents diagnosed with Graves' disease (GD) report difficulty with attention, memory, and organization. The biological basis for neurocognitive abnormalities in hyperthyroidism remains poorly understood. Objectives are: 1) to determine whether patients with hyperthyroidism exhibit neurocognitive deficits at the onset of hyperthyroidism and to define the affected domains; and 2) to examine whether treatment to normalization of thyroid hormone levels results in improved neurocognitive functioning.

**Methods:** For this pilot prospective observational cohort study, patients were age 12-19 years at diagnosis of GD, defined as suppression of TSH with elevated T3 and/or T4 and positive TSI. Exclusion criteria included use of beta-blocker or anti-thyroid medication for >72 hours prior to enrollment and previous neurocognitive dysfunction. A computerized neurocognitive battery (CNB) was administered to participants prior to treatment (TP1) and post-treatment after normalization of T3/T4 (TP2). This CNB assesses 5 neurobehavioral domains: executive-control, episodic memory, complex cognition, social cognition, and motor speed.

**Results:** To date, the CNB has been administered to 13 participants with GD at TP1. A subset of participants (n = 5) has been reassessed at TP2. The average duration between TP1 and TP2 was 6 months. Samples were normed to CNB scores from age-matched individuals from a large population-based sample. Compared to the normative sample, GD participants demonstrated lower performance for tests assessing attention, working memory, spatial memory, verbal reasoning, and spatial processing and higher performance for

facial memory and emotion identification. Results for the matching repeated measures analysis showed trends towards improvement in affected domains.

**Conclusions:** Preliminary results for the pre-treatment GD sample demonstrate deficits in working memory and executive control. To our knowledge, this is the first study using validated neurocognitive testing to examine the effects of hyperthyroidism on the developing brain in pediatric patients. Further recruitment and analysis is underway, to more fully define the domains of neurocognitive dysfunction as well as whether normalization of T3 and T4 are associated with resolution of hyperthyroidism associated deficits.

P2-1718

**THE EVALUATION OF MYOCARDIAL DEFORMATION IN CHILDREN WITH EUTHYROID HASHIMOTO’S THYROIDITIS BY SPECKLE TRACKING AND TISSUE DOPPLER METHODS**

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**Objectives:** In the present study, it was aimed to investigate additional cardiac problems in adolescents and pediatric patients with euthyroid Hashimoto's thyroiditis (HT)

**Methods:** The speckle tracking echocardiography (STE) and tissue Doppler imaging (TDI) were performed in 46 children with euthroid HT (mean age 12,4 years) and 19 healthy children (mean age 12,6 years). The analysis of myocardial deformation [strain (S) and strain rate (SR)] was performed globally in two planes [longitudinal (L) and mid-circumferential (C)] at both left ventricle (LVLGS, LVLGSR, LVCGS, LVCGSR) and right ventricle (RVLGS, RVLGSR). The tissue Doppler studies [Sm, Em, Am, isovolumic contraction time (ICT), isovolumic relaxation time (IRT) and ejection time (ET)] were performed at base of interventricular septum (IVS), LV and RV.

**Results:** Of the 46 children with euthyroid Hashimoto's thyroiditis, 37 (80.4%) were female and 9 (19.6%) were male. Among tissue Doppler parameters, ET at IVS, LV and RV obtained were significantly lower in patients compared to controls (p<0.05). There were no significant differences in S, E,A and E/A values between patients and controls. Moreover, MPI value in patients with Hashimoto’S thyroiditis was significantly in higher than controls. The LVLGS, LVLGSR, LVCGS, LVCGSR and RVGS, RVGSR values obtained were significantly lower in patients compared to controls (P<0,05, Table-1).

**Conclusions:** Hashimoto thyroiditis is the most common form of thyroiditis in childhood. Previous studies have found myocardial dysfunction of varying magnitude in patients with

autoimmune diseases, which is considered a cardiovascular risk factor. Present results suggest that Myocardial function is impaired in euthyroid children with hashimoto thyroiditis. STE methods are a sensitive technique that allows detection of myocardial deformation and function in euthyroid subjects with a high risk of developing thyroid failure.

Table-1: STE and TDI findings in Hashimoto's thyroiditis and controls subjects.

	Patients	Controls	p value
LVLGS	20,9±2,74	24,05±3,08	0.01
LVLGSR	0,82±0,24	1,06±0,245	0.01
LVCGS	21,08±4,41	26,94±3,23	0.001
LVCGSR	0,81±0,26	1,04±0,29	0.007
RVGS	19,78±4,14	24,15±0,26	0.001
RVGSR	0,75±0,22	1,14±0,20	0.001
IVSET	248,7±24,10	270,4±24,8	0.001
LVET	248,7±24,3	268,4±23,7	0.004
RVET	241,9±23,8	262,7±60,9	0.001
MPI RV	0,48±0,631	0,43±0,04	0.002

P2-1719

**NEONATAL SCREENING PROGRAMS FOR CONGENITAL HYPOTHYROIDISM: NORMOGRAMS OF BLOOD SPOT TSH VALUES BASED ON DATA OBTAINED FROM 92.657 NEWBORNS MAY LEAD TO A MORE PERSONALIZED TSH CUT-OFF LIMIT.**

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**Objectives:** Congenital Hypothyroidism (CH) is the most frequently encountered congenital endocrinopathy and, if not diagnosed and treated promptly, may lead to mental subnormality. For this reason, neonatal screening programs are currently applied worldwide. Screening is based on the measurement of TSH in dry blood spots collected postnatally in Guthrie cards (usually between days 2 to 5 after birth). Physiologically, TSH values are relatively high at birth and gradually decline thereafter. Therefore, TSH values may vary depending upon the postnatal day at sampling as may be

influenced by other factors such as gestational age, gender etc. These important factors are not taken into account when evaluating TSH within the context of CH screening since, the same (general) TSH cut-off limit is applied to all newborns irrespective of their basic characteristics and differences. We aim to form normograms of blood spot TSH values based on multiple parameters, investigate whether these factors should be taken into account when evaluating TSH within the context of CH screening and examine if it is beneficial to move from a general to a more personalized TSH cut-off limit.

**Methods:** Information included in the initial Guthrie card (such as date of birth, gestational age, birth weight, day of sampling, gender etc) of all neonates born in Greece in 2015 (n=92657) were entered in a database. Appropriate statistical methods were applied.

**Results:** Normograms of TSH values were formed based on multiple parameters such as gestational age, gender, postnatal day at Guthrie card sampling etc.

**Conclusions:** Although neonatal CH screening programs are applied worldwide, a consensus with respect to the TSH cut-off limit has not been reached. Nevertheless, within each screening program, the same TSH cut-off limit is applied without taking into account basic differences between newborns and without considering the distinct characteristics of a particular neonate. Normograms of TSH based on multiple parameters may help move from a general to a more personalized TSH cut-off limit, facilitate TSH evaluation and our decision process with respect to CH and, optimize neonatal CH screening programs.

P2-1720

#### APPROACH TO THE MOLECULAR DIAGNOSIS OF CONGENITAL HYPOTHYROIDISM WITH A EUTOPICALLY-LOCATED GLAND-IN-SITU USING NEXT-GENERATION SEQUENCING TECHNOLOGIES

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**Objectives:** The origin of congenital hypothyroidism (CH) with eutopically-located gland-in-situ (GIS) is complex and highly heterogeneous. Defects in genes that regulate the synthesis of thyroid hormones, states of resistance to the action of TSH and defects are the most frequent causes in the absence of iodine deficiency and maternal autoimmune processes. Identification and characterization of the molecular basis of patients diagnosed with CH with GIS on neonatal screening using next-generation sequencing (NGS) technologies.

**Methods:** Eighty CH patients with GIS confirmed by scintigraphy and / or ultrasound study, were studied using an

NGS panel that includes the following genes (TSHR, SLC5A5, TPO, DUOX2, DUOX2A2, TG, IYD, SLC26A4 and PAX8).

**Results:** Eighty potentially pathogenic variants were found in 61 patients: 29 variants (36.2%) in the TG gene, 14 (17.5%) in TPO, 11 (13.8%) in DUOX2, 8 (10%) in PAX8, 3 (3.7%) in IYD, 7 (8.8%) in SLC26A4, 7 (8.8%) in TSHR and 1 (1.2%) in SLC5A5. Non-pathogenic variants were found in 7 patients, and 12 did not present any variant. In 36 patients, variants were identified in a single gene: 19 were heterozygous with a single mutated allele (monogenic ambiguous), 1 homozygous and 16 compound heterozygotes (monogenic resolved). Finally, 25 patients had variants in more than one gene: 11 heterozygous with one allele mutated in more than one gene (ambiguous oligogenic) and 14 had two or more mutated alleles in one gene and one or more mutated alleles in other genes (resolved oligogenic). Variants with a frequency <1% in the control population were taken into account.

**Conclusions:** The implementation of this molecular diagnostic programme in patients with CH with GIS permitted us to identify their monogenic or oligogenic origin in 38.7%. The most prevalent causes were defects in TG, TPO and DUOX2 genes. The pathogenic potential of variants identified in monogenic or oligogenic heterozygosis should be established through the specific design of functional studies

P2-1721

#### EARLY THYROXINE TREATMENT IN DOWN SYNDROME AND THYROID FUNCTION LATER IN LIFE

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**Objectives:** The hypothalamus-pituitary-thyroid (HPT) axis set point develops during the fetal period and first two years of life. We hypothesized that thyroxine treatment during these first two years, in the context of a randomized controlled trial (RCT) in children with Down syndrome, may have influenced the HPT-axis set point and may also have influenced the development of Down syndrome associated autoimmune thyroiditis.

**Methods:** We included 123 children with Down syndrome 8.7 years after the end of a RCT comparing thyroxine treatment vs placebo and performed thyroid function tests and thyroid ultrasound. We analyzed TSH and FT4 concentrations in the subgroup of 71 children who were currently not on thyroid medication and had no evidence of auto-immune thyroiditis.

**Results:** TSH concentrations did not differ, but FT4 was significantly higher in the thyroxine treated group compared with the placebo group (14.1 vs. 13.0 pmol/L;  $P=0.02$ ). There was an increase in anti-TPO positivity, from 1% at age 12 months, to 6 % at age 24 months and 25% at age 10.7 years

with a greater percentage of children with anti-TPO positivity in the placebo group (32%) compared with the thyroxine treated group (18.5%) ( $P=0.12$ ). Thyroid volume at age 10.7 years (mean 3.4 ml; range 0.5–7.5 ml) was significantly lower ( $P<0.01$ ) compared with reference values (5.5 ml; range 3–9 ml) and was similar in the thyroxine and placebo group.

**Conclusions:** Thyroxine treatment during the first two years of life led to a mild increase in FT4 almost 9 years later on, and may point to an interesting new mechanism influencing the maturing HPT axis set point. Furthermore, there was a trend towards less development of thyroid autoimmunity in the thyroxine treatment group, suggesting a protective effect of the early thyroxine treatment. Lastly, thyroid volume was low possibly reflecting Down specific thyroid hypoplasia.

P2-1722

#### VERY EARLY ONSET OF ACQUIRED AUTOIMMUNE THYROIDITIS IN TOLTERS

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**Objectives:** In infant under than 3 years of age, acquired hypothyroidism caused by autoimmune thyroiditis is very rare compared to congenital hypothyroidism and the diagnostic is hard to performed.

**Methods:** We here report 3 children aged of 18, 19 et 24 months (2 boys and 1 girl) who initially presented with cutaneous pallor, associated to severe constipation and/or global asthenia.

**Results:** Clinical examination revealed myxedema and because of a clear statural growth deceleration during the last 3–6 months, thyroid function was analysed showing raised TSH  $> 400\text{mUI/L}$  and very low free T4 level revealing thus hypothyroidism. Neonatal screening for congenital hypothyroidism was normal and thyroglobulin as well as thyroid peroxidase antibodies were positive, leading to the final diagnosis of acquired hypothyroidism due to autoimmune mechanism, in accordance to the thyroid ultrasonographic aspect. For 2 out of the 3 infants, one of the two parents was affected by chronic autoimmune thyroiditis, suggesting familial predisposition. The thyroxine replacement therapy rapidly normalized the clinical and biochemical abnormalities as well as the initial moderate pericardial effusion observed in 2 infants.

**Conclusions:** In conclusion, although the screening for congenital hypothyroidism is routinely performed, a severe hypothyroidism can anyway occur early in life. Growth chart need to be systematically analysed as clinical signs are commun and unspecific and as growth failure appear as an important sign of acquired auto-immune thyroiditis in children.

P2-1723

#### GENOTYPIC AND PHENOTYPIC FEATURES AND TREATMENT RESULTS OF A SELENOCYSTEINE INSERTION SEQUENCE-BINDING PROTEIN 2 (SECISBP2) MUTATION

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**Objectives:** Thyroid hormone metabolism is regulated by iodothyronine deiodinases. SECISBP2 deficiency is characterized by decreased T4, low T3, high rT3 and mildly elevated TSH levels due to decreased deiodinase 1 and 2 activities. To date, the SECISBP2 gene defect was described in only a few patients. Data regarding the clinical spectrum and treatment of the disease is limited. We aimed to identify the genotypic and phenotypic features of an index patient and his family members and to present treatment results.

**Methods:** Physical and biochemical examinations, electromyography (EMG), neuropsychiatric tests and SECISBP2 gene analysis were performed in the index case and his family members. The response to selenium treatment in the index case was evaluated.

**Results:** A 10-year-old obese boy was found to have high fT4, low T3, high TSH and high rT3. He has been diagnosed with attention deficit disorder and complained of poor school performance, weakness in her legs and fatigue quickly. There was no goiter. Neurological examination revealed Gowers finding. WISC-R test showed normal intelligence score. In the SECISBP2 gene sequence analysis, a novel homozygous mutation c.800\_801insA (p.E269X) was detected at exon 5. Parents were euthyroid and heterozygous for the same mutation. Early stop codon formation, family segregation, and in silico analysis predicted the mutation to be disease causing. An EMG showed myogenic involvement and MRI revealed fatty infiltration in the muscles. Serum selenium level was low. A trial with sodium selenite was initiated. After six months of treatment, although serum selenium, TSH and sT3 levels normalized, no clinical or EMG improvement was observed. Two-year follow-up revealed growth retardation despite normal pubertal development. Due to insufficient responses in growth hormone stimulation tests growth hormone therapy was also initiated.

**Conclusions:** SECISBP2 deficiency leads to multisystemic clinical findings as it affects the synthesis of selenoproteins other than deiodinases. Reporting new cases has a big influence on the better understanding of the characteristics of the disease. The data available is insufficient to estimate the long-term effects of selenium treatment.



## A NOVEL MUTATION IN THYROGLOBULINE GENE IDENTIFIED IN A BOY WITH GIANT GOITER

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**Objectives:** Patients with thyroglobuline (Tg) synthesis defects show goiter. Several mutations have been identified in them. The aim was to present a patient with giant goiter and a mutation of Tg gene.

**Methods: Case report.** A 12-yr-old boy presented with progressive goiter. Four months before, he noted an augmented and sudden swelling without dysphagia. He had been treated with levothyroxine (LT), but he had stopped it. **Familial antecedents.** Father was born in Salta, Argentina. Mother was born in Bolivia. No familial thyroid diseases. **Physical exam.** Puffy facies, coarse voice, yellowish earthy pallor and dry skin. Giant goiter with firm consistence. **Results: Laboratory data.** TSH 76.7  $\mu$ UI/ml (NR: 0.5-5); T4 3.7  $\mu$ g/dl (6.09-12.23); T4I 0.17 ng/dl (0.58-1.24); TPO and Tg Ab negative. Cardiovascular control: minimal pericardial effusion. **Thyroid ultrasound.** Gland size augmented with multiple rounded echogenic images in both lobes, adenomatous hyperplasia. Right lobe: 114 x 51 x 52.4 mm. Left lobe: 109 x 48.3 x 49.6 mm. **Treatment.** LT 100  $\mu$ g/d. **Fine needle biopsy.** Hyperplasia in follicular-epithelial cell flaps, with minimal focal anisocariosis. Surgery was indicated. He persisted with big goiter, with irregular surface. Laboratory. TSH 4.47 uUI/ml; T4 1.8  $\mu$ g/dl; T4I 0.22 ng/dl; T3 284 ng/dl receiving LT at an adequate dose. Tg 0.2 ng/ml. Molecular biology sample was taken to study Tg gene. Surgery was performed one year later because of presence of multinodular goiter. **Anatomopathology.** Total thyroidectomy. Piece weight 229 grs. Irregular surface, predominantly solid light brown colour, with little cavities. Microscopic exam samples revealed follicles with epithelial hyperplasia, others with very much dilated lights of varied sizes between follicles septum of connective tissue that clutter as nodules. **Molecular biology analysis.** DNA sequencing identified the presence of a novel c.7093T>C [p.W2346R] homozygous mutation in the Tg gene. **Diagnosis.** Nodular hyperplasia. Multinodular goiter. **Follow up.** Although repeated titrations of LT dose, TSH persisted elevated and T4 low, with frequent missed doses. **Conclusions:** A new mutation in the region of homology to the acetylcholinesterase, (ACHE-like) p.W2346R in homocigosity that affect intracellular Tg transport has been found.

## MYXEDEMA COMA DUE TO HASHIMOTO'S THYROIDITIS: A RARE BUT REAL PRESENTATION OF FAILURE TO THRIVE IN INFANCY

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**Objectives:** To report a case of myxedema coma (MC) secondary to auto-immune thyroiditis in a 10 month old with failure to thrive (FTT), which to our knowledge, is unreported in infancy in this combination.

**Methods:** Case Report

**Results:** A 10 month old term Caucasian female presented to the Emergency Department with 2 days of lethargy and worsening dysphagia and 5 months of milestone regression. On growth chart, length and weight crossed percentiles since birth. Her presentation also involved hypotension (blood pressure 56/28 mmHg) requiring 100 mL/kg fluid bolus, bradycardia with pulse 20-30 beats/min, apnea requiring intubation, and hypothermia (temperature 93.6F). Pertinent labs: Cr 0.49 (0.10- 0.30 mg/dL), glucose 48 mg/dL, Hgb 9.1 (10.5- 13.5 g/dL) with macrocytosis. Infectious work-up was negative. Thyroid function tests (TFTs) showed TSH 422 (0.7- 6.6 uIU/mL) and free T4 <0.5 (0.7-1.8 ng/dL), with a random cortisol of 16.4 mcg/dL. TSH on newborn screen (NBS) was normal. Auto-immune thyroid workup: anti-thyroid peroxidase antibodies > 10,000 (< 35 IU/mL) and thyroglobulin antibody 209 (< 1 IU/mL). Treatment for MC was initiated with L-thyroxine 10 mcg/kg/day intravenously (IV) in three divided doses for 24 hrs. As a precaution, since relative adrenal insufficiency may co-exist, IV stress dose hydrocortisone was administered for the first 24 hrs. After 24 hrs, L-thyroxine dosing was decreased initially to 3 mcg/kg/day IV, then 6 mcg/kg/day orally once she restarted enteral feeds. Dose increased to 8 mcg/kg/day after 1 week when TSH trended upward. Once extubated and tolerating feeds, she was discharged. TSH decreased appropriately to 79 at 2 weeks and 7.7 at 5 weeks post L-thyroxine initiation. Clinically, gross and oro-motor function improved as compared to pre-treatment.

**Conclusions:** Despite a normal TSH on NBS, auto-immune thyroiditis is a rare but possible etiology of FTT, milestone regression, and eventually MC leading to respiratory failure. Not only will identifying thyroid dysfunction result in proper treatment, it may also prevent further loss of IQ points and significant mortality. In addition, showing thyroid auto-immunity may allow an exploration of other co-existing immune mediated disease states.

**HYPERTHYROIDISM WITH A GENETIC TWIST**

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**Objectives:** Children with Down syndrome are at increased risk to develop a wide range of thyroid disorders, from congenital hypothyroidism to autoimmune-mediated hypothyroidism and hyperthyroidism, resulting in the recommendation for routine thyroid screening labs in patients with this syndrome. However, this appears to be the first report on the development of Grave’s disease in a Down syndrome adolescent being treated for congenital hypothyroidism.

**Methods:** A 16 year old male with Down syndrome was diagnosed with mild congenital hypothyroidism by the California State Newborn Screening Program. Repeat laboratory testing revealed an initial venous TSH of 19.8, and he was initiated on levothyroxine therapy as a neonate. Unable to wean from levothyroxine at 3 years of age, he continued on relatively low dose levothyroxine supplementation for his age and size. At 15 4/12 y/o, his thyroxine levels inexplicably increased, his TSH levels dropped, and his levothyroxine dose was subsequently weaned to 25 mcg, the same dose he was initiated on as a neonate. At that point, thyroid stimulating immunoglobulins were drawn and were found to be elevated at 346% (normal 0-129%). His levothyroxine was discontinued, and he was initiated on suppressive methimazole therapy, with subsequent normalization of his thyroid tests and tapering of his methimazole therapy in response to his thyroid levels.

**Results:**

Age (years)	T4 (mcg/dl) (normal range)	TSH (mIU/ml) (normal range)
14 4/12	7.6 (4.7-13.3)	5.27 (0.34-4.82)
14 5/12	6.6 (4.7-13.3)	3.71 (0.34-4.82)
15 4/12	13.1 (4.7-13.3)	0.01 (0.34-4.82)
15 6/12	11.8 (4.7-13.3)	< 0.01 (0.34-4.82)
15 9/12	14.1 (4.7-13.3)	< 0.01 (0.34-4.82)
16 2/12	16.4 (4.7-13.3)	< 0.01 (0.34-4.82)
16 3/12	17.1 (4.7-8.6)	< 0.01 (0.6-3.6)

**Conclusions:** Congenital hypothyroidism does not preclude the development of autoimmune-mediated hyperthyroidism in patients at higher risk to develop autoimmune thyroid disease. This case continues to broaden the spectrum of thyroid disease observed in patients with this genetic condition.

**CONGENITAL HYPOTHYROIDISM ASSOCIATED WITH ALPORT SYNDROME**

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**Objectives:** Hypothyroidism rarely associates with nephrotic syndrome. Alport syndrome is an inherited nephritis, a basement membrane disorder and is caused by a gene mutation of the type IV collagen protein family group. Reported cases of Alport syndrome with hypothyroidism were due to Hashimoto's thyroiditis with (+) antithyroid antibodies (ATAs).

**Methods:** Medical records are reviewed retrospectively. **Results:** A 8 yrs old boy referred for short stature with hypothyroidism. Recent height velocity was less than 3cm/yr. At 3 yrs old, the patient showed proteinuria and gross hematuria. The percutaneous renal biopsy showed corresponding findings to Alport syndrome. The gene analysis was done, and a compatible gene mutation was found. Sensorineural hearing loss was also associated with . Hypothyroidism was found incidentally. Blood free T4 was 0.17 ng/dL (normal; 0.8-2.2), and TSH was 871 mIU/L (normal; 0.7-6.4). ATAs were all negative. Thyroid USG showed a hypoplastic thyroid gland in normal position. Mental retardation related to congenital hypothyroidism was also found. Levo-thyroxine was started at very low-dose, and then increased gradually. Two months later, thyroid function returned to normal. **Conclusions:** We report a first case of congenital hypothyroidism due to thyroid hypoplasia associated with Alport syndrome. Further gene study is necessary on the basis of concomitant occurrence of these two diseases.

**A MUTATION IN PAX8 PRESENTING AS CONGENITAL HYPOTHYROIDISM WITH INCOMPLETE TSH RESPONSE TO APPROPRIATE TREATMENT**

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**Objectives:** To identify the genetic cause of hypothyroidism in a child diagnosed in newborn screening, who had persistently elevated TSH despite mid-normal fT4 under levothyroxine treatment, and to study the clinical course after identification of a PAX8 mutation. **Methods:** Persistently elevated TSH prompted us to screen for mutations in the TSH receptor (TSHR) gene and PAX8 by Sanger sequencing. Clinical phenotype was documented over 4.5 years. **Results:** Sequencing of TSHR gene was normal. A heterozygous variant was found in exon 3 of the PAX8 gene (c.160A>G, p.S54G), which was described before in association with nongoitrous congenital hypothyroidism (OMIM 167415).

Thyreoglobulin level was normal, thyroid autoantibodies were negative. Surprisingly, TSH was persistently elevated (between 10.4-52.6µU/ml) while maintaining fT4 at the upper limit of normal. TSH normalization could only be achieved with a short course of increased treatment to supraphysiological fT4 levels. Periodic ultrasound revealed unremarkable parenchymal structure except for a single solitary cyst of 1-2mm in diameter. Thyroid volume was first possible to measure at 2.5 years of age and showed a mildly hypotrophic gland.

**Conclusions:** Although *PAX8* mutations are known to show broad phenotypic variability, there are only single scattered reports worldwide showing incomplete TSH normalization despite fT4 in the target range based on a *PAX8* mutation. Therefore, congenital hypothyroidism with persistently elevated TSH despite appropriate treatment with mid- to high-normal fT4 should prompt genetic testing for candidate genes which have impact on thyroid dysgenesis. In our case overtreatment could be avoided by targeting treatment to achieve fT4 in the normal range and observing the clinical follow up rather than normalizing TSH.

P2-1729

#### LANGUAGE DELAY AS FIRST MANIFESTATION OF CONGENITAL HYPOTHYROIDISM IN SUSPECTED CASE OF MCT8 MUTATION

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**Objectives:** Language delay can be a manifestation of congenital hypothyroidism (CH). In many countries, newborn screening is based in TSH determination and, thus, only diagnoses primary CH. Central CH is only suspected in the advent of new clinical signs or symptoms or during hypopituitarism investigation. **Aim:** Report the case of a 3.5-year-old female patient with language delay as the only manifestation of CH due to defective transport of thyroid hormones into neuronal cells.

**Methods:** She was the first baby to be born of a 38-week twin pregnancy, weighing 2680g and measuring 47cm long. Newborn screening revealed TSH 0.4 mIU/mL. She was first admitted to the clinic when 1.7 years old but parents had suspected language delay since the age of 10 months.

**Results:** Initial investigation revealed TSH 1.3 mIU/mL and total T4 (TT4) 5.4 mg/dl. Significant improvement in language development was noticed after starting thyroxin replacement (10 mg/Kg/day). Serum TSH and TT4 during treatment were 0.6 mIU/mL and 7.6 mg/dl, respectively. At 3 years old, thyroxin was discontinued for investigation purposes. Without treatment serum TSH and TT4 levels were 1.5 mIU/mL and 5.7 mg/ml, respectively. Molecular analysis of the deceased twin brother revealed c.826G>A p.G276R mutation of *MCT8* in the X chromosome (Xq13.2), in heterozygosis. **Discussion:** *MCT8* encodes the

monocarboxylate transporter 8 (MCT8), responsible for the transmembrane transport of T3 into the neuron. The severity of clinical findings is variable. Changes in neurodevelopment and mental retardation are more frequently observed in male patients while heterozygous females are usually normal and do not require treatment. However, symptoms can be present depending on the inactivation of the X chromosome. Increased serum T3 is the most common finding associated with low or normal-low TT4. TSH can be normal or slightly elevated.

**Conclusions:** It has been considered that this patient could harbour the same heterozygous *MCT8* mutation as her brother. This rare condition should be suspected in patients with impaired language or neurodevelopment, despite a normal newborn screening.

P2-1730

#### CRETINISM DUE TO CENTRAL HYPOTHYROIDISM IN A 4 YEARS OLD GIRL

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**Objectives:** Cretinism is related to primary hypothyroidism (PHT). Late thyroxin replacement causes irreversible damage to brain development; however, children with central hypothyroidism (CHT) are usually diagnosed during the investigation process for short stature, with no reports of developmental or mental impairment. **Objective:** To describe the case of a child with clinical features of cretinism caused by CHT.

**Methods:** A baby girl, born after 38 weeks of gestation, weighing 3000g, and measuring 49.5cm long was first admitted when 3 months old. The parents reported stunted neurological development and difficulty in gaining weight and feeding.

**Results:** Newborn screening revealed TSH<0.1mU/ml. At physical examination, a typical cretinism face was observed, with depressed nasal base, pig nose, and infiltrated eyelids. An umbilical hernia, reduced muscle tone, short length (53cm, <P10), and low weight (4200g, <P10) were also noted. Biochemical analysis revealed Free T4<0.1ng/ml, Total T4=0.9ng/ml, TSH<0.1mU/ml, and IGF-I<25ng/ml. Following thyroxin replacement, there was an improvement in the neurological development. Height velocity and weight gain also improved and her height gradually moved from bellow P3 to P90 by 3 yrs of age. IGF-I concentration increased to 70 ng/ml (P50). The treatment was discontinued for 1.5yr. When readmitted to the clinic (aged 4.5 yrs), her features were typical of severe cretinism: slow movements, difficulty in walking, height velocity close to zero cm/yr, height<P25, grotesque facial features, dry skin, myxoedema, muscular

pseudohypertrophy, bradycardia, feeding difficulty, excessive sleeping, and neurological impairment. Serum IGF-I and cortisol levels were <25ng/ml and 3.2ug/dl, respectively. A low thyroxine treatment (1.5 ug/Kg/day) was initiated following 3 days of glucocorticoid replacement. Speed of movement and food acceptance improved after few days.

**Conclusions:** Depending on its aetiology, CHT can be associated with cretinism and extremely low TSH and T4. Most of the screening programs do not measure T4 levels; however, T4 determination should be considered in cases of undetectable or extremely low TSH in order to prevent adverse neurodevelopmental outcomes.

P2-1731

#### **NON-CONGENITAL HYPOTHYROIDISM IN EARLY INFANCY AS THE FIRST MANIFESTATION OF PSEUDOHYPOPARATHYROIDISM**

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**Objectives:** Retrospective case report.

**Methods:** A 6 year old boy was referred to our clinic for hypothyroidism. He was born at 38 weeks of gestation with a birth weight and length at the 3<sup>rd</sup> percentile, head circumference at 15th percentile and a normal newborn screen. He was evaluated at 2 months of life for hypotonia, poor feeding, and intermittent desaturations. Laboratory studies revealed a TSH of 8.210 mIU/mL (0.36-3.74), FT4 0.94 ng/dL (0.70-1.48), serum calcium (Ca) 10.1 mg/dL (9.0-11.0), and serum phosphorus (P) 6.6 mg/dL (4.8-8.0). At 4 months, his TSH was 13.6 mIU and FT4 1.08 ng/dL, and he was started on 25 mcg of levothyroxine. An X-ray wrist at 4 years of age reported a bone age of 4 years and 10 months with mild osteopenia. The patient was eventually lost to follow up.

Physical exam in our clinic revealed a short build, round facies, down slanting palpebral fissure, ptosis, micrognathia, high arched palate, short neck, broad hands and feet with stubby fingers, and developmental delay. His weight and height were at the 98<sup>th</sup>ile and 8<sup>th</sup> percentile respectively. Microphallus couldn't be assessed due to patient anxiety. There was no history of fractures or tenderness in limbs. He was restarted on 37.5 mcg of levothyroxine and 1000 IU of vitamin D daily.

**Results:** Laboratory studies after 6 weeks showed a TSH of 11.6 mIU/mL, FT4 0.94 ng/dL, serum Ca 7.6 mg/dL, serum P 8 mg/dL, urinary Ca/creatinine ratio 0.19, urinary P/creatinine ratio 1.02 (0.33-1.19), vitamin D 25-OH 29 ng/mL (30-100), and PTH 410 pg/mL (15-65). He was started on cacitriol 0.25 mcg daily and elemental calcium carbonate 300 mg QID . On follow up, his calcium and phosphorus had improved (8.5 mg/dL and 6.3 mg/dL). However his TSH was elevated and still continued to be elevated despite increase in his levothyroxine dose to 62.5 mcg. His growth velocity was 7 cm/year.

**Conclusions:** We describe a case of pseudohypoparathyroidism where the initial manifestation was hypothyroidism. This case highlights the importance of following calcium and phosphorus levels closely in children with unexplained hypothyroidism diagnosed outside the neonatal period. Additionally, growth and pubertal progression should be monitored as there can be defects in gonadotropin or growth hormone action.

P2-1732

#### **THERAPEUTIC COOLING: A POSSIBLE CAUSE OF A FALSE POSITIVE TSH NEWBORN SCREENING TEST RESULT?**

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**Objectives:** To report an infant who had a whole blood TSH above the newborn screening (NBS) cut-off on a sample taken during therapeutic cooling and whose TSH after cooling ended was normal.

**Methods:** A girl was born at term to a G1P1 mother, weighing 3350 g. Severe neonatal asphyxia (APGAR 1<sup>1</sup>-3<sup>5</sup>-4<sup>10</sup>) was attributed to the umbilical cord being wrapped four times around the neck. The baby was transferred to a tertiary care center and cooling was started at 4h of life for 72h. Whole blood TSH on the Guthrie card collected at 48h for NBS was 24.7 mU/L (cut-off >15 mU/L). As per protocol, total T4 was measured on the same sample and was 97 nmol/L (N > 120), prompting immediate referral to pediatric endocrinology. On day 7, a second Guthrie card was sent to the NBS laboratory and serum was taken, on which fT4 was 20.61 pmol/L (N 11.00-43.00) but on which TSH could not be measured (insufficient quantity); a scintigraphy with sodium pertechnetate showed a normal thyroid; treatment with levothyroxine was started at 25 mcg/day.

**Results:** The results of TSH measured on the second Guthrie card came back normal (at 1.41 mU/L) and levothyroxine was stopped at five weeks. At two months, serum TSH was 1.44 mU/L (N 0.36-5.50) and fT4 13.19 pmol/L (N 10.70-24.00) and at three months, serum TSH was 1.34 mU/L.

**Conclusions:** a) Therapeutic cooling, which has become standard of care for asphyxiated term newborns, may transiently increase TSH to above NBS cut-offs; indeed, physiological cooling from intra-to extrauterine life is thought to contribute to the sharp neonatal rise in serum TSH (Fisher and Odell, JCI 48:1670,1969); b) Although this is controversial, asphyxia itself may increase TSH; a systematic review of TSH at NBS in newborns undergoing cooling and asphyxiated controls is therefore planned; c) If confirmed on larger numbers, our findings may justify that Guthrie cards be only obtained after the end of therapeutic cooling.

# A CASE OF THYROGLOBULIN MUTATION IN CONGENITAL HYPOTHYROIDISM CONFIRMED BY DIAGNOSTIC EXOME SEQUENCING

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**Objectives:** Congenital hypothyroidism can be caused by various etiologies which include thyroid gland dysgenesis or dyshormonogenesis. Mutation of the gene thyroglobulin resulting in defects of thyroglobulin (Tg) synthesis can be characterized by goitrous congenital hypothyroidism and absent or low levels of thyroglobulin.

**Methods:** Sanger sequencing of gene TSHR (TSH receptor) and diagnostic exome sequencing of 23 genes associated with congenital hypothyroidism were performed.

**Results:** The male newborn was brought to the hospital due to the elevated TSH level on newborn screening test. Initial thyroid function test showed that 3.17 ng/dL of total triiodothyronine, 0.228 ng/dL of free thyroxine, and more than 100 mIU/L of TSH. Serum level of thyroglobulin was 5.53 ng/mL without thyroglobulin antibody, Thyroid sonography revealed diffuse parenchymal disease of both thyroid gland, highly suggestive of thyroiditis.

After the thyroid hormone replacement, serum levels of thyroxine, triiodothyronine, and TSH became normalized and thyroglobulin level was less than 1 ng/mL.

Initial DNA sequencing of gene TSHR (TSH receptor) showed no mutation. We performed diagnostic exome sequencing of 23 genes associated with congenital hypothyroidism which revealed Tg gene mutation of p.Cys1264Arg (in exon 17) and p.Gln1353\* (in exon 19). Family study showed maternal Tg mutation of p.Cys1264Arg and paternal Tg mutation of p.Gln1353\*. Mutation of Tg with p.Gln1353\* seems to be novel.

Now he is taking synthroid of 75 ug daily. His intelligence is good with weight of 22.2kg (75-90 percentile) and height of 117.8 cm (90-95 percentile).

**Conclusions:** Here we report a case of congenital hypothyroidism caused by novel mutation of the gene thyroglobulin in a 5 year and 5 month old boy who has been taking thyroid hormone since the age of 16 days.

center, Seoul, Korea, Republic Of; Youn-Hee Lim, PhD; Yun-Chul Hong, MD PhD, Seoul National University College of Medicine Environmental Health Center, Seoul, Korea, Republic Of; Choong Ho Shin, MD; Sei Won Yang, MD, Seoul National University College of Medicine, Seoul, Korea, Republic Of

**Objectives:** To investigate association between thyrotropin (TSH) levels and insulin resistance in 4-year-old children

**Methods:** Five hundred and thirty six children (286 boys, 3.8-4.6 years) born appropriate-for-gestational-age, who visited between 2013 and 2015, were included in this study. Body mass index (BMI) was calculated based on height and weight at the visit. The presence of goiter was evaluated by pediatric endocrinologist. Birth weight, parental BMI and education levels, breastfeeding, daily calorie intake, and weekly exercise hours were investigated. Fasting plasma glucose, insulin, lipid panels, adiponectin and TSH levels were measured. Insulin resistance by Homeostasis model assessment (HOMA-IR) was calculated.

**Results:** A higher-than-normal TSH levels was detected in 27 children (5%). Goiter was palpated in 59 children (11%) with female predominance (45 girls,  $p < 0.001$ ). No significant relationship between goiter and TSH levels was found. Overweight or obese children ( $n = 66$ ) showed a higher TSH levels than lean children, with marginal significance ( $p = 0.05$ ). There was no interaction of sex on the relationship between TSH levels or BMI and HOMA-IR. While relationships of TSH with adiponectin, HDL-cholesterol and LDL-cholesterol were not significant, TSH was significantly correlated with triglyceride levels. In univariate analysis, HOMA-IR was correlated with age ( $p = 0.012$ ), sex ( $p = 0.037$ ), BMI Z-scores ( $p = 0.006$ ), maternal BMI ( $p = 0.019$ ), paternal education ( $p = 0.041$ ) and TSH ( $p = 0.002$ ). In multivariable models after adjusting for age, sex, maternal BMI, paternal education, and TSH (including significant covariates in univariate analysis), the positive relationship between TSH and HOMA-IR was significant ( $p = 0.002$ ). After additionally adjusting for birth weight, paternal BMI, maternal education, breastfeeding, weekly exercise hours, and daily calorie intake (including all previously well-known covariates), TSH levels was positively correlated with HOMA-IR ( $p = 0.001$ ).

**Conclusions:** This study suggests a significant association between thyrotropin levels and insulin resistance in 4-year-old children, even after adjusting for adiposity.

# RELATIONSHIP BETWEEN THYROTROPIN LEVELS AND INSULIN RESISTANCE IN 4-YEAR-OLD CHILDREN

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**POSTER SESSION 2**  
**Friday, September 15, 2017, 11:30am-12:30pm**  
**P2 - Type 1 diabetes**  
**P2-1800 – P2-1852**

P2-1800

**MEMORY AND GLYCEMIC CONTROL: DOES THE AGE OF DIABETES ONSET INFLUENCE FUTURE HBA1C LEVELS?**

*Tim Aeppli, MD, University Children's Hospital Zurich/Kantonsspital Graubünden, Zürich, Switzerland; Daniel Konrad, MD, PhD, University Children's Hospital , Zurich, Switzerland*

**Objectives:** Strict glycemic control in children and adolescents with type 1 diabetes mellitus (T1DM) is important to prevent future microvascular complications. We hypothesized that children diagnosed with T1DM at an age before acquiring active memory of a life without diabetes have better future glycemic control.

**Methods:** We conducted a retrospective cohort study at the University Children's Hospital in Zurich, Switzerland. We included all patients diagnosed with T1DM at an age of 0 to 7 years between 1990 and 2012. Their follow-up was at least 3 consecutive years. Patients were divided in to 3 groups according to age at diagnosis: 0-2.9 years (assumed no active memories of life without diabetes, group 1) 3.0-4.9 years (intermediate; group 2) and 5.0-6.9 years (with early memories; group 3). Mean HbA1c levels were calculated yearly up to 17 years after diagnosis (until the age of 18). The HbA1c levels of the 3 groups were then compared regarding years after diagnosis as well as biological age. Comparison was performed using Anova with Stata (Stata/IC13.1 Texas).
**Results:** 217 children were included (49% male) with a mean age of 4.2 years at diagnosis of T1DM. HbA1c values did not differ significantly 12 years after diagnosis between children in group 1 (n=67) and older age groups 2 (n=64) and 3 (n=86). When comparing HbA1c levels of the 3 groups in regard to biological age, group 3 showed significantly lower values between the age of 7 and 9 years (p<0.05).

**Conclusions:** Children diagnosed with T1DM at an early age before acquiring active memory of a life without diabetes show similar glycemic control compared to children diagnosed later. The observed difference in HbA1c levels in group 3 between the age of 7 and 9 years is most likely due to shorter duration of T1DM.

P2-1801

**CONTINUOUS GLUCOSE MONITORING SYSTEM IS A WINDOW FOR EARLY DETECTION OF GLUCOSE ABNORMALITIES IN CHILDREN: CASE SERIES**

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*Doha, Qatar; Fareeda Umer , BSN, Hamad Medical Corporation, Doha, Qatar*

**Objectives:** To compare the glucose sensor values (GS) versus, fasting blood glucose (FBG), postprandial blood glucose (PPBG) and HbA1C in the diagnosis of diabetes.

**Methods:**

Three boys sibling aged 4, 7 and 9 years with normal growth and development presented with intermittent symptoms of polyuria and polydipsia for several months. There was no history of polyphagia, weight loss, abdominal pain or vomiting. Mother had history of gestational diabetes and father has T2 diabetes. The siblings were not obese with no acanthosis nigrican.

Glucose profiles for three siblings were measured over 5 days using the CGMS (Medtronic iPro®2 recorder, Northridge, CA). Laboratory tests (Serum level of FBG, PPBG, Fasting insulin, Fasting C-peptide and HbA1C) were measured and HOMA-IR was calculated for all siblings.

**Results:** The data showed hyperglycemia (45%, 45% and 32 % of glucose values above 140 mg/dl) and the highest GS values (206, 233 and 182 mg/dl) for four, seven and nine year old siblings respectively). Laboratory tests (FBG, PPBG, insulin, HbA1C) and HOMA-IR showed normal results for all siblings.

**Conclusions:**

CGMS reveals glycemic abnormalities which were not detected by FBG, PPBG and HbA1c especially in children at high risk for diabetes. Further studies need to be conducted to confirm our findings

**Table 1: Patients Anthropometrics, Laboratory Results and CGMS data**

	4 Years old	7 Years old	9 Years old
<i>HT cm</i>	<b>99cm</b> (-1.2SD)	<b>117.6cm</b> (-1.35SD)	<b>128.3cm</b> (-1.4SD)
<i>BMI kg/m2</i>	<b>14.6</b> (-0.8SD)	<b>15.3</b> (-0.1SD)	<b>13.4</b> (-1.1SD)
<i>Fasting BG (mg/dl)</i>	<b>91.8</b>	<b>84.6</b>	<b>81</b>
<i>Post Prandial BG (mg/dl)</i>	<b>111.6</b>	<b>124.2</b>	<b>91.8</b>
<i>Fasting Insulin mU/mL</i>	<b>2.6</b>	<b>3.1</b>	<b>2.4</b>
<i>Fasting C-peptide ng/mL</i>	<b>0.50</b>	<b>0.57</b>	<b>0.56</b>
<i>HbA1C%</i>	<b>5.2</b>	<b>5.5</b>	<b>5.3</b>
<i>HOMA score</i>	<b>0.59 (N)</b>	<b>0.65 (N)</b>	<b>0.48 (N)</b>
<i>MBG (Mean BG)</i>	<b>136</b>	<b>140</b>	<b>133</b>
<i>Highest Sensor glucose value (mg/dl)</i>	<b>206</b>	<b>233</b>	<b>182</b>
<i>No of excursions</i>	<b>16</b>	<b>27</b>	<b>15</b>
<i>MAD</i>	<b>10.6%</b>	<b>8%</b>	<b>9.9%</b>

P2-1802

**ACUTE KIDNEY INJURY ACCORDING TO PRIFLE CRITERIA IN CHILDREN WITH DIABETIC KETOACIDOSIS**

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*Medicine, Izmir, Turkey; Bumin Nuri Dündar, MD, Katip Çelebi University, Izmir, Turkey; Tolga Ünüvar, MD, Adnan Menderes University, Aydın, Turkey*

**Objectives:** Acute kidney injury (AKI), formerly called acute renal failure, is one of the well-known complications of diabetic ketoacidosis (DKA). There has been no study evaluating AKI in children with DKA. The aim of this study is to determine the frequency and characteristics of AKI in children with DKA.

**Methods:** Children and adolescents with Type 1 diabetes mellitus who were diagnosed with DKA between 2014 and 2016 were included in the study. The data were retrospectively obtained from hospital records. Children with recognized renal disease or diabetic nephropathy were excluded from the study. DKA treatment protocols were similar in all three centers and appropriate for the 2014 ISPAD recommendations.

**Results:** A total of 86 patients [37 males (43%)] with a mean age of 9.2 years (range, 5-12 years) were included in the study. Sixty one of the cases (71%) were newly diagnosed diabetes. At diagnosis, 51 (59%) patients had AKI, 33 (38%) were in the risk group, 14 (16%) were in the injury group and 4 (5%) were in the failure group. At the 24th hour of treatment, all but one patient had normal renal function, and one patient's renal function recovered on following 8th day. No patient required renal replacement therapy. Frequency of female gender and serum levels of glucose, creatinine, potassium, and effective osmolality were significantly higher in the AKI group than non-AKI group, while calculated creatinine clearance and pH were significantly lower ( $p < 0.05$ ). By using logistic regression model, five risk factors for AKI were identified as followings: female gender (estimated relative risk 1.912,  $p = 0.008$ ), effective osmolality (estimated relative risk 1.031,  $p = 0.03$ ), glucose (estimated relative risk 1.004,  $p = 0.024$ ), potassium (estimated relative risk 3.333,  $p = 0.001$ ) and pH (estimated relative risk 0.0011,  $p = 0.029$ ).

**Conclusions:** AKI is common in patients with DKA. AKI usually occurs secondary to dehydration and recovers following parenteral fluid therapy. However, even rare, kidney function may deteriorate permanently, thus close monitoring of renal function during the treatment of DKA is very important. Female gender, high levels of glucose, effective osmolality and potassium, as well as low pH are likely risk factors for developing AKI in DKA patients at admission

P2-1803

#### **EATING DISORDERS AND ITS RELATIONSHIP TO GLYCEMIC CONTROL IN EGYPTIAN ADOLESCENTS WITH TYPE 1 DIABETES**

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**Objectives:** To detect eating disorders in children with T1D and its relationship to glycemic control

**Methods:** The study included 170 adolescents aged (11-18) years with T1D for more than one year. Male and Female adolescent randomly selected from diabetes clinic at Suez Canal university Hospital. Last year average hemoglobin A<sub>1c</sub> Was calculated. Adolescents with T1D completed a Self-reported diagnostic survey for eating disorders (modified). Subjects classified as having a full syndrome eating disorder based on DSM-IV criteria (anorexia nervosa, bulimia nervosa, or "eating disorder not otherwise specified"). A minimum of four clinical symptoms over the past three months based on DSM-IV criteria were necessary for the diagnosis of anorexia or bulimia nervosa.

**Results:** Thirty eight percent of adolescents with T1D have eating disorders. Binge eating found in 25%. Eight percent of adolescents reported dieting for weight control. Nearly 6% of adolescent indulged in heavy exercise for weight loss. There were no cases of anorexia nervosa. Males and females adolescents are nearly equal to have eating disorders (28.2% vs. 25.6%) with odd's ratio 1. The Mean hemoglobin A<sub>1c</sub> concentration was higher in diabetic subjects with an eating disorder (9.6%) than in those without (8.1%)  $P = 0.036$ . Adolescents with poor glycemic control are at higher risk nearly 2.7 times more to have eating disorders than those with good metabolic control. There was no significant difference in socioeconomic status between adolescents with eating disorder and those without.

**Conclusions:** Adolescents with T1D who have eating disorders have higher hemoglobin A<sub>1c</sub> concentrations than those without eating disorders.

P2-1804

#### **SLEEPOVERS AND DIABETIC KETOACIDOSIS: A CROSS SECTIONAL CHART REVIEW OF DKA ADMISSIONS IN ESTABLISHED PATIENTS WITH TYPE 1 DIABETES**

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**Objectives:** - To establish association of sleepovers with occurrence of diabetic ketoacidosis (DKA) episodes in children with established type 1 diabetes (T1DM).

- To delineate concurrence of other risk factors for DKA.

**Methods:** Admissions (N = 124) for DKA in 84 unique patients aged 8 to 18 years with known T1DM were randomly sampled from a total of 189 DKA admissions (141 unique patients) at an academic medical center, from January 1, 2013 to April 30, 2016.

Retrospective chart review of DKA patients was completed to compare those with history of a sleepover within 24 hours before presentation (sleepover group, SG) with other patients (non-sleepover group, NSG). A sleepover was defined as spending one or more nights away from primary caregiver.



Associations were determined using unpaired T tests and odds ratios (OR).

**Results:** Patients had a mean age of  $14.4 \pm 0.2$  years and diabetes duration of  $7.8 \pm 0.4$  years. Thirty-four percent were male, 49% African-American, 44% Caucasian. Seventy-two percent of DKA admissions were in patients on Medicaid. Patients on insulin pump therapy comprised only 18% of DKA admissions. The cause of DKA was attributed to non-adherence in 70.9% of admissions, acute illness in 18.5%, and pump malfunction in 9.6%.

A recent history of sleepovers was found in 19.4% of DKA episodes. The sleepover was with a non-guardian parent in 29%, with a non-parent relative in 29%, and with a friend in 42%. We found no significant difference in average diabetes duration, insurance, race or sex in SG versus NSG. Patients admitted in DKA after being at sleepovers had higher reports of recent lack of supervision (OR 10.2) and omitted insulin doses (OR 2.85). They were also less likely to have called the diabetes team (OR 1.5) or checked ketones (OR 1.6) before presentation. A history of involvement of child protective services was more prevalent in patients in SG (OR 2.7).

**Conclusions:** In our retrospective chart review, 1 in every 5 DKA admissions were in patients who had been at a sleepover within the past 24 hours. This shows a need for targeted education interventions aimed at formulating protocols and educating families regarding sleepovers in children with T1DM.

P2-1805

#### IMPROVEMENT OF FINAL HEIGHT IN TYPE 1 DIABETES MELLITUS PATIENTS AFTER 20 YEARS OF INTENSIVE INSULIN THERAPY

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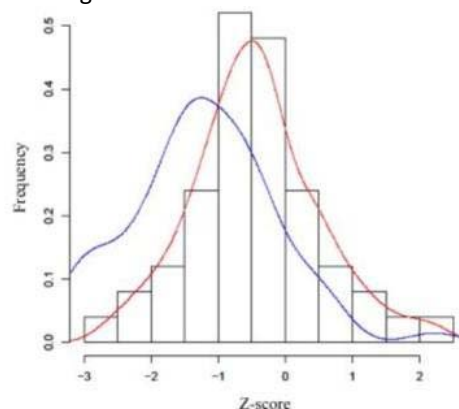
**Objectives:** To evaluate the final height of type 1 diabetes mellitus (DM1) patients who were followed-up in an University Hospital and the related factors.

**Methods:** Cross-sectional evaluation of 50 DM1 patients (ADA criteria) who attained final height until 2016. They should have completed pubertal development (Tanner criteria) and had grown less than 1cm in the latest year. They were under intensive basal-bolus insulin therapy, implemented from 1999 in the institution. Metabolic control was evaluated according HbA1c levels ( $RV \leq 7.5\%$ ) during the whole period of follow-up. A comparison with data of 72 DM1 patients followed-up in the same institution and evaluated in 1995 was made. Until that year, those 72 patients were under conventional insulin therapy.

**Results:** In 2016, 50 patients (56% females) were  $18.5 \pm 1.80$  years and had  $12.4 \pm 4.64$  years of DM1 diagnosis. The final height-for-age z-score (HAZ) was  $-0.44 \pm 0.45$ , being  $-0.51 \pm 0.87$  for female and  $-0.35 \pm 1.05$  for male. The final HAZ is

within reference range when compared to the NCHS reference for 18 years. The curve shows stature impairment with a deviation to the left, when compared to the NCHS population (74% of the sample HAZ below average). Unsatisfactory metabolic control ( $HbA1c 9.8 \pm 1.7\%$ ) was observed in 58% of patients. In multiple linear regression analysis final HAZ was associated only to the target height ( $p < 0.001$ ). In 1995, 72 patients (73.6% females) were  $21.2 \pm 3.2$  years and had  $11.9 \pm 5.7$  years of DM1. Their final HAZ was  $-1.23 \pm 1.05$ , being  $-1.16 \pm 0.99$  for female and  $-1.42 \pm 1.25$  for male when compared to the same NCHS reference. At that time, the curve shows a huge deviation to the left, when compared to the NCHS population (88.9% of the sample HAZ below average). Final HAZ 2016 results showed an improvement when compared to the 1995 results. Final HAZ is within reference range, but it is still compromised in relation to the NCHS population.

**Conclusions:** DM1 patients presented an improvement of final height compared to previous data, after the implementation of the intensive insulin therapy. The results suggest that the maintenance of an insulin treatment regimen closer to the physiological status could have contributed to the improvement of final height, even in the absence of a good metabolic control.



Graphic 1: Comparison of the final height of DM1 patients evaluated in 1995 and 2016 at the pediatric endocrinology department.

P2-1806

#### VITILIGO, ALOPECIA AND THYROID ANTIBODIES IN 73,494 CHILDREN AND ADOLESCENTS WITH DIABETES MELLITUS TYPE 1 - A DPV PROJECT

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**Objectives:** Vitiligo and alopecia are classified as autoimmune diseases and associated with other diseases triggered by autoimmunity. A cumulative occurrence was reported in patients with type 1 diabetes (T1d). The same applies for autoimmune thyroiditis.

The aim of our study was, to give an overview of the prevalence of vitiligo and alopecia in a large cohort of children and adolescents with T1d and its association with thyroid antibodies.

**Methods:** Between 1997 and 2017 73,494 T1d patients <21 years were registered (mean age 14.7 years, mean diabetes duration 5.9 years) in the DPV database.

**Results:** N=86 patients had documented alopecia areata (AA) (38 females:48 males), n=190 patients suffered from vitiligo (92 females:98 males). 4.7% of patients with AA showed simultaneously vitiligo and therefore significantly more often in comparison to patients without AA (0.3%,  $p<0.0001$ ). 2.1% of patients with vitiligo additionally had AA, patients without vitiligo only with a frequency of 0.1% ( $p<0.0001$ ). The OR calculated for patients with vitiligo to have also a diagnosis of AA, was – after adjustment for age (categorised) and gender –19.2 (95% CI 7.0-53.0). AA patients as well as patients with vitiligo showed a significantly higher percentage of positive thyroid antibodies compared to T1d patients without AA and/or vitiligo: 39.4%/42.8% with AA/vitiligo; 18.0%/18.0% without AA/vitiligo;  $p<0.0001$ , respectively. After adjustment for age and gender, an OR of 3.3 (95% CI 2.3–4.5) for positive thyroid antibodies with pre-existing vitiligo and 3.1 (95% CI 2.0–5.1) with pre-existing AA could be determined via logistic regression.

**Conclusions:** T1d patients with vitiligo or AA have a substantially increased risk for additional autoimmune diseases. To recognise these diseases in a timely manner and to initiate therapeutic measures where appropriate, we suggest regular clinical screening for vitiligo or AA in patients with T1d.

P2-1807

#### RELATIONSHIP BETWEEN GLYCEMIC CONTROL AND DIFFERENCES BETWEEN PARENTAL AND CHILD MEASURES OF DIABETES RELATED STRESS IN CHILDREN WITH TYPE 1 DIABETES

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**Objectives:** Parents play a role in providing emotional support to children with type 1 diabetes mellitus (DM1). Few studies have assessed parental perceptions of diabetes-related stress (DRS).

This study used the Problem Areas in Diabetes (PAID) scale to screen for DRS in order to determine accuracy of parental perceptions of DRS and hemoglobin A1C to measure glycemic

control. The PAID scale has been validated and uses statements about negative emotions to assess mood, social support, coping skills and health beliefs.

We hypothesized that DRS would be associated with higher A1Cs and a higher rate of discordance in parent and child scores.

**Methods:** In this 6 month cross-sectional study, subjects and parents completed a modified version of the PAID scale in order to assess the child's DRS. Those who screened positive were referred to a mental health specialist. Inclusion criteria included DM1 diagnosis >1 year, English fluency, and ages 10-21.

**Results:** 25% screened positive for DRS. Baseline characteristics are in Table 1. The main differences between groups were more subjects who screened positive administered insulin via injections vs pump (50% vs 8%,  $p=0.01$ ), had an underlying psychiatric diagnosis (50% vs 8%,  $p=0.01$ ), and had higher A1Cs (10.4 vs 8.2,  $p=0.03$ ). There was child-parental discordance in PAID scores when comparing those diagnosed greater than or less than the median length of diagnosis of eight years (-3.5 vs 6.3,  $p=0.05$ ). However, there was no significant difference between child and parent scores for those who screened negative and those who screened positive (1.3 vs 0.6,  $p=0.5$ ) and between child and parents scores for those above and below the median A1C of 8.2 (-0.6 vs 2.8,  $p=0.3$ ).

**Conclusions:** As demonstrated previously, DRS is associated with higher A1Cs. While this study was unable to demonstrate a difference in subject and parent scores in DRS and in those with higher A1Cs, we did discover significant parental-child discordance with shorter length of diagnosis suggesting experience with DM1 improves parental perception of child DRS.

This study was limited by size and lack of diversified socioeconomic status.

P2-1808

#### DISCUSSING DIABETES COMPLICATIONS: A QUALITATIVE STUDY OF PARENTS AND TEENS WITH TYPE 1 DIABETES (T1D)

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**Objectives:** Acknowledgment and talk of diabetes complications are difficult for teens with T1D, their parents, and diabetes providers. This study describes parent and teen perceptions of diabetes complications, current sources of complication knowledge, and desires for additional information surrounding diabetes complications.

**Methods:** Semi-structured interviews were conducted with parents and teens with and without elevated CVD risk (age 13-19 years, T1D >1 year). Interview transcripts were coded and evaluated using content analysis to extract central themes.

**Results:** Interviews (N=47) were completed with parents (n=25, 84% female, 84% non-Hispanic white) and teens (n=22,

age 17.8±1.6 years, T1D duration 7.7±3.5 years, 50% with CVD risk, 67% female, 76% non-Hispanic white). Teens and parents had similar perceptions of diabetes complications. For both, some believed greater emphasis on complications would be “counterproductive” or “scary” while others wanted to “actually know”. Four key themes emerged.

1) *Emphasize prevention*: both believed that providers should focus on individualized risk factors and behaviors to “avoid” or “prevent” complications. 2) *Knowledge motivates behavior change*: many parents and some teens believed that hearing about complications would encourage teens “to make smarter decisions” or adhere to diabetes management. 3) *Avoid scare tactics*: Parents and teens were wary of “scare tactics” and wanted the topic “approached delicately” and “without scaring”. 4) *Outside sources may overestimate complication risk*: parents and teens described negative reactions to “exaggerated” views of neighbors/friends as well as “drastic” TV commercials. Notably, themes did not differ between the teens with CVD risk (or their parents) and teens without CVD risk (or their parents).

**Conclusions:** While teen and parent interest in diabetes complications was highly variable, common themes emerged. In discussions of diabetes complications with teens and parents, providers should highlight actions that are preventive and avoid “scary” worst-case scenarios. Providers should invite teens and parents to direct discussions on complication risk given their range of responses.

P2-1809

#### CHILDHOOD DIABETES: A MYTH OR REALITY- PERCEPTION OF PUBLIC FROM A LOW INCOME COUNTRY

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**Objectives:** The diagnosis of Type 1 diabetes [referred therein as childhood diabetes] is almost always missed even in the best of centers in Nigeria. Knowledge about childhood diabetes is a prerequisite for individuals and communities to recognize, report and control the disease. However, research to assess knowledge deficiencies and their relation to attitude is lacking in most low income countries including Nigeria. This study intends to survey the beliefs and perceptions of caregivers of children towards diabetes in childhood and factors associated with such beliefs.

Specific objectives

1. To assess the levels of awareness of the caregivers (general population) on the existence of diabetes in children (prevalence)
2. To assess **community (public) attitude towards diabetes**
3. To determine the relationship between knowledge and attitude among caregivers
4. Association between level of education with knowledge and attitude.

**Methods:** A descriptive study involving 500 respondents from different areas in Enugu metropolis, South East of Nigeria. A

structured interviewer administered questionnaire was used to gather data on the respondents. The questionnaire showed an internal consistency with a Cronbach alpha of 0.8.

**Results:** Almost all the respondents (99.8%) have heard of diabetes in adults, However, with regards to diabetes in childhood, 43.2% had no idea that diabetes could occur in children. Only 24.8% showed good knowledge of the different aspects of diabetes such as causes, signs and symptoms, complications and treatment. Good knowledge refers to two or more correct answers. There was no gender influence with respect to knowledge of childhood diabetes ( $p=0.06$ ). Positive association existed between knowledge and attitude as well as education [ $p<0.001$ ]. Conversely, 82.6% of the respondents with good knowledge of the different aspects of diabetes had poor attitude.

**Conclusions:** There is poor knowledge of the existence of Childhood diabetes in Nigeria. More astounding is the poor attitude towards the illness even among those that had good knowledge. Creation of awareness through diabetes education with consequential improvements in knowledge, attitudes and skills will aid in changing the perception of childhood diabetes from a myth to reality, resulting in a better management outcome of the condition.

P2-1810

#### OBSERVATIONAL RETROSPECTIVE FOLLOW-UP STUDY OF FACTORS ASSOCIATED WITH ACUTE AND VASCULAR COMPLICATIONS IN TYPE 1 DIABETES MELLITUS.

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**Objectives:** To analyze the presence over time of acute and chronic complications in patients diagnosed with Type 1 Diabetes Mellitus (DM1) before the age of 15 years. Studied acute complications were: hypoglycemia (HG), diabetic ketosis (DK) and diabetic ketoacidosis (DKA); microangiopathic complications were retinopathy and nephropathy; while analyzed macroangiopathic complications were angina, infarction, transient ischemic attack, stroke and peripheral arteriopathy.

**Methods:** The study included patients diagnosed with DM1 before 15 years of age and currently ≥18 years old in Navarra (Spain) since January 1990. Data from *Diabetes Registry of Navarra* were used: age, sex, age at onset, mean Hb1Ac, mean BMI, smoking status as well as acute and chronic complications. Independent variables were assessed by multivariate binomial logistic regression for the studied 3 dependent variables: acute, microangiopathic and macroangiopathic complications.

**Results:** 272 patients, 55.9% male. Mean onset age 9.8 ± 3.3 SD years. Mean age of 26.4 ± 5.9 SD years, mean Hb1Ac 8.1 ± 1.1 SD%. Acute events 37.4%: (DK 8.1%, HG 25.2%, DKA 16.7%). Microangiopathic complications 35.3%: (retinopathy 25.7%, nephropathy 15.8%). Macroangiopathic complications 1.1% (acute myocardial infarction 0.4%, peripheral

arteriopathy 0.7%, rest of macrovascular complications 0%. Age and mean HbA1c were independently associated with the risk of acute and chronic complications as showed herein:

	Acute Complications		Microvascular complications		Macrovascular complications	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Current age	1.05 (1,00-1.10)	0,037	1.16 (1,10-1.22)	<0,001	1.42 (1,04-1.95)	0,029
Mean HbA1c	1.57 (1,22-2.02)	<0,001	1.90 (1,43-2.51)	<0,001	3.41 (1,25-9.33)	0,017

**Conclusions:** Metabolic control and age determine the development of acute and chronic complications in DM1. The pediatric diabetological team must work to achieve a good control of the disease, owing to the impact it has on the appearance of complications.

P2-1811

**SLEEP DISORDERED BREATHING AND QUALITY OF SLEEP IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES**  
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**Objectives:** According to meta-analysis in 2016, children with type 1 diabetes (T1D) slept shorter than their peers. Conclusions were not done in aspect of sleep quality and sleep disordered breathing (SDB). The aim of work was to examine sleep quality by polysomnographic examination (PSG) in the group of children with T1D and to determine the influence of short-term and long-term metabolic compensation (HbA1c) on sleep quality in children with T1D. **Methods:** 44 children (28 girls and 16 boys) aged 10-18 years with T1D were included to the study after exclusion of children with hypoglycemia before and during PSG. The group was divided into two subgroups, The first group (n=23) consisted from children with sub-optimal metabolic control of diabetes (HbA1c 7,5-9 %), while children with non-optimal control of diabetes (HbA1c ≥ 9 %) were included to the second group. The subgroups did not differ in aspect of anthropometric parameters and diabetes duration. Results of continuous glucose monitoring and PSG were analysed in subgroups.

**Results:** We did not find significant difference in parameters of sleep latency, sleep effectivity, percentage of time spendend in NREM N1, NREM N3, AHI and OAHl. Children with worse metabolic control of T1D (HbA1c ≥ 9 %) spent significantly more time in sleep stage of NREM N2 (51,352 % vs. 45,565 %, p = 0,008), and had significantly lower effectivity of deep sleep NREM N3 (45,114 % vs. 49,913 %, p = 0,028) comparing to children with long-term better metabolic control of diabetes. Obstructive sleep apnoe (OSA) was diagnosed in only one patient, 9 children had mild degree of central SDB.

**Conclusions:** Children with non-optimal metabolic control of T1D spent more time in sleep stage of NREM N2 and had significantly decreased effectivity of deep sleep. Approximately one fifth of children with T1D had mild central SDB, the prevalence of OSA was comparable with general pediatric population. We did not find difference in the occurrence of SDB in relation to compensation of T1D in children and adolescents. The work was supported by VEGA 1/0262/14 and by project "CEKR2" ITMS: 26220120034

P2-1812

**MENTAL HEALTH AND BEHAVIORAL SCREENING IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES**  
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**Objectives:** To describe the findings of mental health and behavioral screening performed as part of routine pediatric type 1 diabetes care **Methods:** A retrospective chart review focused on children aged 11 to 17 with type 1 diabetes cared for in a multidisciplinary pediatric endocrinology practice. As part of routine diabetes care, the Strengths and Difficulties Questionnaire (SDQ) self-reported version was completed by patients as a behavioral and mental health screening tool. Scores from each of the 5 domains of the SDQ and the impact supplement were collected and compared to age-matched normative data from parent-reported SDQ. **Results:** SDQ results were collected from 128 patients with type 1 diabetes. A significantly higher proportion of the group aged 11 to 14 with type 1 diabetes had an abnormal score in the impact category when compared with normative data (28.4% vs 15.1% respectively, p = 0.002). All other domains were similar between the two groups. For patients aged 15 to 17 years, there was a significantly higher proportion of type 1 diabetes patients with abnormal scores across multiple domains, including total difficulties (20.4% vs 10.9%, p = 0.02), emotional problems (23.7% vs 14.2%, p = 0.04), peer problems (38.9% vs 19.8%, p = 0.0002), and impact score (25.4% vs 13.7%, p = 0.009). **Conclusions:** This study suggests that patients with type 1 diabetes, particularly older teenagers, have a higher burden of behavioral issues and emotional symptoms when compared to their peers without diabetes. Older teens scored higher in domains suggesting risk for psychologic

disorders including anxiety and depression, in addition to difficulty interacting appropriately with peers. Furthermore, the significant elevation of the impact score indicates that these patients perceive that there has been some impairment of their daily function. These findings highlight the importance of routine behavioral and mental health screening in pediatric patients with diabetes, in addition to underscoring the need for a multidisciplinary management team including social work and psychology.

P2-1813

**LIVER STIFFNESS BY TRANSIENT ELASTOGRAPHY AS A NON-INVASIVE TOOL FOR DETECTION OF HEPATOPATHY-INDUCED FIBROSIS IN PEDIATRIC PATIENTS WITH TYPE 1 DIABETES**

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**Objectives:** To identify the effect induced by hepatopathies of different etiologies among children and adolescents with T1DM using transient elastography (TE) and its relation to glycemic control.

**Methods:** One hundred patients with T1DM (at least 5 years disease duration) were studied stressing on liver function tests, fasting lipid profile, HbA1c, hepatitis C virus (HCV)-RNA using PCR, serum immunoglobulins, autoimmune antibodies; Anti-nuclear antibody (ANA), Anti-smooth muscle Antibody (ASMA), and Anti-Liver Kidney microsomal antibody (anti-LKM) using indirect immunofluorescence methods. Pelvi-abdominal ultrasound was performed and TE was done for patients with elevated ALT, HCV, positive autoimmune antibody and/ or abnormal ultrasound findings. Liver biopsy was done when indicated after parental consent.

**Results:** 31% of patients were found to have one or more abnormalities; clinical hepatomegaly in 8%, elevated ALT in 10%, HCV in 6 %, autoimmune hepatitis (AIH) in 11% (10 were positive for ASMA and 2 were positive for ANA while anti-LKM antibodies were negative) and abnormal hepatic ultrasound in 20% (5 AIH, 2 HCV, 1 Mauriac Syndrome, 9 non-alcoholic fatty liver disease and 3 non-alcoholic steatohepatitis). Mean liver stiffness in those 31 patients was  $7.0 \pm 2.1$  kPa (range, 3.1– 11.8 kPa); 24 were Metavir F0-F1, 7 were F2-F3 while none were F4. Type 1 diabetic patients with abnormal ultrasound had significantly higher FBG, HbA1c and total cholesterol than those with normal liver ( $p<0.05$ ). Patients with AIH had higher HbA1c than those with negative autoimmune antibodies ( $p=0.012$ ). Liver stiffness was significantly higher in patients with abnormal ultrasound compared with normal liver ( $p=0.039$ ). Significant positive correlations were found between liver stiffness and HbA1c and ALT.

**Conclusions:** Hepatic abnormalities are prevalent in young patients with T1DM and related to poor metabolic control. TE provides a reliable method for detection of hepatopathy-induced fibrosis.

P2-1814

**CLINICAL EXPERIENCE ON THE CONTINUOUS SUBCUTANEOUS INSULIN INFUSION TREATMENT IN CHILDREN WITH TYPE 1 DIABETES. BENEFITS COMPARED WITH CONVENCIONAL MULTIPLE DAILY INJECTIONS.**

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**Objectives:** The aims of our study has been to analyze some epidemiological characteristics of the type 1 diabetic patients who are treated with continuous subcutaneous insulin infusión (CSII) in our hospital, as well as evaluating its effectiveness to reduce the daily insulin dose required and to improve the HbA1c (glycated hemoglobin) level after changing from multiple daily injection (MDI). We have also evaluate the effect of sensor-augmented pump (SAP) therapy on HbA1c in some patients.

**Methods:** Retrospective longitudinal study. Including all diabetic type 1 patients with insulin pump therapy follow-up at our hospital's Pediatric Endocrinology Unit, on February 2017.

**Results:** Total diabetic type 1 patients: 179; CSII treated: 56 (31,3%). Sex: 23.65% of from the total of boys; 39.53% of from the total of girls. Mean age when the insulin pump therapy starts:  $9.15 \pm 4.63$  SDS years.

Daily insulin dose needy evolution at 6 months, 1 year and 2 years of CSII treatment compared with MDI last control. Table 1.

HbA1c evolution at 6 months, 1 year and 2 years of CSII treatment compared with last year A1C mean with MDI (Excluded patients whose pump indication were: frequent hypoglycaemia or very low insulin doses needed). Table 1

HbA1c at end of follow-up SAP therapy:  $7,5 \pm 0.6$  SDS (baseline HbA1c  $7.9 \pm 0.8$  SDS). N=14.

**Conclusions:** Pump insulin use for intensive diabetes type 1 treatment in children is high in our hospital, higher than the our country average (estimated at 7%). CSII therapy offer benefit over MDI, like as lower insulin doses required and metabolic control improvement in selected patients.

SAP therapy provides a sustained improvement in glycaemic control in children.

	Insulin dose mean (UI/Kg/day) 95% C.I.	p	N	HbA1c mean 95% C.I.	p	N
MDI	0,919 ± 0,194 (0,860; 0,978)	<0,001	44	7,617±0,532 (7,402; 7,831)	0,004	26
6 month CSII	0,824 ± 0,189 (0,766; 0,882)			7,304±0,627 (7,051; 7,557)		
MDI	0,915 ± 0,205 (0,849; 0,981)	< 0,001	39	7,615±0,543 (7,391; 7,839)	0,024	25
1 year CSII	0,841 ± 0,172 (0,784; 0,896)			7,356±0,435 (7,176; 7,536)		
MDI	0,942 ± 0,192 (0,874; 1,010)	0,007	33	7,599±0,585 (7,332; 7,865)	0,002	21
2 year CSII	0,858 ± 0,156 (0,802; 0,913)			7,114±0,487 (6,893; 7,336)		

Table 1. Daily insulin dose needy evolution and A1C evolution at 6 months, 1 year and 2 years of CSII treatment compared with MDI. (MDI: multiple daily injection. CSII: continuous subcutaneous insulin infusión. HbA1c: glycated hemoglobin).

**A LITERATURE REVIEW OF THE EVIDENCE FOR THE MANAGEMENT OF CHILDREN IN DIABETIC KETOACIDOSIS, INCLUDING THOSE UNDER FIVE YEARS OF AGE, IN ORDER TO REDUCE THEIR RISK OF CEREBRAL OEDEMA.**

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**Objectives:** The aim of this study was to review the risk factors for the development of cerebral oedema in children with Type 1 Diabetes (T1D) with Diabetic Ketoacidosis (DKA). As early management of DKA has been found to be associated with cerebral oedema, the objectives of this review were to investigate what is the pathogenesis of cerebral oedema in DKA and to review current DKA guidelines to assess their relevance to children under five years old.

**Methods:** A systematic search strategy was undertaken. Critical analysis of relevant included studies was performed. The chosen guidelines were ISPAD and NICE and these were reviewed with the evidence used in creating them analysed.

**Results:** There are a number of plausible theories for the development of cerebral oedema in children with DKA, but the exact mechanism is still unknown. These include: osmotic theory; hypoxic-ischaemic response; inflammatory response; Anti-Diuretic hormone (ADH) involvement; insulin involvement; hypocapnia.

**Conclusions:** Children under five years old are at high risk of developing cerebral oedema. There are a number of reasons for this association, including the immature brain with an underdeveloped autoregulation system, the severity of DKA and dehydration and the difference in their water volume status leading to inappropriate fluid and electrolyte regimes administered to very young children. The current guidelines are relevant to very young children but more research in this area is required.

**DOES IRON STATUS EXPLAIN RACIAL DISPARITY IN MEAN BLOOD GLUCOSE INDEPENDENT HBA1C OUTCOME FOR CHILDREN WITH TYPE 1 DM?**

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**Objectives:** Blacks patients have been found to have higher HbA1c than whites which is independent of differences in MBG and RDW-CV (J Pediatr 176:1987). Decreased iron status has been associated with increased HbA1c, independently of MBG, and in the absence of frank anemia. We hypothesized that low iron status may account for higher HbA1c in black patients.

**Methods:** We evaluated iron status in a mixed race population of youth with T1D who self-identified as either black or white. At the time of clinic visit labs were obtained for ferritin, soluble transferrin receptor (sTfR), HbA1c and CBC. MBG was derived from patient's home glucose meter

records over the last 30 days. Statistical analysis was performed by t-test and multiple variable analysis  
**Results:** A total of 48 patients (19 Black, 29White; 31female/ 17male) were recruited. Comparison of variables between groups by t-test are presented in the Table below. Glycemic indices (HbA1c and MBG) were higher in Blacks than Whites.

HbA1c and MBG were highly correlated with each other. Ferritin was correlated with Hb but not HbA1c or MBG. The differences in Ferritin and sTfR between the two groups were not statistically significant. sTfR was correlated with MCV, MCH, and RDW-SD . WBC and platelet levels were not different between groups. In multiple variable analysis race (p=0.0241) and MBG (p=0.0042) were statistically influential on HbA1c,  $r^2=0.34$ ,. p=0.0002. Fe, sTfR or ratio were not statistically significant when added to the model.

**Conclusions:** After adjustment for race and MBG, iron indices were not independent predictors of HbA1c levels. These observations indicate that factors besides iron status contribute to MBG-independent racial disparity in HbA1c between black and white pediatric patients.

Table: Differences between black n=19 and white n=29 patients except where noted.

	Blacks	Whites	p
Age (years)	14.5±2.4	14.2±4.1	ns
HbA1c (%)	10.2±1.7	8.8±1.6	0.0071
MBG (mg/dl)	241.8±64.8	206.4±53.3	0.05
Hb (gm/dl)	13.3±1.6	13.8±1.1	ns
RDW-CV (%)	13.3±1.5	12.2±0.6	0.0065
RDW-SD (fl)	39.9±3.1	37.0±1.9	ns
MCV (fl)	84.1±6.8	83.3±3.5	ns
MCH (pg)	27.9±2.4	28.2±1.8	ns
MCHC (gm/dl)	33.2±1.1	33.8±1.2	ns
Ferritin (ng/ml)	44.3±30.6	30.2±21.3	ns
sTfR (mg/dl)	4.5±1.2, n=12	4.4±0.6, n=18	ns
Fe/sTfR Ratio	11.1±9.9, n=12	11.4±7.9, n=18	ns

**PANCREATIC CALCIFICATION AMONG CHILDREN WITH CHILDHOOD DIABETES IN NIGERIA: COULD THIS BE FIBROCALCULOUS PANCREATIC DIABETES?**

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**Objectives:** To study the prevalence, profile and outcome of children managed for diabetes mellitus with pancreatic calcification.

**Methods:** This is a cross- sectional study of children who were managed for diabetes mellitus between January 2010 and December 2015 in paediatric endocrine unit of a tertiary hospital in Nigeria. All patients who consented underwent ultrasonography of the pancreas and plain abdominal radiograph. We undertook a case note review in order to identify factors that may be associated with pancreatic calcification.

**Results:** Thirty seven (37) children were diagnosed with diabetes mellitus in the study period. Mean age was 12.3 years (5 – 17 years), 21 males and 16 females. 20/37 (54.1%) were screened for pancreatic calcifications using abdominal ultrasound and plain abdominal radiograph. 17/37 were not studied as 9/37(24.3%) patients had died and 6 lost to follow up while 2 patients declined to participate. Mean duration of diabetes mellitus was 2.7 years (3 months – 8 years). All were managed with pre-mixed twice daily insulin regimen. Pancreatic calcification was seen in 7/20(35%), and was commoner among males and older children ( $p=.27$ ,  $p=.11$ ). The average HbA1c was 13 and 11 and average HT/WT SDS was -1.9/-1.9 and -1.03/-1.02 in those with calcification and those without, respectively ( $p=.08$ ,  $p=.05$ ).

**Conclusions:** Pancreatic calcification is common among children diagnosed with diabetes mellitus in Nigeria and is associated with more severe morbidity. Routine pancreatic ultrasonography and plain abdominal radiograph of patients may be important.

P2-1818

#### ROLE OF SOCIAL FACTORS IN GLYCEMIC CONTROL AMONG MINORITY CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES

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**Objectives:** With the rising incidence of Type 1 diabetes (T1DM), it is important to recognize deficiencies in care to provide better resources for T1DM patients. The objective of the study was to recognize self reported social factors and compliance barriers affecting A1c level in minority children and adolescents with T1DM.

**Methods:** Study questionnaires were distributed to patients with T1DM during pediatric endocrine clinic visits at our institution. Knowledge score (KS) was calculated based on 14 questions. Patients' charts were reviewed retrospectively. T-tests, one-way ANOVA and Spearman correlation were used for analysis.

**Results:** Eighty four T1DM patients, ages 3 to 21 years, 52% males, 87% African American participated in the study. Mean A1c was 10.4% and mean KS was 10.1 out of 14. There was no significant correlation ( $r=0.12$ ,  $p=0.26$ ) between A1c and patients' KS. Patients with more frequent blood sugar (BS)

checks (3-4 x/day) had 2 points lower A1c (9.6 vs 11.6 %, 95% CI 0.2-3.7,  $p=0.03$ ) than those with 2 or less x/day. There was no significant difference in A1c between 3-4x/day vs >4x/day BS checks. Some patients reported 'forgetfulness' (20%) followed by 'time consuming' (17.8%) and 'discomfort checking around friends' (14%) as important barriers to BS checks. Most patients (85%) reported friends were aware of the diagnosis. There was no significant difference in A1c between pen or pump users (10.5 vs 10.2 %,  $p=0.55$ ). Frequencies of home supervision are: always (21%), most times (30%), sometimes (25%) and never (24%). Surprisingly, those with home supervision had higher A1c than those without (10.7 vs 9.4 %,  $p=0.04$ ) while there was no significant difference between those with or without nurse supervision at school (10.5 vs 9.9 %,  $p=0.33$ ). Those with happy mood interestingly had higher A1c than those with sad/depressed mood (10.7 vs 9.4 %,  $p=0.04$ ). On multiple linear regression analysis, frequency of BS checks, home supervision and mood were the most significant predictors of A1c and all together explained 20% of the variability.

**Conclusions:** Frequent BS check is associated with lower A1c. Supervision at home and school did not improve A1c. Sad mood did not worsen A1c contrary to that reported in other studies.

P2-1819

#### PERIOPERATIVE OUTCOMES FOR CHILDREN WITH DIABETES MELLITUS

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**Objectives:** To determine if hemoglobin A1C and glycemic control is associated with perioperative systemic infections, wound infections, and hypoglycemic events in elective, non-cardiac procedures in children with diabetes mellitus.

**Methods:** Retrospective chart review of patients from January 2012 to April 2016 undergoing elective, non-cardiac procedures at Texas Children's Hospital. Preoperative factors gathered included age, BMI, ethnicity/race, ASA, HbA1C, preoperative glucose, type of diabetes, type of diabetes treatment, and a use of preoperative screening service. Intraoperative factors included type of surgery, operative time, and intraoperative glucose measurements. Postoperative factors included postoperative diabetic ketoacidosis and glucose measurements. Primary outcomes were systemic infections including systemic blood stream infections, pneumonia or urinary tract infection, wound infections or disruptions, and hypoglycemia events. Secondary outcomes were hospital length of stay, intensive care unit length of stay, escalation of postoperative disposition, unplanned admission within 30 days, unplanned procedures within 30 days, and postoperative diabetic ketoacidosis.

**Results:** There were 256 elective, non-cardiac surgeries from January 2012 to April 2016 in pediatric patients with diabetes mellitus. Of these 13 had a systemic infection, wound complication or hypoglycemia event. However, the HbA1C



and mean glycemic control was not found to be significantly correlated with the outcomes.

**Conclusions:** In pediatric patients with diabetes mellitus undergoing elective, non-cardiac surgery at our large, diverse, multidisciplinary children's hospital, preoperative HbA1C and perioperative glycemic control was not found to correlate with systemic infections, wound infections, or postoperative hypoglycemic events.

P2-1820

#### INCREASED PREVALENCE OF DISORDERED EATING IN INDIVIDUALS WITH TYPE 1 DIABETES AND CELIAC DISEASE

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**Objectives:** Disordered eating refers to a wide range of abnormal eating behaviors, many of which are shared with diagnosed eating disorders. Individuals with type 1 diabetes mellitus (T1DM) as well as individuals with celiac disease (CD) have increased risk for disordered eating due to food restriction and preoccupation with food. The aim of the present study was to assess the existence of disordered eating in adolescents and young adults with a dual diagnosis of T1DM and CD, in comparison to individuals with either of the diagnoses alone.

**Methods:** In a multicenter study, 40 individuals with T1DM and CD, 120 with T1DM and 120 with CD were assessed for disordered eating by completing the Eating Attitudes Questionnaire (EAT-26) and the Diabetes-specific Eating Problems Survey-Revised (DEPS-R).

**Results:** The mean age of our 280 responders was  $18.7 \pm 8.9$  years, mean duration of T1DM was  $8.3 \pm 4.2$  and of CD  $5.2 \pm 3.3$  years. There was no difference of disease duration between those with T1DM and those with T1DM and CD. Males with both T1DM and CD had four-fold increased risk to develop disordered eating: 20% compared with 5.1% and 1.7% in those with T1DM only and CD only respectively ( $p=0.02$ ). Females with both T1DM and CD had two-fold increased risk to have disordered eating (22.7%) compared to the T1DM (12.5%) or CD (12.8%) groups ( $p=0.52$ ).

**Conclusions:** Individuals who are affected by the dual diagnoses of T1DM and CD are at increased risk to acquire disordered eating patterns compared to those with either of these diagnoses.

P2-1821

#### PARTIAL CLINICAL REMISSION IN TYPE 1 DIABETES: A COMPARISON OF INSULIN-DOSE ADJUSTED HEMOGLOBIN A1C OF $<9$ AND THE TOTAL DAILY DOSE OF INSULIN OF $<0.3$ UNITS/KG/DAY.

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**Objectives:**  $>50\%$  of pediatric patients with new-onset type 1 diabetes (T1D) will not enter partial clinical remission (PCR).

These patients are at an increased risk for long-term complications of diabetes, but there is no consensus on simple and easily usable tools for the detection and monitoring of PCR in pediatric patients. The objective of this study was to determine whether the gold standard test for the detection of PCR in new-onset T1D, the insulin-dose adjusted Hemoglobin A1c (IDAA1C) of  $\leq 9$ , is superior to a new and simpler tool, total daily dose of insulin (TDD) of less than 0.3 units/kg/day.

**Methods:** A retrospective analysis of 204 subjects of ages 2-14 years (mean age  $7.9 \pm 3.2$  years) with new-onset T1D. Anthropometric and biochemical data were collected at baseline and every 3 to 6 months for the first 36 months of disease. PCR was defined by both IDAA1C  $\leq 9$  and TDD less than 0.3 units/kg/day.

**Results:** There were 86 (42.4%) remitters (age  $9 \pm 3.0$  years; 57% male) by IDAA1C  $\leq 9$  criterion, and 82 (40.2%) remitters (age  $7.3 \pm 2.8$  years; 50% male) by TDD less than 0.3 units/kg/day. The duration of PCR was  $9.2 \pm 5.5$  months using IDAA1C and  $10.0 \pm 6.1$  months using TDD  $<0.3$  units/kg/day ( $p=0.379$ ). Peak prevalence for PCR was at 6-12 months by either definition; more subjects were in PCR at 6 months by IDAA1C  $\leq 9$  than by TDD  $<0.3$  units/kg/day (72.1% and 52.4%, respectively,  $p=0.011$ ). Subjects stratified by TDD  $<0.3$  units/kg/day had 1.44 times increased probability of entering PCR than those stratified by IDAA1c, after adjusting for BMI, bicarbonate, and HbA1c at diagnosis (OR=1.44, 95%CI [1.03-2.00],  $p=0.033$ ).

**Conclusions:** There were no significant differences in the number of remitters, duration of PCR, or the time of peak remission defined by IDAA1C or TDD of 0.3 units/kg/day. TDD could serve as a simpler clinical tool for PCR detection.

PLEASE SEE TABLE ON THE FOLLOWING PAGE

Comparison of the anthropometric and biochemical characteristics of remitters and non-remitters using insulin dose-adjusted hemoglobin A1c or total daily dose of <0.3 units per kg per day to define partial remission in patients with new-onset type 1 diabetes

Definition of PCR	IDAA1C ≤ 9			TDD <0.3 units/kg/day		
	Remitters (n=86)	Non-Remitters (n=118)	p	Remitters (n=82)	Non-Remitters (n=123)	p
Age (yr)	9.1 ± 3.0	7.0 ± 3.1	<0.001	7.3 ± 2.8	8.2 ± 3.4	0.038
Sex (male; female)	49/86 (57%); 37/86(43%)	48/118 (40.7%); 70/118(59.3%)	0.021	41/82 (50%); 41/82 (50%)	57/123(46.3%); 66/128 (53.7%)	0.665
*Height SDS	0.2 ± 1.0	0.3 ± 1.0	0.348	0.2 ± 0.8	0.3 ± 1.1	0.797
*Weight SDS	0.5 ± 1.0	0.4 ± 0.9	0.587	0.6 ± 0.8	0.4 ± 1.0	0.037
*BMI SDS	0.6 ± 1.0	0.5 ± 1.0	0.140	0.6 ± 0.9	0.4 ± 1.1	0.005
HCO <sub>3</sub> (mmol/L) at diagnosis	21.4 ± 5.9	18.3 ± 8.3	0.006	20.7 ± 6.9	18.8 ± 7.9	0.088
Duration of PCR (mo)	9.2 ± 5.5	0.1 ± 1.1	<0.001	10.0 ± 6.1	0.0 ± 0.0	<0.001
TDD (units/kg/day) at diagnosis	0.5 ± 0.3	0.5 ± 0.2	0.334	0.4 ± 0.2	0.6 ± 0.2	<0.001
TDD at 6 mo	0.3 ± 0.2	0.5 ± 0.2	<0.001	0.2 ± 0.2	0.6 ± 0.2	<0.001
TDD at 18 mo	0.5 ± 0.2	0.7 ± 0.2	<0.001	0.5 ± 0.2	0.7 ± 0.2	<0.001
TDD at 24 mo	0.5 ± 0.3	0.7 ± 0.3	<0.001	0.6 ± 0.2	0.7 ± 0.3	<0.001
TDD at 36 mo	0.7 ± 0.3	0.8 ± 0.3	0.169	0.7 ± 0.3	0.8 ± 0.3	0.443
HbA1c (%) at diagnosis	11.4 ± 2.4	11.5 ± 2.1	0.584	10.8 ± 2.2	11.9 ± 2.2	0.001
HbA1c at 3 mo	7.5 ± 1.0	8.6 ± 1.3	<0.001	7.8 ± 1.3	8.3 ± 1.3	0.015
HbA1c at 6mo	7.3 ± 1.3	8.8 ± 1.3	<0.001	7.9 ± 1.2	8.3 ± 1.7	0.060
HbA1c at 9 mo	7.8 ± 1.0	8.7 ± 1.0	<0.001	8.1 ± 0.9	8.4 ± 1.2	0.076
HbA1c at 12 mo	7.9 ± 1.1	8.7 ± 1.0	<0.001	8.2 ± 1.0	8.5 ± 1.2	0.056
HbA1c at 15 mo	8.1 ± 1.0	8.7 ± 0.9	<0.001	8.3 ± 1.0	8.5 ± 1.0	0.183
HbA1c at 18 mo	8.2 ± 1.1	8.7 ± 1.2	0.008	8.5 ± 1.0	8.6 ± 1.3	0.712
HbA1c at 24 mo	8.5 ± 1.1	8.8 ± 0.9	0.068	8.9 ± 1.1	8.6 ± 0.9	0.087
HbA1c at 30 mo	8.5 ± 1.1	8.8 ± 1.0	0.134	8.5 ± 1.0	8.7 ± 1.1	0.394
HbA1c at 36 mo	8.4 ± 1.2	8.8 ± 1.0	0.087	8.6 ± 1.2	8.7 ± 1.0	0.676

IDAA1C = insulin-dose adjusted hemoglobin A1c; TDD = total daily dose; SDS = standard deviation score; BMI = mass index; HCO<sub>3</sub> = bicarbonate; mo = month; HbA1c = hemoglobin A1c \*Comparison made by Linear mixed in this study, partial clinical remission (PCR) was defined by both TDD <0.3 units/kg/day; and also by IDAA1C. Th for IDAA1C is: HbA1c (%) + [4 X insulin dose (units/kg/24h)].

Experiment Building Library (PEBL)), which measure working memory, planning, and cognitive flexibility, respectively. A primary caregiver completed the Behavior Inventory of Executive Functioning (BRIEF) survey. The BRIEF Global Executive Composite (GEC) score includes both a Behavioral Regulation Index (BRI) and Metacognition Index (MI). A GEC T-score >65 indicates poor EF. Insulin regimen, HbA1c, and number of blood sugar (BS) tests/day were extracted from the medical record. Mean ± SD were calculated and correlations between variables of interest were assessed.

**Results:** 54 adolescents (33 male) age 15.29±1.95 yrs with T1D for 6.54±4.09 yrs participated. Mean HbA1c was 9.5%±1.8%. Subjects tested their BS 3.3 ±1.6 times/day. HbA1c negatively correlated with BS tests/day (r = -0.26), in line with data from national T1D registries. BRIEF T-scores correlated with HbA1c for all indices, BRI (r=0.47), MI (r=0.29) and GEC (r=0.42). The plan/organize aspect of MI negatively correlated with BS tests/day, indicating that planning diabetes care activities is important to optimize glycemic control. None of the direct measures of EF correlated with HbA1c or average BS tests. GEC T-score correlated with Corsi Block memory span (r = -0.28) for the cohort.

**Conclusions:** These observations indicate that while parental perception of EF does not correlate with direct measures of subject EF, EF provides a target for one type of self-regulation to improve glycemic control in adolescents with T1D.

P2-1823

## NEUROSPECIFIC MARKERS IN ADOLESCENTS WITH DIABETES MELLITUS TYPE 1 AND COGNITIVE IMPAIRMENT

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**Objectives:** To study neurospecific proteins and association with cognitions in adolescents with diabetes mellitus type 1 (T1DM).

**Methods:** Were examined 58 patients with T1DM at the age 17.4 ±0.2 years, the control group consisted of 29 healthy teenagers, matched by sex and age. Complex examination included clinical and metabolic tests, screening of cognitive functions– MoCa test. We studied neurospecific markers of neurodegenerative process– protein S100, glial fibrillary acidic protein (GFAP), myelin basic protein (MBP). Statistical data processing was carried out by methods of variation statistics using software packages «R-system».

**Results:** An average level of HbA1c in patients with T1DM was 8.84±1.8%, fasting glucose corresponded 11.52±4.9 mmol/l. The study revealed elevated levels of protein neurospecific – S100 (121.65±66.39 ng/l), myelin basic protein (0.13±0.043 ng/ml) and glial fibrillary acidic protein (0.11±0.041 ng/ml) in patients with T1DM compared with the control group (p<0.001). Patients with T1DM had cognitive impairment (total score of 25 points) to 72.2% while in the control group cognitive functions were normal in 100% (total score of 30 points). We recorded a statistically significant reduction of

P2-1822

## GLYCEMIC CONTROL AND EXECUTIVE FUNCTION IN ADOLESCENTS WITH TYPE 1 DIABETES (T1D)

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**Objectives:** Type 1 diabetes (T1D) is a chronic disease requiring daily adherence to prevent complications. Adolescence is a challenging period for maintaining self-management skills. Executive function (EF) measures include problem-solving, self-monitoring, and working memory, skills inherent for T1D management. Poor EF may prevent youth with T1D from adhering to diabetes care plans. Prior studies show that parental report of child EF correlates with adherence scores. We hypothesize that adolescents with poorer diabetes control have worse EF as measured by parental report and direct tasks.

**Methods:** Adolescents with T1D for >1 year were recruited from our outpatient diabetes center. In this single visit cross-sectional study, subjects completed direct tasks of EF (Corsi block-tapping, Tower of London, ptraits; Psychological

parameters that assess short-term memory and attention in patients T1DM compared with the control group. Cognitive decline was correlated with all neurospecific proteins.

**Conclusions:** The data suggest that in patients with T1DM are characterized by significantly higher levels of all surveyed neurospecific proteins, that associated with brain cognition.

P2-1824

**RISK FACTORS FOR DIABETIC KETOACIDOSIS IN PATIENTS WITH NEW ONSET TYPE 1 DIABETES MELLITUS**

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**Objectives:** Diabetic ketoacidosis (DKA) is a serious, potentially lethal complication of type 1 diabetes mellitus (T1D) and may be the initial presentation for patients with new onset T1D.

**Aims:**

1. Identify factors associated with the presentation of new onset T1D patients in DKA.
2. Compare the rate of DKA and risk factors to a similar study at the same institution 15 year ago.

**Methods:** Retrospective chart review of new onset T1D from 2010 to 2013. Patients with and without DKA at presentation were compared with respect to age, sex, type of insurance, median household income, evaluating physician, timing of diagnosis (delay vs. no delay), signs and symptoms and HbA1c.

**Results:** Two hundred and seventy six patients, less than 18 years old, presented with new onset T1D with mean age 9.6 and mean HbA1c 11.3%. Fifty two percent were male; 43% percent had Medicaid and 57% had private insurance. Overall, 29% presented in DKA. Thirty eight percent of the patients who presented in DKA had Medicaid compared to 20% who had private insurance,  $p = 0.002$ . Median household income of patients with DKA tended to be lower ( $p = 0.0667$ ). Symptoms associated with DKA included weight loss ( $p=0.02$ ), lethargy ( $p<0.0001$ ), abdominal pain ( $p<0.0001$ ) and Kussmaul breathing ( $p<0.0001$ ).

There were 77/275 subjects (28%) who were diagnosed at a second or later visit. In 27 of these, the diagnosis was missed and in the remaining 50, the diagnosis was deferred. Fifteen of the 27 (55.6%) in whom the diagnosis was missed presented in DKA compared to 10 of the 50 (20%) in whom the diagnosis was deferred ( $p=0.0015$ ).

Compared to the study 15 years ago, the rate of DKA was lower (29% vs 38% in prior study,  $p=0.0018$ ). However, in both, almost 1/3 of the patients who presented in DKA had a delay in diagnosis.

**Conclusions:** DKA remains a common mode of presentation of T1D. Lack of private insurance is associated with higher rate of DKA. While there has been a reduction in the overall rate of DKA at presentation in T1D in this population, almost 1/3 of the patients with DKA at presentation had a delay in diagnosis. Increased education directed at both pediatricians

and the public is necessary to attempt to reduce the rate of DKA.

P2-1825

**A PSYCHOLOGICAL INTERVENTION FOR STRENGTHENING PARENTAL AUTHORITATIVENESS TO IMPROVE GLYCEMIC CONTROL AMONG TYPE 1 DIABETIC ADOLESCENTS – A PILOT RANDOMIZED CONTROLLED STUDY**

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**Objectives:** We previously reported that an authoritative style in fathers of Type 1 diabetic adolescents was associated with better glycemic control and adherence.

In this study, we evaluate the effect of a psychological intervention for improving parental authoritativeness on the glycemic control of adolescents with suboptimal glycemic control.

**Methods:** 33 couples of parents of adolescents (age 10-18) with suboptimal glycemic control ( $HbA1c > 8$ ) participated in this prospective, stratified-randomized controlled trial. Participants were randomly assigned to 3 treatment groups with each group holding five meetings: (a) the psychological intervention group ( $n=9$ ), a short term intervention focused on strengthening parents’ authoritativeness in parenting style in diabetes related issues; (b) the diabetes education group consisting of joint training of nurses and dieticians ( $n=9$ ), and (c) the treatment as usual control group ( $n=15$ ). The outcome measure was HbA1c level at 12 months.

**Results:** HbA1c levels of the three groups at pre-treatment and at 12 months follow up are presented in table 1. A significant improvement in HbA1c levels was found only among adolescents whose parents participated in the psychological intervention group ( $p<.05$ ). No improvement in HbA1c levels was evident in the other treatment groups.

Table 1. HbA1c levels at pre-treatment and 12 months

	HbA1c Pre treatment			HbA1c 12 month follow up			T
	Mean	Median	IQR	Mean	Median	IQR	
Psychological intervention	8.9%, SD .83	8.5%	8.2-9.5	8.2%, SD .70	8.1%	7.4-8.8	2.86*
Diabetes education	9.1%, SD .62	8.7%	8.6-9.8	9.0%, SD 1.75	8.3%	8.0-9.9	n.s.
Treatment as usual	9.0%, SD .87	8.8%	8.2-9.3	8.9%, SD 1.31	8.7%	7.9-9.7	n.s.

\* $P<.05$

**Conclusions:** Psychological intervention for improving parental authoritativeness among parents of adolescents with poor glycemic control significantly improved glycemic control.

# THE ASSOCIATION OF HLA-A, B, DR, DQ, DP, AND CTLA4 POLYMORPHISMS WITH THYROID AUTOIMMUNITY IN JAPANESE CHILDREN WITH TYPE 1A DIABETES.

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**Objectives:** We have made it clear that among Japanese children with Type 1A diabetes (T1AD), the prevalence of thyroid autoantibody (TA) is 26.6%, higher in girls, and increases depending on age in girls. The aim of this study was to identify the genetic factors influencing TA in Japanese children with T1AD.

**Methods:** HLA-DRB1 and DQB1 were analyzed for the registered 909 Japanese children with T1AD (the average age at the time of the registration was 12 years and 5 months old, 217 children had TA and 11 children had Graves' disease) in the Japanese Study Group of Insulin Therapy for Childhood and Adolescent Diabetes, and whether these genotypes were associated with an increased risk of TA (someone with more than one of the anti-thyroid peroxidase antibody and the anti-thyroglobulin antibody) was evaluated. HLA-A, B and DPB1 were analyzed for the registered 399 T1AD patients. CTLA4 rs231775 and rs3087243 polymorphisms were analyzed for 905 T1AD patients and compared with 455 healthy controls. Then, the risk of CTLA4 SNPs in susceptibility to TA was evaluated in 905 T1AD patients. To investigate the independent effects of HLA-DRB1, DQB1, and CTLA4 polymorphisms, gender and age on susceptibility to TA, the logistic regression analysis was applied that assumed these factors explanatory variables.

**Results:** HLA-A, B, DRB1, DQB1, and DPB1 alleles, haplotypes and genotypes were not associated with TA in T1AD children. In CTLA4 rs231775 SNP, the frequency of the G allele in the T1AD group was significantly higher than in the controls (OR: 1.56,  $p<0.001$ ) and in CTLA4 rs3087243 SNP, the frequency of the G allele only in the T1AD group with TA was significantly higher than in the controls (OR: 1.87,  $p<0.001$ ). In the two SNPs of CTLA4, T1AD group with TA had a significantly high frequency of G allele compared with T1AD group without TA.

The age (OR: 3.55~4.98), the sex (OR: 2.11) and CTLA4 rs3087243 SNP (OR: 1.63) had significant effects on susceptibility to TA in T1AD children with logistic analysis. **Conclusions:** This study demonstrates that HLA-A, B, DRB1, DQB1, and DPB1 polymorphisms do not confer the susceptibility to thyroid autoimmunity and the susceptibility to thyroid autoimmunity depends on the age, the gender, the CTLA4 rs3087243 SNP in descending order, in Japanese children with T1AD.

P2-1827

# IMPACT OF ADVERSE CHILDHOOD EVENTS ON GLYCEMIC CONTROL AND LIPIDS AMONG CHILDREN WITH TYPE 1 DIABETES

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**Background:** The incidence of type 1 diabetes mellitus (T1DM) is increasing worldwide. Among adults, adverse childhood events (ACE) have been associated with health hazards such as obesity, depression and suicidal ideation. There is limited data regarding the relationship of ACEs with glycemic control and lipids of children with T1DM. **Objective:** The objective of this study is to examine the effect of ACEs in children with T1DM and in their parents on the overall glycemic control and lipids.

**Methods:** Parents of children with T1DM who attended the multidisciplinary diabetes clinic at Mayo Clinic, Rochester completed a validated ACE questionnaire (9 questions). One parent answered a questionnaire pertaining to his or her experience and another one regarding their child's exposure to ACEs. Linear regression was used to assess the association between the ACE score in parents and children to HbA1C, lipids and BMI z-scores of children.

**Results:** 104 children (mean age 12.53±3.86 years; male: 56.7%; mean duration of T1DM: 5.23±4.2 years) were enrolled in the study. The prevalence of any ACE was 27.9% among children and 49.04% among parents. Living with household member who was depressed, mentally ill or attempted suicide (13.46%) and substance abuse among parents (25%) were the most common ACEs in the child and parent questionnaire respectively. After adjusting for age, sex and BMI z-scores, HbA1c ( $\beta$ : 0.66%;  $p=0.03$ ) and Non-HDL cholesterol ( $\beta$ : 17.07,  $p=0.04$ ) were significantly increased among children who lived with a household member who served time in jail. HbA1c was higher among children who had witnessed or had been a victim of violence in the neighborhood ( $\beta$ : 0.73%;  $p=0.01$ ), after adjusting for age, sex and BMI z-score. Additionally it was found that HDL cholesterol was negatively associated with ACE score among the boys ( $\beta$ : -3.78 mg/dl;  $p=0.04$ ). Exposure of children to one

or more ACE was associated with lower prevalence of obesity (OR:0.17;  $p=0.03$ ).

**Conclusions:** ACEs were highly prevalent among children with T1DM and they have a negative impact on their glycemic control and lipids. We suggest that ACE assessment be adopted as part routine psycho-social evaluation among children with T1DM.

P2-1828

#### "IMPACT OF MONITORING HEALTH-RELATED QUALITY OF LIFE IN CLINICAL PRACTICE IN CHILDREN WITH TYPE 1 DIABETES MELLITUS"

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**Objectives:** To test whether the systematic monitoring of health-related quality of life (HRQOL) in clinical practice in Spanish pediatric patients with T1DM helps improve their daily life in a multicenter follow-up study

**Methods:** One hundred thirty-six patients participated from five centers from Barcelona, Spain (72 girls, mean age 13.4 years). Complete data was collected for 119 patients (85%). Pediatricians were randomly assigned to the HRQOL intervention ( $n=70$ ), or control group ( $n=49$ ). The intervention group discussed the results of HRQOL face to face with the doctor, quarterly over a year. The control group received care as usual. HRQOL was assessed using KIDSCREEN-27 collected online. Standardized mean differences (effect size, ES) and generalized estimating equation (GEE) were computed to compare group differences between baseline and follow-up taking into account sociodemographic and clinical variables

**Results:** Statistically significant higher scores were seen in the intervention group at follow-up for the dimensions of Psychological well-being ( $ES=0.56$ ), School environment ( $ES=0.56$ ) and the KIDSCREEN-10 index ( $ES=0.63$ ). No differences were found in the control group. GEE analysis showed an improvement in HRQOL at follow-up a little bit largest in the intervention group, with statistically significant association of the intervention on Psychological well-being ( $B=4.32$ ;  $p=0.03$  for the interaction of group by follow-up) and School environment ( $B=4.64$ ;  $p=0.02$  for the same interaction term).

**Conclusions:** Routine assessment and face to face patient-physician discussion of HRQOL results improved HRQOL scores after a year of follow-up, specially in Psychological well-being and School environment.

P2-1829

#### EFFECT OF METFORMIN ON HYPERANDROGENISM IN GIRLS WITH TYPE 1 DIABETES.

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**Objectives:** To assess the effect of metformin on hyperandrogenism and ovarian function in adolescent girls with T1D

**Methods:** This was a prospective study conducted in the outpatient clinic of Diabetes, endocrine and Metabolism Pediatric Unit (DEMPU), Children hospital, Cairo University where 28 T1D females regularly following at the diabetes outpatient clinic showing signs of hyperandrogenism were included in the study. History taking (detailed disease history as well as menstrual history) and anthropometric measures (weight, height, BMI, waist and hip circumference) were initially performed, then the patients were assessed for manifestations of hyperandrogenism (acne, hirsutism as well as pelvic U/S for ovarian morphology). Biochemical evaluation for ovulation (progesterone assessment during the luteal phase), sex steroids (estradiol, testosterone, DHEAS, androstenedione), prolactin, glycemic control (HbA1c) and gonadotropins (FSH, LH) was done. Patients were subjected to 500 mg metformin twice daily orally for one year, then patients were re-evaluated regarding clinical and biochemical parameters (only 24 patients completed the study).

**Results:** Study included 28 girls with mean age of 15.62 yrs and mean diabetes duration of 5.75 yrs. Acne was found in 21 (75%) of them, hirsutism score (using Ferriman Gallwey score) ranged from 9 to 29 with a mean of 16.5 and 84.6% had polycystic ovarian morphology by ultrasound examination. Metformin therapy for a year resulted in a significant reduction in weight ( $p=0.001$ ), BMI ( $p=0.002$ ), acne ( $p=0.008$ ), hirsutism score ( $p=0.007$ ), LH ( $p=0.002$ ), testosterone ( $p<0.001$ ) and androstenedione levels ( $p=0.028$ ) in adolescent girls with T1D. Regarding menstrual irregularities, there was significant reduction in the number of patients with oligomenorrhea (68%) with a  $p$  value of 0.000. However, there was no significant reduction in the daily insulin requirements ( $p=0.782$ ) or HbA1c ( $p=0.068$ ). Nausea and /or abdominal pain were the commonly reported side effects for metformin (64%).

**Conclusions:** Metformin as an insulin sensitizing agent improved BMI and cycle regularity together with the clinical manifestations of hyperandrogenism in T1D adolescent girls. However, it did not improve the glycemic control in those patients significantly.

### COMPUTER BASED SEMI-AUTOMATED AUDIT OF ALL HbA1C LEVELS IN A TYPE 1 PAEDIATRIC DIABETES SERVICE

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**Objectives:** Standards of care, multidisciplinary team ratios and HbA1c targets in childhood type one diabetes mellitus (T1DM) are well established. Use of electronic data management systems is limited in Republic of Ireland and manual audit is laborious and may be inaccurate. Development of an electronic audit tool would facilitate clinical audit to identify deficits and target quality improvement initiatives for children and adolescents with T1DM

The objective of this study are to systematically audit all HbA1c results reported in children (< 16 years) with T1DM in a single centre to identify all affected patients, assess compliance with best practise guidelines in terms of monitoring frequency (aim > 3/year) and to identify patients with poor control who may benefit from intensive intervention.

**Methods:** All HbA1cs results from 2015 were exported electronically from the clinical laboratory system. Non type 1 patients (Type 2 DM, Cystic fibrosis related diabetes, metabolic patients) and results within 3 months of diagnosis were excluded. The mean annualised individual HbA1c and the total centre mean and median HbA1c were calculated.

**Results:** A total of 316 patients with T1DM identified. The median age was 12 years and median HbA1c was 66 mmol/mol. Forty-eight % of patients met the target of >three HbA1cs determinations, 42% had three and 10% had two. Target HbA1c was only achieved in 9% of patients (< 54 mmol/mol) with a further 35% achieving levels between 54-64. Ten % had very suboptimal control of >80mmol/mol.

**Conclusions:** This system of semi-automated data collection enabled creation of a clinically meaningful dataset that facilitated audit of key performance indicators. Patients failing to meet targets were identified, and new baselines established for comparison with future performance. Capture of electronic data facilitating audit has a key role in optimising care and should be prioritised for national rollout.

P2-1831

### EVALUATION OF THE HEALTH RELATED QUALITY OF LIFE OF CHILDREN WITH TYPE 1 DIABETES MELLITUS AGED 5-18 YEARS SEEN IN SOUTH EASTERN NIGERIA

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**Objectives:** To evaluate the health related quality of life of children with type 1 diabetes mellitus aged 5-18years compared with that of healthy controls and children with T1DM in other countries. To identify the effects of age, gender, age at onset of diabetes, duration of diabetes, metabolic control and socioeconomic status on the perception of HRQoL.

**Methods:** This was a multi center cross-sectional hospital/community based study of children with and without T1DM aged 5-18years. A questionnaire was completed recording their socio demographic informations. The quality of life scores were obtained using the pediatric quality of life inventory. The diabetes and generic module were administered to 58 children with diabetes and their parents. The generic module was completed by 58 age and sex matched control and their parents. The glycosylated haemoglobin levels of the children with T1DM was determined.

**Results:** Two hundred and thirty two participants took part in the study. Mean age of the children with T1DM was 13.9+/-0.3 while that of the control was 14.1+/-0.44. Mean age at onset of diabetes was 11.6years. Mean duration of diabetes was 2.2years. Mean HbA1c was 10.7% (range 6.4-14%). The mean total generic quality of life scores of the children with and without diabetes were 80.5+/-1.7 and 82.5+/-1.2 respectively (p=0.3). Children with T1DM had a significantly lower score compared to the control in the school functioning domain 63.3+/-2.9 and 73.9+/-2.0 respectively (p=0.003). Lower HbA1c values(p=0.04), short duration of diabetes (p=0.002) and young age (p=0.01) were associated with better quality of life scores.

**Conclusions:** The perception of HRQoL was apparently similar in the children with T1DM and the control. However, the school functioning domain was significantly impaired in the children with T1DM. Young age, lower HbA1c values and short duration of diabetes were strong determinants of better HRQOL in the children with T1DM.

Key words: Health related quality of life, T1DM., children, short duration of diabetes, HbA1c.

P2-1832

### UNUSUAL INSULIN DOSE, AN INDICATOR FOR THYROID DYSFUNCTION IN CHILDREN WITH TYPE 1 DIABETES

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**Objectives:** Can Insulin daily dose requirement be used as an indicator for screening thyroid dysfunction in Type 1 diabetes children?

**Methods:** Thyroid disorders can have a major impact on glucose control, and untreated thyroid disorders affect the management of diabetes in patients. ISPAD recommends thyroid screening in type 1 diabetes children on every second year in asymptomatic individuals without goitre and more

frequent assessment is indicated if goitre is present. In resource limited countries screening may not always be possible and other clinical indicators of thyroid dysfunction may be helpful.

Here we discuss two cases of thyroid dysfunction, one each of hypothyroidism and hyperthyroidism in type 1 diabetes children picked up based on total daily insulin dose which were unusual from normal requirement.

**Results:** A 13 year boy, known T1DM since age 5 referred for recurrent hypoglycaemia. His daily insulin dose requirement was at 0.3 units/kg/day. His thyroid test showed strongly positive anti TPO antibodies with TSH > 100 mIU/ml.

Another case, 13 year old girl, known T1DM for past 1 year was on basal bolus insulin regime. She had suboptimal and fluctuating glycaemic control of 300 to 450 mg/dl despite being on total daily insulin dose at 1.4 units/kg/day. Thyroid reports showed TSH < 0.005 mIU/ml, FT4 > 100 pmol/L and strongly positive for Anti TPO antibodies.

#### **Discussion :**

As in hypothyroidism, glucose metabolism is affected via several mechanisms. A reduced rate of liver glucose production and reduced insulin clearance from the system is observed in hypothyroidism.

Hyperthyroidism has long been recognised to promote hyperglycaemia. During hyperthyroidism, the half life of insulin is reduced most likely secondary to an increased rate of degradation and an enhanced release of biologically inactive precursors.

**Conclusions:** In both cases, the insulin requirements were outside the normal usual range in a pre-pubertal age outside the honeymoon phase (0.7 to 1.0 units/kg/day). In resource limited situation, insulin daily dose requirement can be utilised as an indicator for screening thyroid status in selected cases.

P2-1833

#### **DISPARITIES IN DIABETES TECHNOLOGY USE AMONG US MILITARY DEPENDENTS WITH TYPE 1 DIABETES WITHIN AN EQUAL ACCESS HEALTHCARE SYSTEM**

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**Objectives:** Disparities in the care of type 1 diabetes are well established. Differences persist even in the US military healthcare system (MHS) despite equal access to healthcare for all military service members and their families. There has been an increase in the available technology for the management of diabetes, and some have reported better glycemic control with technology use. We sought to determine if within the MHS, disparities may exist in the use of diabetes technology (insulin pumps and continuous glucose monitors [CGM]), and if glycemic control differs in those using diabetes technology from those who are not.

**Methods:** Retrospective chart review of patients 2-19 years with type 1 diabetes with a military service member parent seen in our military pediatric endocrinology clinics between

Jan2006 and Aug2016. Exclusion criteria: diabetes duration <1 year, insulin dose <0.5 units/kg/day, underlying conditions with a higher hemoglobin A1c (A1c) goal.

**Results:** 405 patients met criteria. Median age was 16 years (IQR 12-18), median diabetes duration 6 years (IQR 4-9), median A1c 8.7% (IQR 7.9-9.7). 46.2% female, 68.1% white, 53.8% Officer's children (vs Enlisted). 49.1% treated with insulin pump, 20.2% used CGM, 16.5% had both pump and CGM. Insulin pumps were used more often by those of white race (OR 2.7, 95% CI 1.8-4.2) and Officer's children (OR 2.3, 95% CI 1.6-3.5). CGM was also used more often by those of white race (OR 2.0, 95% CI 1.1-3.6) and Officer's children (OR 1.9, 95% CI 1.1-3.1). Patients using an insulin pump were more likely to have a CGM (OR 6.5, 95% CI 3.5-11.8). Those on a pump had a lower median A1c than those on MDI (8.4% vs 9.1%, p<0.001). Those who used CGM also had a lower median A1c than those who did not (8.1% vs 8.9%, p<0.001). Diabetes-related hospitalizations did not differ whether a pump or injections were used (30.2% vs 30.6%, NS). Only 19.5% of those with CGM had a history of hospitalization vs 33.1% of those without a CGM (p=0.016).

**Conclusions:** Our results show that disparities in the utilization of currently available diabetes technology, even within an equal access healthcare system, do exist and could be contributing to differences in glycemic control between certain patient populations.

P2-1834

#### **EVALUATION OF THE LIFE AND SLEEP QUALITY AND THE DETERMINATION OF THE RELATION WITH METABOLIC CONTROL IN CHILDREN AND ADOLESCENTS WITH TYPE-1 DIABETES MELLITUS**

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**Objectives:** Health-related quality of life is a multidimensional concept that shows the individual reactions to illnesses affecting the level of personal satisfaction with their living conditions. In this study, we aimed to evaluate health related life and sleep quality in children and adolescents with type-1 diabetes and to determine their relation with metabolic control.

**Methods:** The study included 40 healthy children/adolescents (control group) and 40 children/adolescents who were followed up for at least 6 months with Type-1 diabetes diagnosis and who had no complaints of co-morbidity/complication of diabetes. The data was obtained using the 'Demographic Data Collection Form', 'Quality of Life for Childhood Scale' (QLCS) and 'Pittsburg Sleep Quality Index' (PSQI). In patients with diabetes, HbA1c level was evaluated as <7.5% optimal, 7.5-9.0% suboptimal, and >9.0% high risk.

**Results:** The mean age of the diabetic patients is 13,3±3,0 years (8-18) and 55% is female (n=22) while the mean age of



the control group was 12,5±3,3 years(8-18) and 67,5%(n=27) were girls. There is no difference between groups in terms of age and gender. Whereas there is no difference in the scores of Physical Health Total Score and Scale Total Score in QLCS between the patients with type 1 diabetes and the control group, Pediatric Psychosocial Health Total Score was found to be low in the diabetic patient group (p=0.007, p=0.003 respectively). It has been observed that the PSQI score was higher in the diabetic patient group (p=0.04) and that the poor sleep quality ratio was higher in the diabetic patients than the control group (p=0.02). 40% (n=16) of the diabetic patients has good, 25% (n=10) moderate, and 35% (n=14) poor metabolic control. There was no difference between the groups as to good, moderate and poor metabolic control in QLCS and PSQI and as to good or bad rates of sleep quality. A negative correlation was found between the PSQI scores and the QLCS scores in the study groups.

**Conclusions:** We found that sleep quality in diabetic children/adolescents and quality of life in the psychosocial area were lower than their peers. Since Type-1 diabetes is a lifelong disease, while good metabolic control in the treatment of diabetes is provided, the promotion of sleep and quality of life of patients should not be overlooked.

P2-1835

**EFFECTIVENESS OF LACTOBACILLUS REUTERI ORAL ADMINISTRATION ON PERIODONTAL DISEASE IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES**

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**Objectives:** There is disagreement on the effect of diabetes on oral hygiene. It has been suggested that probiotics could create a biofilm and protect the oral tissues against the action of periodontal pathogenic bacteria. We aimed to assess the effects of the administration of *Lactobacillus reuteri* as probiotic upon the oral health of children and adolescents with type 1 diabetes.

**Methods:** Forty-three patients (11.3±2.77 yrs.; T1D duration 58.2±38.0 months) were enrolled and randomly assigned to Group A (probiotic – 10<sup>8</sup> CFU/day for 3 months) and Group B (no probiotic). Oral health index [Full Mouth Plaque Score (FMPS), Full Mouth Bleeding Score (FMBS)], insulin dose (IU/kg/day), and HbA1c were measured at baseline (T0) and 3-months after (T1).

**Results:** FMPS significantly improved in both Group A and B (p<0.05). In Group B daily insulin dose increased (p=0.01) and HbA1c improved (p<0.001) at T1, while in Group A the metabolic control was unchanged. We performed a telephone survey to evaluate the probiotic compliance in Group A. 13 out 22 patients reported a regular probiotic intake (Group A1), while the other ones used it sporadically (Group A2). Despite FMPS and FMBS values were not different between groups at T0, they were significantly lower

(p<0.05) in Group A1 respect to Group A2 at T1. Specifically, FMPS and FMBS longitudinally decreased in Group A1 but not in Group A2 (Table).

**Conclusions:** Our preliminary data suggest that 3-months oral administration of probiotic might improve the oral health of children and adolescents with type 1 diabetes and confirm that, glycemic control have also an influence on oral health.

Table - FMPS and FMBS changes.

	Group A1	Group A2	p
<b>T0</b>			
FMPS (%)	88.8 ± 11.2 (90.0)	92.8 ± 12.5 (100.0)	0.367
FMBS (%)	64.6 ± 28.7 (60.0)	78.3 ± 24.1 (80.0)	0.317
<b>T1</b>			
FMPS (%)	70.0 ± 27.1 (80.0) p=0.017 vs. T0	86.1 ± 27.5 (100.0) p=0.465 vs. T0	0.038
FMBS (%)	49.6 ± 23.7 (50.0) p=0.074 vs. T0	78.9 ± 28.4 (95.0) p=0.787 vs. T0	0.025

P2-1836

**A PILOT STUDY : THE ROLE OF HEAT SHOCK PROTEIN (HSP) 60 IN METABOLIC CONTROL DUE TO TUBERCULOSIS INFECTION IN CHILDREN WITH DIABETES MELLITUS TYPE 1 IN CIPTO MANGUNKUSUMO HOSPITAL, JAKARTA, INDONESIA**

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**Objectives:** There has been a growing attention regarding correlation between diabetes mellitus (DM) and tuberculosis (TB) infection. However, it has not been investigated the implication of poor metabolic control and exact incidences of TB infection in children with type-1 diabetes mellitus (T1DM). Additionally, previous study reported a role of Hsp60 in immune system in individuals with DM

**Methods:** Patients aged 5-18 year-old with T1DM who visited the Pediatric Endocrinology policlinic of Cipto Mangunkusumo Hospital, Jakarta, from May to July 2016 were informed regarding the study. Those who were included into the study were initially assessed for their demographic status, history of T1DM, and possible clinical manifestations of TB. All subjects had blood test drawn to measure the level of HbA1c, IGRA and Hsp60. Afterwards, they were tested for Mantoux test

**Results:** Thirty-two patients with T1DM were enrolled into this pilot study. Of which, 4 of them (12.5%) had positive IGRA result. No patient in this study had undernourished status, however 75% of patients with possible overweight (BMI/A) status had a significant (p=0.001) positive IGRA result. We found no correlation between uncontrolled metabolic (as measured by HbA1c >9.0) nor Hsp60 levels with the incidence of positive IGRA result in T1DM patients, however these findings should be interpreted cautiously due to minimal sample size and lack of investigations in this issue. Individuals with positive IGRA result and/or Mantoux test were then referred to the pediatric pulmonologist for further examination and therapy.

**Conclusions:** There are 12.5% incidence of T1DM patients to be infected by TB, even higher in those with malnourished status. No correlation between uncontrolled HbA1c nor Hsp60 levels with the incidence of positive IGRA result in T1DM patients. More extensive studies should be conducted by considering the drawbacks of this pilot study

P2-1837

#### **MONITORING THERAPEUTIC RESPONSE AMONG CHILDREN WITH DIABETIC KETOACIDOSIS: COMPARISON BETWEEN CAPILLARY BETAHYDROXYBUTIRATE AND URINE KETONES**

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**Objectives:** Diabetic Ketoacidosis (DKA) is a life threatening complication of Diabetes Mellitus (DM). Capillary Betahydroxybutirate ( $\beta$ -OHB), which assesses the concentration of main ketone bodies in blood stream, is considered superior compared to routine urine ketones test

(acetoacetate). Comparing capillary  $\beta$ -OHB concentration to urine ketones as a tool to monitor therapeutic response among children with DKA

**Methods:** We did a prospective study to children diagnosed with DKA episode, who were admitted to the intensive or intermediate care ward Cipto Mangunkusumo Hospital, Jakarta between June 2006 and March 2011. All patients were followed until DKA episode resolved. Random blood glucose, capillary  $\beta$ -OHB concentration, and urine ketones were measured every hour, and blood gas analysis and electrolyte were measured every four hours.

**Results:** There were 37 DKA episodes (9 mild DKA, 13 moderate DKA, 15 severe DKA). Median time to resolution was 21 hours, although there was one case that resolved in more than 48 hours. When compared to urine ketones, capillary  $\beta$ -OHB concentration showed stronger correlation with pH ( $r = -0.52$ ,  $p = 0.003$  vs  $r = -0.49$ ,  $p = 0.005$ ) and bicarbonate level ( $r = -0.60$ ,  $p = 0.000$  vs  $r = -0.48$ ,  $p = 0.007$ ) during the median time of DKA resolution. All capillary  $\beta$ -OHB measurement yielded negative results at median time of DKA resolution, while urine ketones were still detected up to nine hours after resolution

**Conclusions:** Capillary  $\beta$ -OHB concentration showed better correlation with pH and bicarbonate level as a tool to monitor therapeutic response in DKA, when compared to routine urine ketones test.

P2-1838

#### **ENVIRONMENTAL PARAMETERS OF YEAR AND WEATHER ARE ASSOCIATED WITH TYPE 1 DIABETES MELLITUS PRESENTATION BEFORE THE AGE OF 4 YEARS**

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**Objectives:** The incidence of T1DM has been increasing, particularly in preschool children in recent years, albeit the reasons are yet unknown. Certain factors originating from the environment and the perinatal period are suspected of contributing to the trend. The aim of our study was to investigate demographic and environmental parameters with age of presentation by birth year.

**Methods:** A cross-sectional analysis of T1DM patients who reached the age of 10 years at time of analysis in 13 centers in Israel was performed. Medical Records of patients born during 1997-2005 were reviewed for information regarding birth (season, weight week), presentation season, and family and self-history of autoimmune-mediated diseases. Univariate and multivariate regression analysis was performed.

**Results:** Records of 1571 T1DM patients were included in the study, age at data collection  $14.36 \pm 2.5$  years, 48.8% males. Three hundred and thirty six of them presented with T1DM prior to the age of 4 years, mean age at presentation  $2.4 \pm 0.9$  years, 49.7% males. Of the 1235 who presented after the age of 4 years were 48.6% males, mean age of presentation was  $9.45 \pm 2.9$  years. Recent year of presentation, older gestational age, larger birth weight, birth during the moderate weather months (September, October, March and April) and presentation during April through December were each significantly associated with T1DM presenting before 4 years of age by univariate analysis. However, by multivariate analysis, only birth year, birth season and presentation season were significantly associated with presentation of T1DM before the age of 4 years (OR = 1.06, 95% CI = 1.02–1.1,  $p = 0.003$ , OR = 1.68, 95% CI = 1.17–2.4,  $p = 0.005$ , and OR = 1.57, 95% CI = 1.05–2.35,  $p = 0.03$  respectively). Similar findings were demonstrated with significant differences for analysis of presentation age younger than 3 years and 5 years of age. Ethnicity, family history of T1DM and/or other autoimmune diseases in family and self were not associated with earlier age of presentation.

**Conclusions:** More recent presentation year, moderately warm season of birth and presentation during April through December are associated with T1DM presentation before the age of 4 years.

# CLINICAL DIFFERENCES AND THE PLASMA LEVEL OF C PEPTIDE IN PATIENTS WITH A CLINICAL DIAGNOSIS OF TYPE 1 AND MODY DIABETES MELLITUS BETWEEN 2 AND 18 YEARS OF AGE.

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**Objectives:** To establish clinical and laboratory differences allowing for diagnosis orientation between Maturity-Onset Diabetes of the Young (MODY) and DM type 1 in patients between 2 and 18 years of age in a Colombian population  
**Methods:** Case-control study in patients between 2 and 18 years of age classified into DM type 1 and MODY, non-obese, attended at four institutions in Bucaramanga, Colombia. Measurement of fasting plasma peptide C was performed on all patients. The clinical and laboratory characteristics of each group were compared.

**Results:** 89 patients who met the ADA criteria for DM were identified. A total of 20 (22.5%) patients were diagnosed as MODY and 69 (77.5%) were type 1 DM. Of the MODY patients, 13 (65.0%) were women, a similar proportion to the type 1 DM group (58.0%  $P = 0.573$ ). Age at diagnosis was 2-7 years in 43 (62.3%) of type 1 and 6 (30.0%) of MODY ( $p = 0.671$ ). Regarding the family history of DM, 18 MODY patients (90.0%) were shown to be positive compared to 40 (58.0%) of type 1 ( $p = 0.030$ ). As for the use of insulin after the diagnosis, 5 (25%) MODY were required to take it for the first 5 years, compared to 68 (98.6%) of type 1 ( $p < 0.001$ ). The patients with MODY, 18 (94.7%) never presented ketoacidosis or ketosis, compared to 16 (23.2%) of type 1 ( $p < 0.001$ ). The median C-peptide concentration among MODY patients was 0.58 ng / mL (RIQ 0.49 to 0.93), versus 0.51 ng / mL (RIQ 0.30 to 0.74) among type 1 DM ( $p = 0.077$ ).

**Conclusions:** The presence of a family history of first-degree diabetes, age at diagnosis, absence of ketoacidosis, the need for insulin during the first 5 years after diagnosis, and C-peptide value are characteristics that should be evaluated to classify the pediatric patient between type 1 or MODY

# HIGH INCIDENCE OF EARLY MICROVASCULAR COMPLICATIONS IN A COHORT OF HAITIAN CHILDREN AND ADOLESCENTS WITH DIABETES

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**Objectives:** Determine the prevalence of microvascular complications in a cohort of Haitian children and adolescents with type 1 diabetes.

**Methods:** Cross-sectional retrospective review of pediatric patients with diabetes referred to a pediatric chronic disease center in Haiti, from 12/01/2012-11/01/2016. Data collection included demographic and anthropometric information, total daily insulin dose (TDD) in IU/kg, timing and result of eye examination by a local ophthalmologist, peripheral neuropathy assessment, point-of-care HbA1c and spot AM urine microalbumin-to-creatinine ratio.

**Results:** Of 67 patients (53.7% female, mean age at diagnosis 14.6 $\pm$ 3.9 years, mean diabetes duration 3.3 $\pm$ 3.0 years, mean HbA1c 9.8 $\pm$ 2.0%, mean current insulin requirement 0.49 $\pm$ 0.28 IU/kg/day), diabetic retinopathy was diagnosed in 10/57 (17.5%), cataracts in 10/62 (16.1%), microalbuminuria in 8/49 (16.3%), and peripheral neuropathy in 4/47 (8.5%) at a mean age of 19.0 $\pm$ 4.3, 19.1 $\pm$ 3.3, 19.5 $\pm$ 2.5, and 24.8 $\pm$ 3.7 years, respectively. Diabetes duration was 4.9 $\pm$ 5.4, 3.0 $\pm$ 1.5, 4.1 $\pm$ 3.5 years and 7.6 $\pm$ 6.8 years at the time of diagnosis of retinopathy, cataracts, microalbuminuria and peripheral neuropathy, respectively. At least one diabetic complication was present in 25 (37.7%) patients at a mean age of 19 $\pm$ 3.5 years and mean diabetes duration of 3.9 $\pm$ 3.6 years. In adjusted regression models, age at complication, diabetes duration, insulin requirement, sex and mean HbA1c did not predict development of any single complication, although in the model predicting any complication, diabetes duration was a significant predictor ( $p < 0.009$ ).

**Conclusions:** In this cohort of Haitian children and adolescents with diabetes living in a resource-limited setting, microvascular complications and cataracts occur prematurely and as early as at diagnosis. Metabolic control alone does not explain this phenomenon. Low insulin requirements years after diagnosis, possibly allowing for prolonged undetected hyperglycemia pre-diagnosis, may associate with complication risk. The phenotypes and natural evolution of diabetes in pediatric populations of African ancestry may be distinct and need further investigation. Ophthalmologic evaluation should possibly start at diagnosis and screening guidelines may need to be adapted.

# IMPACT OF PSYCHOLOGY SERVICES IN AN INTEGRATED PEDIATRIC ENDOCRINOLOGY CLINIC

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**Objectives:** Type 1 diabetes (T1D) management is complex and requires adherence to behaviors such as blood glucose monitoring and insulin administration in order to improve glycemic control. Including psychology services in pediatric endocrinology clinics is one approach that may help improve patient’s adherence to diabetes management behaviors, and as a result, glycemic control. However, a further understanding of the impact of psychological services on patient outcomes and cost savings is needed.

**Methods:** Data from 325 patients with T1D (50% female; 56% Caucasian; *M* age=11.9 years) was obtained via medical chart review. Mean T1D duration was 4.3 years (*SD*=3.5) and mean HbA1c was 9.45% (*SD*=1.63). Patients were excluded from analyses if their average HbA1c <7.5% and length of diagnosis <1 year.

**Results:** Analyses revealed that patients experienced significant improvements in HbA1c following psychology visits (*b* = -0.12, *p* = 0.049). There was also a trend toward average HbA1c moderating this effect (*b* = -0.07, *p* = 0.069) such that patients with higher average HbA1cs were more likely to benefit from psychology services.

**Conclusions:** Providing psychology services, especially for patients with poorly controlled glycemic control, may help improve patient outcomes. Given these findings, the impact of psychology services on cost savings will also be examined. Overall, results will help determine the impact of psychology involvement on health and financial outcomes in the context of pediatric endocrine clinics.

P2-1842

**LEG LEAN MASS IS CORRELATED WITH BONE MINERAL DENSITY IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES**

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**Objectives:** Previous studies have noted increased fracture risk, decreased bone mineral density (BMD), and lower lean mass in children, adolescents and adults with Type 1 Diabetes (T1D).

- To determine how lean mass (leg lean mass) is related to measurements of BMD at the lumbar spine, hip and total body less head all adjusted for height in children and adolescents with T1D for at least 3 years duration.

**Methods:** Subjects: 32 children and adolescents, ages 10 to 17.99 years diagnosed with Type 1 Diabetes for at least 3 years and without another condition or medication that could affect growth or bone quality (thyroid or celiac disease; history of stimulants, Depo-Provera, anti-epileptic drugs, or chronic glucocorticoids)  
DXA measurements: Z scores for leg lean mass; bone mineral content (BMC) and bone mineral density (BMD) at lumbar spine, hip and total body less head  
DXA outcomes were converted to sex and race-specific Z-scores relative to age using national (BMDCS) Hologic

reference data. Bone Z-scores outcomes were adjusted for height z-score. Leg lean mass Z-score was adjusted for leg length Z-score.

**Results:** Z scores for leg lean mass were correlated with Z scores for bone mineral density in children and adolescents with Type 1 Diabetes (T1D) in the hip (correlation coefficient, *R*=0.52, *p*=0.0022) and total body less head (correlation coefficient, *R*=0.51, *p*=0.0026) when adjusted for height Z score.

Correlation with Z scores for bone mineral density at lumbar spine trended toward significance (correlation coefficient, *R*=0.33, *p*=0.065).

**Conclusions:** Z scores for leg lean mass are correlated with Z scores for bone mineral density in children and adolescents with Type 1 Diabetes (T1D) in the hip and whole body less head when adjusted for height. These results are similar to those previously reported in premenarchal and adolescent girls, associated with high-impact, strength-building exercises. In our study, it is unclear what is contributing to differences in leg lean mass. These results may suggest an important role for muscle mass development during growth to maximize peak bone density and overcome deficits in bone density associated with T1D.

**Table 1:** Baseline patient characteristics

Characteristic	T1D (n=32)
<b>Demographics</b>	
Age, years (median, range)	15.67 (10.37-17.71)
Sex	
Male (%)	62.5
Race	
Hispanic (%)	18.75
Non-Hispanic (%)	81.25
White (%)	84.4
Asian Indian (%)	6.3
Mixed race (%)	6.3
Other (%)	3.1
Height, Z (mean, SD)	0.15 +/- 0.88
Weight, kg (mean, SD)	60.4 +/- 13.7
BMI, Z (mean, SD)	0.45 +/- 0.87
Fracture ever (% yes)	59.4
HgbA1C %, at visit (mean, SD)	8.14 +/- 1.32

**Table 2:** Patient outcomes

Outcome	T1D (n=32)
<b>DXA (all Z scores adjusted for height)</b>	
Lumbar BMD BMDCS Z score (mean, SD)	-0.05 +/- 0.90
Hip BMD BMDCS Z score (mean, SD)	-0.19 +/- 1.18
Radius BMD BMDCS Z score (mean, SD)	0.05 +/- 0.97
Whole body less head BMC Z score (mean, SD)	-0.27 +/- 0.91
Leg lean mass Z score (mean, SD)	-0.10 +/- 1.01

P2-1843

**PREVALENCE OF PERIPHERAL NEUROPATHY IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS**

*Anju Seth, MD; Dharendra Pratap Singh, MD; Satinder Aneja, MD, Lady Hardinge Medical College, New Delhi, Delhi, India*

**Objectives:** Peripheral neuropathy (PN) is the commonest among diabetic neuropathies. The current study was

undertaken to assess the prevalence of PN in children with T1DM and to determine their predictors.

**Methods:** This cross sectional study was conducted at Pediatric endocrine clinic and neurophysiology laboratory at a leading Children's Hospital at Delhi from November 2013 to March 2015. Subjects included 50 children aged 8-18 years with T1DM for > 2 years, stable on insulin therapy, free from acute complications and under regular follow up ( $\geq 2$  visits). Clinical assessment for PN was done using diabetic neuropathy symptom score (DNS score  $\geq 1$  considered significant) and assessment of touch, vibration and pain sensations, muscle power and ankle jerks using standard techniques. Nerve conduction study (NCS) was performed for all subjects to evaluate for subclinical neuropathy. This included assessment of distal latencies, amplitude of compound muscle action potential, nerve conduction velocity (NCV) and F waves in motor nerves, and amplitude of sensory nerve action potential and NCV in sensory nerves. Fasting blood sugar, lipid profile, HbA1C and spot urinary albumin /creatinine ratio were tested for all subjects.

**Results:** Mean age and duration of diabetes in enrolled subjects were  $7.1 \pm 3.3$  years and  $5.1 \pm 2.1$  years respectively. No subjects had clinical evidence or DNS score suggestive of PN. Twenty-eight of 50 (56%) subjects demonstrated evidence of subclinical neuropathy on NCS. Proportion of children with pure motor, pure sensory and mixed motor-sensory involvement was 40% (20/50), 2% (1/50), and 14% (7/50) respectively. Of 27 children with motor neuropathy, 25 had axonopathy, while demyelinating changes were recorded in 7. Mononeuropathy was observed in 36% (18/50), while 20% (10/50) subjects had polyneuropathy. The peroneal nerve was the most common motor nerve affected while the all sensory nerves (median, ulnar, sural) were affected in the same frequency. Poor glycemic control (HbA1c  $>9\%$ ) and longer diabetes duration ( $>5$  years) were significantly associated with development of PN.

**Conclusions:** A large proportion of children and adolescents with T1DM had subclinical PN. Poor glycemic control and the longer duration of diabetes are risk factors for nerve dysfunction.

P2-1844

#### KETOACIDOSIS AT ONSET OF TYPE 1 DIABETES IS A PREDICTOR OF LONG-TERM GLYCEMIC CONTROL

Shlomit Shalitin, MD, Schneider Children's Medical Center of Israel, Petach Tikva, Israel; Sharon Fisher, MD, Tel Aviv university, Tel Aviv, Israel; Michal Y Gavan, PhD; Liat De Vries, MD; Liora Lazar, MD; Yael Lebenthal, MD, Schneider Children's Medical Center of Israel, Petach Tikva, Israel; Moshe Phillip, MD, Tel-Aviv University, Petach Tikva, Israel

##### Objectives:

Few studies have evaluated the impact of diabetic ketoacidosis (DKA) at diabetes onset on the long-term glycemic control in patients with type 1 diabetes (T1D).

We aimed to determine any differences in long-term glycemic control between children/adolescents with T1D presenting with DKA at diabetes onset and those without.

##### Methods:

This retrospective study comprised 335 patients diagnosed with T1D from September 2007 to December 2012, among which 132 (39.4%) presented with DKA.

Variables compared between patients with DKA at onset and those without included: yearly HbA1c levels, daily insulin dose, yearly rates of severe hypoglycemia and DKA, and percent of patients achieving target HbA1c levels.

##### Results:

After the first year of diabetes the mean daily insulin dose and HbA1c level were significantly higher in the group with DKA ( $0.74 \pm 0.26$  vs.  $0.69 \pm 0.27$  units/kg/day,  $p=0.049$ , and  $7.85 \pm 1.13\%$  vs.  $7.49 \pm 0.94\%$ ,  $p=0.01$ , respectively), despite similarity of therapy (MDI or CSII), with a similar but not statistically significant trend subsequently. Mean HbA1c during total diabetes duration (HbA1c-TDD) was significantly higher in the DKA group ( $8.08 \pm 0.95\%$  vs.  $7.86 \pm 0.95\%$ ,  $p=0.025$ ). A significantly higher percentage of patients in the group without DKA at onset achieved a mean level of HbA1c-TDD within glycemic targets (32% vs. 20.5%,  $p=0.02$ ). In the DKA group the frequency of subsequent DKA episodes per diabetes years was significantly higher ( $p=0.042$ ).

##### Conclusions:

DKA at diagnosis was associated with less favorable long-term glycemic control as assessed by HbA1c and the rate of DKA episodes. T1D patients presenting with DKA may therefore need stricter treatment and tight follow-up.

P2-1845

#### NO NEED THE INVESTIGATION FOR CELIAC DISEASE 5 YEARS AFTER THE DIAGNOSIS OF DIABETES MELLITUS TYPE 1.

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**Objectives:** The prevalence of celiac disease (CD) in children with diabetes mellitus type 1 (DM1) ranges from 1.6 – 12.3%. In most cases, CD is diagnosed by screening tests in patients with no clinical symptoms. Due to the high prevalence in this population, it is recommended to perform periodic tests, but there is no scientific basis for the frequency of performance of such tests. The purpose of this study was to investigate the incidence of the appearance of CD in children with DM1 and to identify risk factors for the development of CD.

**Methods:** All celiac antibody screening tests and small bowel biopsy results taken from 1998 until 2015 were collected from patients with DM1. Based on these results, the prevalence of celiac antibodies and the yearly incidence of CD following the diagnosis of DM1 was computed.

**Results:** The charts of 314 children diagnosed with DM1 were examined. 31 (9.87%, 95% CI 6.8-13.7) were found to have positive celiac antibodies. 25 of those underwent small

bowel biopsy. 16 were positive, 7 negative and 2 were inconclusive. In 6 patients, biopsy was not performed, 2 of whom were diagnosed because of high levels (10 times normal) of antibodies, in 3 there was a spontaneous normalization of celiac antibodies with no dietary treatment, and 1 was lost to follow-up. Kaplan-Meier survival analysis showed that the probability of developing antibodies increases with the length of time after diagnosis of DM1 and reaches a peak of 17.69% after 13 years. A total of 18 subjects were diagnosed with CD (5.73%, 95% CI 2.7-7.8), 3 were diagnosed at initial diagnosis of DM1. Kaplan-Meier survival analysis showed that the probability of developing CD increases with the length of time after diagnosis of DM1 and reaches a peak of 8.49% after 5.3 years.

**Conclusions:** This study shows that screening for CD is recommended at diagnosis of DM1 and thereafter yearly for the following 5 years only. There is no benefit for screening after 5 years after diagnosis of DM1.

P2-1846

#### **DEXTROSE-SULFONYLUREA CHALLENGE AS A SCREENING TEST FOR MONOGENIC DIABETES IN PATIENTS DIAGNOSED WITH TYPE I DIABETES**

*Aurelia CH Wood, MD; Bess A Marshall, MD; Maria Remedi, PhD; Colin Nichols, PhD, Washington University in St. Louis, St. Louis, MO, United States*

**Objectives:** Monogenic diabetes subtypes due to *ABCC8*, *KCNJ11*, *HNF1A* and *HNF4* can be treated with sulfonylurea (SU). The SEARCH for Diabetes in Youth study confirmed most patients with monogenic diabetes are misdiagnosed with Type I Diabetes (T1DM) and treated with insulin. While genetic screening may isolate individuals with mutations in recognized genes, SEARCH also revealed family history and fasting C-peptide do not reliably increase pre-test probability for identification of these defects. Furthermore, genetic testing is expensive and methods to improve yield and cost-benefit ratio do not yet exist. We developed a dextrose-SU challenge to assess C-peptide response to SU as indication of clinically significant underlying  $\beta$ -cell excitation defects. We postulate negative response to hyperglycemia with positive response to SU indicates presence of a genetic defect in glucose-stimulated insulin secretion.

**Methods:** A 240-min fasting dextrose-SU challenge has been completed on 14 pediatric subjects with T1DM treated with insulin. Blood glucose (BG) and C-peptide were obtained at 20, 10, and 0 minutes prior to a 0.5 g/kg IV dextrose bolus (max 20 g), and at 3, 5, 10, and 20 minutes thereafter. A single weight-based dose of glipizide was given (0.3 mg/kg, max 15mg if < 50 kg; 40 mg if > 50 kg) and BG and C-peptide were obtained until study completion.

**Results:** Most (n=9) maintained undetectable C-peptide throughout the study. Five subjects (48  $\pm$  1.79 months since diagnosis) showed marginal C-peptide response to dextrose ( $\Delta$ C-peptide from baseline 0.032  $\pm$  0.03 ng/mL) and increased response after SU (peak 0.37  $\pm$  0.32 ng/mL,  $\Delta$ C-peptide after SU 0.15  $\pm$  0.09 ng/mL) suggesting islets may show modest but

specific response to SU in T1DM years after diagnosis. We previously reported a patient with T1DM with no C-peptide response to dextrose, but an unexpected increase in C-peptide and significant hypoglycemia after SU suggestive of robust excitation-secretion.

**Conclusions:** These data suggest the challenge may serve to elicit and stratify C-peptide response to SU, assist clinicians in categorizing residual  $\beta$ -cell function, support screening for monogenic diabetes, and increase consideration of SU therapy for appropriate patients. Procedures are ongoing.

P2-1847

#### **REAL - LIFE DATA: INSULIN TREGLUDEC IN CHILDREN AND YOUNG ADULTS WITH T1DM**

*Nehama Zuckerman - Levin, MD, Endocrinology unit, Rambam Medical Center, Haifa, Israel; Shalev Zuckerman, MD; Naim Shehadeh, MD, Rambam Medical Center, Haifa, Israel*

**Objectives:** Achieving good glycemic control is a major goal in T1DM. This includes striving for a target HbA1C, weight adjusted insulin dosing, minimizing hypoglycemic episodes, and decreasing blood glucose variability. Tregludec is a new long acting insulin associated with low blood glucose variability. Real life data in adults with T1DM and T2DM demonstrated significant reductions in HbA1C, hypoglycemic episodes, and insulin dose. Our aim was to evaluate glycemic control following switching to Tregludec in children and young adults. The primary end point was change in HbA1C.

**Methods:** We included patients <31 years diagnosed with T1DM with HbA1c > 7.5 who were switched to Tregludec. HbA1C was measured at baseline and 3-6 months after the switch. Dose of basal and total insulin (IU/kg body weight/day) were calculated. Self-monitoring of blood glucose measurements were documented two weeks before and 3 months after the switch.

**Results:** 98 patients (55% girls, age range 2.9-31 years, mean 14 $\pm$ 4.8 years) were included. Mean duration of T1DM was 5.5 $\pm$ 4.8 years. Previous basal insulin treatments were Lantus (67%), Levemir (26%), Toujeo (1.9%), or CSII (5.1%). Mean HbA1C at baseline was 9.04 $\pm$ 1.7. After 3 months of Tregludec treatment mean HbA1c decreased to 8.48 $\pm$ 1.6 (p<0.0001). After 6 months it decreased further to 8.21 $\pm$ 1.3 (p<0.02). Mean basal and total insulin dose at baseline were 0.39 $\pm$ 0.17 IU/kg/day and 0.88 $\pm$ 0.31 IU/kg/day, respectively. After 3 months of Tregludec treatment mean basal and total insulin dose decreased to 0.36 $\pm$ 0.13 IU/kg/day and 0.75 $\pm$ 0.22 IU/kg/day (p<0.0001, p<0.01), respectively. After 3 months mean glucose measurements decreased from 205.8 $\pm$ 67.5 to 189.3 $\pm$ 59 mg/dl (p<0.03) and the percent of patients with very high (>300 mg/dl) and very low (<50 mg/dl) glucose levels decreased significantly (p<0.015, and p<0.017, respectively). Less hypoglycemic episodes were observed after the switch.

**Conclusions:** These results demonstrate that switching to Tregludec as basal insulin in children and young adults with T1DM improves glycemic control.

### EARLY ONSET OF SEVERE DIABETES IN PRADER WILLI SYNDROME- PATHOPHYSIOLOGY, CLINICAL FEATURES AND MANAGEMENT CHALLENGES

Ulla Najwa Abdulhag, MD, Hadassah hospital , Jerusalem, Israel; Harry J Hirsch , MD, Shaare Zedek Medical Center , Jerusalem , Israel; Abdulsalam Abulibdeh, MD, Hadassah hospital , Jerusalem , Israel; Floris Levy Khademi, MD; Varda Gross-Tsur, MD, Shaare Zedek medical center , Jerusalem, Israel; David Zangen , Professor, Hadassah Hebrew University Medical Center, Jerusalem, Israel

#### Objectives:

Prader-Willi syndrome (PWS), a neurogenetic disorder due to a lack of expression of paternal genes on 15q11-q13 is characterized by hyperphagia leading to severe obesity. Impaired glucose tolerance and diabetes mellitus (DM) occur in 7-20% of patients with typical onset in late adolescence or adulthood. Aberrant pro-hormone processing has been recently accounted as responsible for the endocrine features of PWS. This study describes a rare case of severe DM in a 9 year-old child with PWS.

**Methods:** A 9 years old male with PWS diagnosed with anti-GAD negative hyperglycemia and treated initially with 850mg metformin daily presented at 10y Of age with hyperglycemia of 300-350 mg/dl and HBA1C of 13.5%. His weight was 44kg and BMI was 26 kg/m<sup>2</sup>. Laboratory tests revealed elevated liver enzymes and hyperlipidemia; liver ultrasound showed steatohepatitis. Oral and intravenous Glucose Tolerance Test indicated residual insulin secretion.

**Results:** The insufficient partial response to gradually increasing doses of Metformin (up to 2550 mg daily), indicated the addition of increasing doses of basal and bolus insulin. Statins treatment was initiated ( Simvastatin 20mg/d) for Hyperlipidemia. The typically continuous weight gain (W- 50 Kg, BMI – 27.5 kg/m<sup>2</sup>) in spite of the significant efforts as expected in PW patients complicated the metabolic control. Nevertheless, intensive insulin and statins therapy resulted in a decrease in HBA1C from 13 % to 9.4 % and improved liver function test and lipids profile.

**Conclusions:** This unique and unusual overt anti GAD negative diabetes presentation in a patient with PWS already at 9 years of age exerted a prominent therapeutic challenge. The severe hyperphagia complexed by cognitive limitations resulted in uncontrolled high carbohydrates consumption that could not be solved solely by oral hypoglycemic therapy. New insights in the pathophysiology of endocrine abnormalities in PWS can lead to new therapy options in these patients.

### A SWEET GIRL AND HER ACHING SOLES

Niranjana Varadharaju, MBBS; Jeevarathnam Dhivyalakshmi, MD; Saji James, MD; Vinoth Ponnuram Nagarajan, MD; Mahalakshmi R, MD, Sri Ramachandra University, Chennai, India

**Objectives:** Treatment-induced neuropathy (TIN) in diabetes is a rare iatrogenic small fiber neuropathy caused by an abrupt improvement in glycemic control in the setting of chronic hyperglycemia. Any peripheral neuropathy has to be evaluated very carefully in a child with diabetes. Consider TIN, especially if neuropathy presents too early in the course of disease.

**Methods:** A 16 year old girl newly diagnosed type 1 diabetes presented with DKA. She has been symptomatic for past 1 ½ years (HbA1C was 17 gm%). Once DKA resolved she was started on basal & bolus insulin regimen (regular and glargine insulin) along with carbohydrate counting. Baseline complication screening was normal. 1 month later, she had burning sensation of bilateral feet. Her glycemic control was good. Suspecting peripheral neuropathy Vitamin B12, Vitamin D supplements were started. NCS showed sensory motor neuropathy of lower limbs. She was started on gabapentin & amitriptyline. Few days later she developed blurring of vision, hypertension & tachycardia. Fundus examination showed features suggestive of diabetic / hypertensive retinopathy. Nifedepine and atenolol was started in view of autonomic neuropathy. She got symptomatically better. Her followup HbA1c was 7 gm%. In view of diabetic neuropathy (peripheral and Autonomic) too early following diagnosis, work-up for vasculitis was done and was negative.

**Results:** Vast literature search suggested a possibility of Treatment induced neuropathy as child had all 3 criteria of TIN (drop in HbA1C by more than 2 % in 3 months, acute onset of neuropathic pain and/or autonomic dysfunction, neuropathic symptoms observed within 8 weeks of a documented good glycemic control). The treatment options for TIN are supportive pharmacotherapy ± permissive hyperglycemia (avoiding abrupt tighter blood glucose control). Upon follow-up child is doing better, medications gradually withdrawn, retinopathy subsided, hypertension and tachycardia settled, gaining weight and blood glucose was controlled gradually.

**Conclusions:** Possibility of TIN has to be considered in any diabetic child especially with neuropathy presenting too early in the course along with good glycemic control. Instead of abrupt tighter blood sugar control a slow and steady glycemic control is needed for such patients.



DEAD IN BED SYNDROME IN A YOUNG PERSON WITH TYPE 1 DIABETES WITH EVIDENCE OF POOR CONTROL CAPTURED ON FLASH GLUCOSE SENSOR (FGS) DEVICE.

Zainaba Mohamed, MPhil; Josephine Drew, MBBS; Anne Richardson, MBBS, Nottingham Children's Hospital NHS Trust, Nottingham, United Kingdom; Tabitha Randell, MBBS, Nottingham Children's Hospital, Nottingham , United Kingdom; Louise Denvir, MBBS; Pooja Sachdev, MBBS, Nottingham Children's Hospital NHS Trust, Nottingham, United Kingdom

**Objectives:** To report a case that captured the glucose trend hours before the time of death of a teenager with type 1 diabetes(Dead-in-bed).

**Methods:** We describe a 17-year-old-boy with type 1 diabetes diagnosed at age 8, with poor control (median HBA1C of 75mmol/mol) on multiple daily injections of insulin. In an effort to encourage him to check his glucose levels, his parents purchased a 'Libre' Flash Glucose Sensor (FGS) device. While his HBA1c improved to 53mmol/mol, this was at the expense of significant hypoglycaemic episodes secondary to injecting large amounts of quick acting insulin after episodes of binge eating with minimal testing(Figure 1). He was not known to consume alcohol. On the evening prior to death he had been with his parents, retired at around 10pm and was found the next day by father at 9 am sat up in a forward collapsed position, in a state of rigor mortis, suggesting death had occurred in the early hours of the morning. The Libre-glucose monitoring system FGS was found attached to his arm and was downloaded for postmortem study.

**Results:** Autopsy reported dead-in bed-syndrome, no anatomical abnormalities but stated that death could be due to undiagnosed autonomic neuropathy resulting in an acute cardiac arrest. . Post mortem showed obesity with BMI 34 kg/m2, with an enlarged liver, acute pulmonary oedema and diffuse cerebral oedema. The metabolic toxicology showed no evidence of ketoacidosis and the vitreous humour glucose concentration was 1.9ml/L which would suggest death was unlikely to be associated with a hypoglycaemic episode. Histological examination revealed glycogenic hepatopathy. Download of the data that he was scanning more regularly in the week leading up to his death following a clinic consultation. The last recorded reading at 3 am was normal at 6.3. (fig 2 and 3).

**Conclusions:** To our knowledge, this is the first documentation of Libre FGS data capturing information on glucose trends in the days before the death. The patient profile of a teenage male with poorly controlled diabetes fits in with high risk category of dead-in-bed. This report also brings into focus the need for clinicians to look at time in target in addition to HBA1c as a measure of good glycaemic control.

SEE TABLE IN NEXT COLUMN

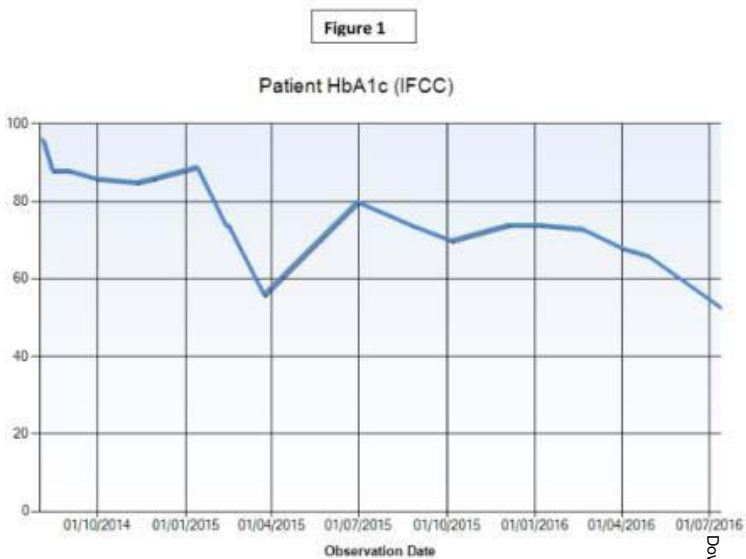


Figure 1: The graph represents HBA1C readings over the previous 2 year period

MILDLY POSITIVE ZINCTRANSPORTER 8 ANTIBODY RESULTING IN SEVERE NEW ONSET TYPE 1 DIABETES IN YOUNG CHILD

Parissa Salemi, DO, Cohen Children's Medical Center, Lake Success, NY, United States

**Objectives:** Type 1 diabetes is characterized by destruction of insulin-producing pancreatic beta cells via the development of one or more autoantibodies directed at the insulin-producing pancreatic beta cells. These autoantibodies include glutamic acid decarboxylase 65 Ab(GAD-65), tyrosine phosphatase IA-2 Ab (IA-2), insulin ab (IAA), islet cell ab (ICA), and zinc transporter 8 (ZnT8) ab.

ZnT8 antibody is a more recently discovered diabetes-related major autoantibody. Roughly 65% to 80% of children with recently diagnosed type 1 diabetes have ab to ZnT8. The ab can be detected as early as 9 months of age but is more common after 2 years. This ab is less frequently tested at the onset of a newly diagnosed presentation of type 1 diabetes. My objective is to evaluate ZnT8 antibody positivity and levels to determine if this is clinically correlated to the severity of presentation in autoimmune-mediated diabetes.

**Methods:** 5 yr and 4 mo old male who initially presented in DKA was initially evaluated for T1DM autoantibodies : GAD-65, IAA, ICA, ZnT8. ZnT8 testing was done via Enzyme-linked immunosorbent assay (ELISA) with an analytical sensitivity: 2.1 U/mL.

<b>Results:</b>			
Zinc Transporter 8 AB	18.1 kronus U/mL	H	0.0-15.0
Islet Cell Antibodies	<5 JDF u		<5
Glutamic Acid Decarboxylase	0.00 nmol/L		<= 0.02
Insulin Antibodies	< 0.4 U/mL		< 0.4
Hemoglobin A1c	12.8	H	< 6.0

**Conclusions:** A mildly elevated ZnT8 ab value with negative GAD-65, ICA, and IA values resulted in a severely progressed presentation of new onset Type 1 diabetes.

Studies have shown ZnT8 ab is more commonly associated with other positive diabetes abs, and less frequently found to be positive in isolation, particularly at a younger age. ZnT8 ab occurs in 3% to 4% of patients with type 1 diabetes who are negative for these other 3 abs. Use of the 4 abs results in 93% to 98% sensitivity encouraging routine ZnT8 testing.

As De Grijse et al. noted, because ZnT8 is located within  $\beta$ -cell secretory granules, ZnT8A expression may not occur until there is enough  $\beta$ -cell damage to make ZnT8 immunologically visible. This may indicate that even low levels obtained during first-degree relative screens (e.g. Trialnet), could implicate imminent progression of diabetes.

P2-1852

#### ENDOGENOUS INSULIN SECRETION AND ITS RELATIONSHIP WITH HLA-MARKERS OF TYPE 1 DIABETES IN YOUNG CHILDREN

*Irina V Osokina, PhD, Siberian Federal University, Krasnoyarsk Science Centre of the Siberian Branch of Russian Academy of Science, Krasnoyarsk, Russian Federation; Irina M. Belovalova, MD, Endocrinology Research Centre, Moscow, Russian Federation; Victor V. Yazdovsky, PhD, National Research Center- Institute of Immunology Federal Medical-Biological Agency of Russia, Moscow, Russian Federation; Ludmila N. Scherbacheva, MD, Endocrinology Research Centre, Moscow, Russian Federation*

**Objectives:** The residual endogenous insulin secretion influences on the clinical course of type 1 diabetes mellitus (T1DM). The aim of our study was to determine relationship of HLA genetic markers of T1DM and the C-peptide levels in young children with type 1 diabetes mellitus.

**Methods:** In order to elucidate the effect HLA-genotype on the residual function of pancreatic  $\beta$ -cells and the course of T1DM, 100 children, 50 boys and 50 girls aged 0.9 to 6.5 years were examined. The age of T1DM manifestation was 0.25 – 6.4 years (mean  $2.7 \pm 1.1$ ); before 1 year – 12 patients, 1-3 years – 64 patients, older than 3 years – 24 children. HLA-phenotype was detected by the standard lymphocytotoxic test. 59 HLA antigens classes I and II (A, B, DR, DQ loci) were taken into consideration. Basal and postprandial (60 and 120 minutes after standard breakfast) C-peptide levels was assessed by radioimmunoassay.

**Results:** The pancreatic insulin-secretory function was dramatically reduced in young children with T1DM. The mean value of basal C-peptide was  $0.13 \pm 0.01$  nmol/l. The residual secretion of insulin was revealed in 56.2% of children. “C-peptide-positive” patients accounted for 79.6% if duration of diabetes was less than 1 year; 46.2% - if duration of T1DM was 1-2 years; 33.7% - if duration of T1DM was 2-3 years; 20.0% - if duration of T1DM was 3-4 years; 16.7% - if duration of diabetes was more than 4 years. HLA-markers of predisposition to T1DM in early childhood were revealed: DQw3, DR3/4, DR4, DR3, B8. The HLA-markers of high risk of

T1DM DR3, DR4 and moreover, DR3/4, as well as the age the diabetes onset and duration of disease were found to influence on the C-peptide level and duration of function of  $\beta$ -cells.

**Conclusions:** Our study shown that insulin-secretory function strongly reduced in young children with T1DM. We found HLA markers of high risk of T1DM in children: HLA - DR3/4, DR3, DR4, DQw3, B8. HLA- DR3, DR4 and moreover, DR3/4, as well as the age the diabetes onset and duration of disease to influence on the residual function of pancreatic  $\beta$ -cells.

#### POSTER SESSION 2

**Friday, September 15, 2017, 11:30am-12:30pm**

#### P2 - Type 2 diabetes and other carbohydrate metabolism

#### P2-1900 – P2-1906

P2-1900

#### INSULIN DYNAMIC AFTER THE STANDARD GLUCOSE LOAD AS A DIABETES MARKER IN OBESE ADOLESCENTS

*Tetyana Chaychenko, PhD; Olena Rybka, MD, Kharkiv National Medical University, Kharkiv, Ukraine*

**Objectives:** Insulin resistance is recognized as a key pathogenic element of metabolic syndrome. Clinically we faced the problem when severely obese insulin resistant subjects are still below glycemic threshold for DM2 diagnosis. We hypothesized that post-load insulin response is the more valid marker of the diabetic beta-cell dysfunction than glucose response.

**Methods:** 64 adolescents aged  $13.56 \pm 2.47$  y.o. with different BMI were examined. The laboratory assessment included fasting glucose and insulin measurement followed by standard oral glucose tolerance test. HbA1C greater than 6.5 % used for grouping for HbA1C “negative” (gr.1) and HbA1C “positive” (gr.2) subjects. Fasting insulin sensitivity assessed by HOMA-IR, QUICKI and whole body insulin sensitivity by Matsuda. Results were analyzed by using StatSoft Statistica 10.

**Results:** HbA1C level was 7.29 % in HbA1C “positive” vs. 5.75 % in HbA1C “negative” ( $p < 0.001$ ). HbA1C “positive” had higher Z-BMI ( $2.28 \pm 1.3$  vs.  $1.04 \pm 1.67$ ,  $p < 0.025$ ) and waist to height ratio ( $0.58 \pm 0.13$  vs.  $0.46 \pm 0.1649$ ,  $p < 0.05$ ) with no gender and age differences. HbA1C “positive” subjects had greater HOMA-IR ( $7.24 \pm 2.46$  vs.  $5.02 \pm 3.93$ ,  $p < 0.001$ ), lower QUICKI ( $0.28 \pm 0.016$  vs.  $0.32 \pm 0.049$ ,  $p < 0.001$ ) and lower Matsuda ( $2.09 \pm 0.77$  vs.  $4.88 \pm 0.72$ ,  $p < 0.001$ ).

There was no difference in glycemic curve. Meantime, the insulin curve was statistically different in groups: fasting -  $22.89 \pm 16.53$  vs.  $34.47 \pm 12.38$ ; at 90 min -  $60.33 \pm 36.82$  vs.  $99.38 \pm 33.61$  ( $p < 0.025$ ); mean  $56.38 \pm 24.37$  vs.  $73.15 \pm 19.99$  ( $p < 0.025$ ).

Some parameters of insulin curve are highly specific for gr.1: no insulin decrease (or the second peak) after 60-th min (Se =

80.95%; Sp= 76.6%) and insulin min-max variability less than 200% (Se = 80.95%; Sp= 86.6%) with PPV=69.57% NPV=85.19 %. Usage of both Sp=96.6% and Se=96.3%.

**Conclusions:** HbA1C “positive” subjects have greater BMI and abdominal adiposity with more deteriorated both fasting and whole body insulin sensitivity.

The insulin curve after the standard glucose load in HbA1C “positive” obese adolescents differs even despite of the absence of diabetic blood glucose level.

Low insulin variability with no decrease (or second peak) after 60 min could be considered as markers of diabetes and indications for pharmacological interventions in obese adolescents.

P2-1901

#### INSULIN SENSITIVITY AND $\beta$ -CELL RESPONSIVENESS IN OBESE EUROPEAN CHILDREN AND ADOLESCENTS

Christian Denzer, MD; Katja Kohlsdorf, MD; Julia Von Schnurbein, MD; Martin Wabitsch, Professor; Josef A. Vogt, PhD, University Medical Center Ulm, Ulm, Germany

**Objectives:** Prevalence rates of T2DM in obese children and adolescents are significantly lower in European countries compared to the United States. Published data from cohorts of obese children and adolescents living in the US suggest a concurrent worsening of insulin sensitivity and  $\beta$ -cell function over the spectrum of glucose homeostasis. If these results can be applied to European populations is currently unknown.

**Methods:** We recently proposed a novel method for mathematical modelling of insulin secretion and disposal from 3h, 8 sample OGTT data in children and adolescents (Vogt et al., Am J Physiol Endocrinol Metab. 311:E82-94, 2016). Here we combine our approach with a minimal model of glucose in order to estimate insulin sensitivity SI,  $\beta$ -cell responsiveness Phi, and the disposition index DI (SI x Phi) in a population of n=133 (n=67 girls) obese children and adolescents (mean age 13.5 years (range 6.3 to 20.4 years), mean BMI z-score 2.83 (range 1.36 to 4.61).

**Results:** Of the total study population, n=4 subjects were diagnosed with impaired fasting glucose, and n=10 subjects had an impaired glucose tolerance. Regrouping the study population into tertiles of fasting glucose (t1: 61-81 mg/dl, t2: 82-87 mg/dl, t3: 88-113 mg/dl) and tertiles of 2h-glucose (t1: 56-97 mg/dl, t2: 98-115 mg/dl, t3: 116-190 mg/dl), respectively, revealed the following: SI decreased significantly over tertiles of fasting glucose and 2h-glucose (each  $p<0.035$ ), whereas Phi remained unchanged over each category. Concordantly, the disposition index DI decreased significantly with increasing tertiles of fasting glucose (t1-t3: -32%) and 2h-glucose (t1-t3: -66%, each  $p<0.03$ ). Adjusted for age, sex, pubertal stage, and BMI z-score, decreases in SI reached only borderline significance in the highest compared to the lowest tertile of fasting glucose ( $p=0.064$ ). After adjustments, SI, Phi, and DI remained unchanged over tertiles of 2h-glucose.

**Conclusions:** In our cohort, increasing levels of fasting glucose and 2h-glucose were predominantly associated with

worsening of insulin sensitivity but not declining  $\beta$ -cell function. This observation may provide a pathophysiological explanation for the comparably low prevalence of T2DM in obese adolescents in Middle Europe compared to obese adolescents from multiethnic backgrounds in the US.

P2-1902

#### INVESTIGATING POTENTIAL ASSOCIATIONS BETWEEN HBA1C AND BLOOD PRESSURE IN ADOLESCENTS WITH TYPE 2 DIABETES MELLITUS

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**Objectives:** Type 2 Diabetes Mellitus (T2D) during adolescence is associated with childhood obesity. There is limited information about T2D associated co-morbidities in adolescents and the potential impact of these conditions on glycemic control. To investigate potential changes from diagnosis to first follow-up in HbA1c and blood pressure in adolescents with T2D.

**Methods:** This is a longitudinal retrospective analysis of 96 adolescents aged 10-17 years diagnosed with T2D at Children's Hospital of Michigan. Demographics and other variables including HbA1c, systolic and diastolic blood pressures (SBP and DBP) were analyzed at diagnosis and first follow-up clinic visit. SBP and DBP were classified as normal (NBP), prehypertensive (PHTN), or hypertensive (HTN) based on norms for age, sex, and height.

**Results:** Mean age was 14.4 $\pm$ 1.9 years at baseline. The cohort was 65.6% female and 81.3% African American. Mean BMI was 37.1 $\pm$ 11.7 kg/m<sup>2</sup>. 93.7% had a family history of T2D. Follow-up at mean 4.8 months showed a decrease in HbA1c from 11.0 $\pm$ 2.9% to 8.1 $\pm$ 2.2% ( $p\leq 0.001$ ), a decrease in DBP from 72.1 $\pm$ 8.5mmHg to 68.0 $\pm$ 8.5mmHg ( $p\leq 0.01$ ) and an increase in SBP from 122.3 $\pm$ 12.0mmHg to 126.7 $\pm$ 13.1mmHg ( $p\leq 0.01$ ). 46.4% [95% CI 0.36, 0.57] of patients had SBP in the NBP range at baseline compared to 24.7% [95% CI 0.16, 0.35] at follow-up; 28.6% [95% CI 0.20-0.39] had SBP in the PHTN range at baseline compared to 25.9% [95% CI 0.18, 0.36] at follow-up; 25.0% [95% CI 0.17, 0.35] had SBP in the HTN range at baseline compared to 49.4% at follow-up. HbA1c change from baseline to follow up was analyzed by follow-up SBP category: NBP -3.40 $\pm$ 0.54 [95% CI -4.47, -2.33]; PHTN -3.85 $\pm$ 0.53 [95% CI -4.89, -2.80]; HTN -2.18 $\pm$ 0.38 [95% CI -2.93, -1.43]. The mean HbA1c difference between PHTN and HTN range was significant, -1.67 $\pm$ 0.65 ( $p=0.04$ ). There was no significant difference in mean HbA1c difference between groups with NBP versus HTN, -1.22 $\pm$ 0.66 ( $p=0.20$ ), or PHTN 0.45 $\pm$ 0.75 ( $p=1.00$ ), which may be due to sample size.

**Conclusions:** There is a possible association between hypertensive blood pressures and smaller improvements in HbA1c.

### ASSOCIATION OF METABOLIC CONTROL WITH THE DISTRIBUTION OF ABDOMINAL FAT IN ADOLESCENTS WITH TYPE 2 DIABETES

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**Objectives:** This study was designed to analyze the distribution of abdominal fat in adolescents with type 2 diabetes mellitus (T2DM). To compare the distribution of abdominal fat in adolescents with T2DM in good metabolic control and adolescents with DM2 in poor metabolic control.

**Methods:** Observational, transversal and comparative study. Fifty-five adolescent patients with T2DM diagnosed according to the criteria of the American Diabetes Association of both sexes and aged between 12 and 16 years, who attended the Diabetes Child Care Clinic of the Children's Hospital of Mexico Federico Gomez, were enrolled in the study. All patients were referred to perform magnetic resonance imaging (MRI) to determine the distribution of abdominal fat. In all, the concentration of HbA1c was determined.

**Results:** To examine the association between abdominal fat and metabolic control, the study cohort was divided into 2 groups depending on HbA1c levels following the ADA 2016 recommendations.

Twenty-two patients entered the controlled group (HbA1c <7%) and thirty-five patients to the uncontrolled group. We did not find differences in age (mean  $14.16 \pm 2.21$  years) and anthropometry. Statistically significant differences were observed in mean diastolic blood pressure ( $p < 0.01$ ), the levels of TC ( $p = 0.002$ ), LDL-C ( $p = 0.007$ ), Tg levels ( $p = 0.038$ ) and HbA1c levels ( $p < 0.001$ ).

As measured by MRI, patients within the highest HbA1c group were found to have a higher proportion of total abdominal fat ( $275.50 \pm 27.62$  cm<sup>2</sup>) compared to patients in good control ( $264.76 \pm 28.41$  cm<sup>2</sup>). This difference was observed by a higher percentage of subcutaneous abdominal fat ( $232.03 \pm 24.61$  cm<sup>2</sup> vs  $221.24 \pm 24.03$  cm<sup>2</sup>), no differences were observed in the distribution of visceral fat ( $43.59 \pm 4.21$  cm<sup>2</sup> vs  $43.52 \pm 5.29$  cm<sup>2</sup> respectively). A statistically significant difference was not observed in the distribution of abdominal fat between the groups ( $p = 0.965$ ).

**Conclusions:** The amount of visceral fat was similar between both groups. There was a trend towards a higher amount of subcutaneous and total fat in poorly controlled patients. If such distribution of abdominal fat is associated with elevated levels of HbA1c, this could condition an increased cardiometabolic risk in patients with T2DM and poor metabolic control.

### BRAIN GRAY MATTER VOLUME DIFFERENCES IN YOUTH WITH TYPE 2 DIABETES

Jacob M Redel, MD; Jennifer Vannest, PhD; Mark DiFrancesco, PhD; Mekibib Altaye, PhD; Lawrence M Dolan, MD; Gregory Lee, PhD; Hermine Brunner, MD; Scott Holland, PhD, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States; Cassandra Brady, MD, Vanderbilt University, Nashville, TN, United States; Amy Shah, MD, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States

**Objectives:** Preliminary work suggests that youth with type 2 diabetes mellitus (T2D) have differences brain structure and poorer cognitive function scores compared to their peers. However, global and regional brain volume has not been comprehensively assessed.

**Methods:** We examined global and regional brain gray matter volumes in 20 youth with T2D (mean duration  $2.8 \pm 2.1$  years and mean hemoglobin A1C  $7.9 \pm 2.1\%$ ) and 20 race, sex and age similar controls, all lacking neuropsychological disease or prior abnormal MRI. Comparisons were made using high-resolution T1-weighted structural MRI scans and voxel-based morphometry analysis. Statistical significance for each voxel was established at  $p < 0.05$ , after adjusting for multiple testing using a family-wise error rate procedure. Only clusters with  $\geq 200$  contiguous voxels are reported.

**Results:** Compared to controls, T2D youth had decreased global gray matter-to-intracranial volume ratio ( $0.51 \pm 0.005$  vs.  $0.53 \pm 0.005$   $p = 0.02$ ). In addition, T2D youth had fourteen regions (nine of these within the temporal or occipital lobes) with significantly less gray matter volume than controls, and six regions (three were subcortical and two were in the frontal lobes) with significantly greater gray matter volume than controls. There was no difference in the white matter-to-intracranial volume ratio in youth with T2D compared to controls.

**Conclusions:** Youth with a short duration of T2D show significant differences in gray matter volume. Whether these findings explain poorer cognitive scores observed previously remains to be determined.

### IS ALBUMINURIA A RISK FACTOR FOR LEFT VENTRICULAR DYSFUNCTION IN YOUTH WITH TYPE 2 DIABETES? ANALYSIS OF THE ICARE COHORT STUDY.

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**Objectives:** The incidence of type 2 diabetes is increasing in childhood. In adults with type 2 diabetes albuminuria is a known risk factor for cardiovascular disease. The objective

was to determine if youth with type 2 diabetes and albuminuria have evidence of increased left ventricular dysfunction compared to youth with type 2 diabetes without albuminuria.

**Methods:** iCARE is a prospective cohort study of youth with type 2 diabetes diagnosed < 18 years of age. Phenotyping of participants including anthropometrics, a fasting lipid profile, HNF 1 alpha G319S polymorphism status, 24-hour blood pressure monitoring, overnight or first morning urine for albumin excretion, left ventricular echocardiography and pulse wave velocity was done at enrollment.

**Results:** Of the 189 youth with type 2 diabetes enrolled, 57 (30.2%) had albuminuria. The majority (>95%) were First Nations. Youth with type 2 diabetes and albuminuria were older (mean 15.7 vs 14.9 years,  $p=0.05$ ) and had a longer duration of diabetes (median 2.7 vs 2.0 years,  $p=0.04$ ). Sex distribution, BMI z-score and HNF1 alpha G319S status did not differ between the groups. Youth with type 2 diabetes and albuminuria had higher total cholesterol, triglycerides and apo B ( $p<0.005$ ). Diastolic (80 vs 55%,  $p<0.001$ ), day time (72 vs 56%,  $p=0.007$ ) and night time hypertension (90 vs 72%,  $p=0.015$ ) were more common in those with albuminuria. No differences in LV function, morphology or arterial stiffness were noted between the groups.

**Conclusions:** Youth with type 2 diabetes complicated by albuminuria have evidence of increased metabolic risk early in the disease course compared to those without albuminuria. A particularly atherogenic lipid profile was observed. Hypertension was also prevalent. Differences in cardiac morphology were not observed perhaps due to the short duration of diabetes. These findings suggest that albuminuria in youth with type 2 diabetes may be associated with increased cardiovascular risk.

P2-1906

## CAN LEPTIN REPLACEMENT ALTER THE COURSE OF DISEASE IN PATIENTS WITH ACQUIRED GENERALIZED LIPODYSTROPHY?

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**Objectives:** Lipodystrophy syndromes (LD) are rare diseases, clinically heterogeneous, inherited or acquired, and often life-threatening disorders. The underlying pathogenesis of generalized lipodystrophy is the irreversible widespread loss of adipose tissue leading to low leptin levels. This report examined the course of the disease in one pediatric patient with acquired generalized lipodystrophy (AGL) over 10 years and the impact of leptin replacement (metreleptin) on disease progression.

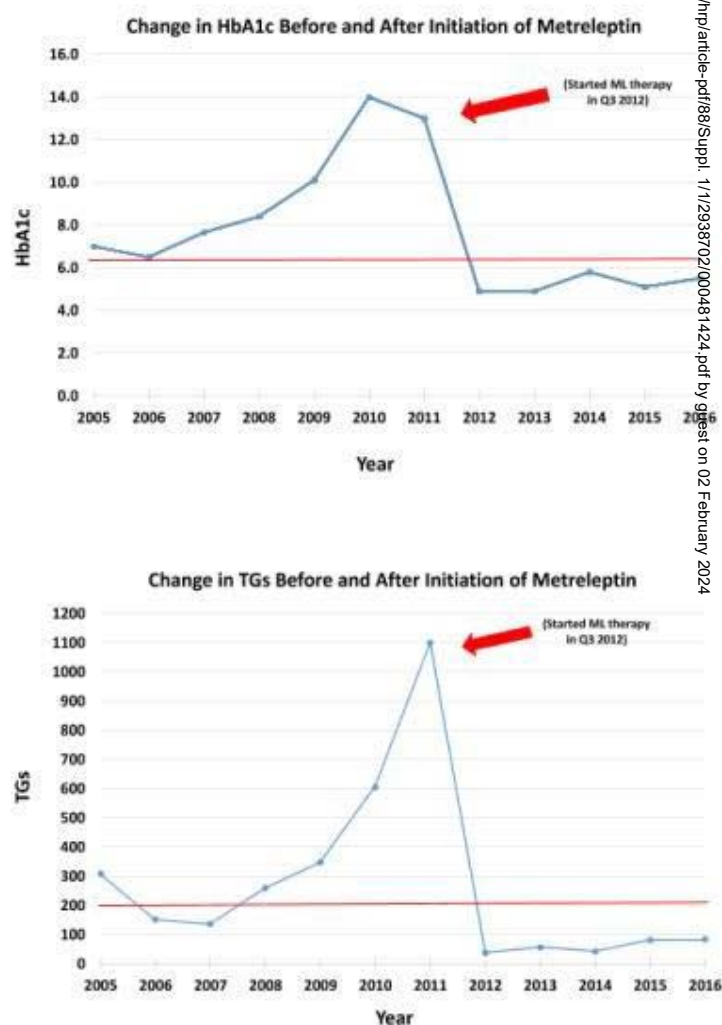
**Methods:** This is a retrospective analysis of a pediatric patient with AGL followed for 10 years at Hospital de Niños Pedro de Elizalde in Argentina. Yearly triglycerides, hemoglobin A1c

(A1c), AST, and ALT were collected for 6 years before the initiation of metreleptin (ML) and 4 years after therapy. The number of hospitalizations were also collected during this 10-year period.

**Results:** At the age of 8, this boy presented with panniculitis in the face which progressed to generalized lipodystrophy. During the 10-year follow-up, this patient had 7 hospitalizations (7 before ML initiation), 6 of which were for infectious diseases. Figure 1 depicts the worsening of metabolic control from 2005 to 2011. Before initiating ML, despite more than 500 units/day of insulin and fenofibrate therapy, A1c was 13% and TGs were 1099 mg/dL. Within 1 year of ML therapy, all antidiabetic medications were discontinued and A1c remained below 6.5. Improvements in liver function tests were also noted.

**Conclusions:** Generalized Lipodystrophy is a progressive disease, refractory to conventional therapy. In this retrospective analysis, leptin replacement therapy with metreleptin, restored this patient's A1c and TG to normal levels. Additional studies are needed to fully understand how metreleptin potentially modifies the course of disease in generalized lipodystrophy.

Figure 1:



## POSTER SESSION 3

Saturday, September 16, 2017, 12:00-1:00pm

### P3 - Adrenals

#### P3-100 – P3-132

P3-100

#### ASCORBIC ACID TREATMENT DECREASES ROS FORMATION AND RESTORES MITOCHONDRIAL MORPHOLOGY IN FIBROBLASTS FROM PATIENTS WITH CORTICOSTEROID DEFICIENCY DUE TO NICOTINAMIDE NUCLEOTIDE TRANSHYDROGENASE MUTATION

Adi Auerbach, MD, Hadassah Hebrew University Medical Center, Jerusalem, Israel; Ariella Weinberg Shokrun, PhD; Ephrat Levy-Lahad, Professor, Shaare Zedek Medical Center, Jerusalem, Israel; David Zangen, Professor, Hadassah Hebrew University Medical Center, Jerusalem, Israel

**Objectives:** Nicotinamide nucleotide transhydrogenase (NNT) mutations were recently found to cause decreased detoxification of reactive oxygen species (ROS) in adrenocortical cells and consequently severe clinical corticosteroids deficiencies.

Ascorbic acid (vitamin C), a known antioxidant, has been satisfyingly used in therapeutic trials in several diseases (e.g. cancer, diabetes and cardiovascular diseases) without major adverse effects.

Given the expression of NNT in fibroblasts, this study aimed to assess the effect of ascorbic acid treatment on the ROS levels and mitochondrial morphology in cultured fibroblasts as a model for adrenocortical cells.

**Methods:** Fibroblasts from 3 affected patients homozygous for NNT mutations and control fibroblasts were maintained in DMEM with or without 10µM L-ascorbic acid.

Cell growth was measured using a colorimetric method with Methylene Blue staining.

Intracellular ROS production was measured using 2',7'-Dichlorodihydrofluorescein diacetate with normalization to the number of cells. Mitochondrial morphology was assessed using mitotracker red staining.

**Results:** Patients' fibroblasts carrying homozygous NNT mutations (p.G200S, p.Y388S) had 23-40% higher ROS levels when compared to control fibroblasts.

Administering 10µM L-ascorbic acid decreased ROS levels in the mutated fibroblasts by 12-30%, and actually normalized ROS formation in the mutated fibroblasts.

Furthermore, pre-treatment mitochondrial morphology in mutated cultured fibroblasts revealed that 57-72% of mitochondria were damaged with punctate instead of reticulo-tubular appearance. Ascorbic acid treatment resulted in a major reduction of the pathological punctate appearance to just 16 to 25% in NNT mutated homozygous fibroblasts. These results indicated in vivo interventional study which is currently conducted.

**Conclusions:** Ascorbic acid reduces ROS content and dramatically improves mitochondrial morphology in NNT mutated patients' fibroblasts.

Further clinical trials are warranted in order to assess ascorbic acid as a steroid sparing medication in NNT impaired patients.

P3-101

#### PREVALENCE OF TESTICULAR ADRENAL REST TUMOURS IN NON-CAH MALE PATIENTS WITH ACQUIRED PRIMARY ADRENAL INSUFFICIENCY

Hedi Claahsen - Van Der Grinten, PhD, Amalia Children's hospital, Radboudumc Nijmegen, Nijmegen, Netherlands; Myrthe Verhees, Medical student; Karin Kamphuis - Van Ulzen, MD; Christiaan Mooij, MD; Ad Hermus, PhD; Nike Stikkelbroeck, PhD, Radboud University Medical Centre, Nijmegen, Netherlands

**Objectives:** In male patients with classic congenital adrenal hyperplasia (CAH) due to 21 hydroxylase deficiency the presence of testicular adrenal rest tumours (TART) is the most common cause of infertility. These tumours are benign, can be detected already in childhood and have steroid producing properties. It is hypothesized that chronically elevated ACTH levels, probably already in utero and early in life are an important factor in the pathogenesis of TART in CAH males.

Aim of our study was to determine the prevalence of TART in a cohort of male non-CAH patients with chronically elevated ACTH levels due to acquired primary adrenal insufficiency later in life.

**Methods:** Male patients (>18 yr) who were regularly seen in our centre for Addison's disease (AD) and patients who underwent bilateral adrenalectomy (BA) for ACTH-dependent Cushing's syndrome, were asked to undergo testicular ultrasound examination by a single experienced radiologist with a linear transducer connected to a Toshiba Aplio500 (Toshiba, Japan) with a central frequency of 12 MHz. The study was approved by the local medical ethical committee.

**Results:** Of the 41 adult patients who were invited to participate, 17 consented to undergo testicular ultrasound (age 26-70 years): 14 patients with AD (age at diagnosis 21 - 54 yrs) and 3 patients after BA for Cushing (age at diagnosis 29.5 - 50.3 yrs). The years since diagnosis was 23 (7 - 43) in AD and 9 (2 - 12) in BA. Testicular ultrasound showed epididymal cysts in 10 out of 17 patients as well as an intra-testicular cyst in one patient. Varicocele, hydrocele and spermatocele were all observed once, in three different patients. These findings were all considered benign. TART was detected in none of the patients.

**Conclusions:** No TART was found in adult male patients with acquired primary adrenal insufficiency suggesting that TART may be a typical finding in patients who are exposed to chronically elevated ACTH from early in life or even prenatally such as in CAH patients.



### CONGENITAL ADRENAL HYPERPLASIA GENETIC RESULTS: SINGLE CENTRE EXPERIENCE

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**Objectives:** Congenital adrenal hyperplasia (CAH) is an autosomal recessive genetic disorder in which an enzyme of cortisol biosynthesis is deficient. Three clinical forms of 21-hydroxylase (21-OH) deficiency, the most common form, are the classical salt-wasting type, simple virilizing and non-classic type. Multiple different mutations are defined in the diagnosis of CAH and the relations between phenotype and genotype are shown in studies. The genotype and phenotype relation in CAH patients and the effects of mutations on clinical and laboratory parameters are investigated in this study.

**Methods:** 69 CAH patients diagnosed by clinical and laboratory evaluation were included in this study. Application complaints, clinical findings and hormonal measurements of all patients were recorded. Results from genetic analysis of whole exome sequencing were compared with phenotype and mutations from other regions of our country in order to reveal local differences.

Genetic analyses of 21 male and 48 female are evaluated. 73.9% of the patients were 21-hydroxylase deficiency, while 11-beta-hydroxylase was 2.9% and 3-beta-hydroxysteroid dehydrogenase was 1.4%. The types of 21-OH deficiency were: 27.9% classical salt-wasting type, 20.6% simple virilizing and 47.1% non-classic type. Most common detected mutations were in promoter and intron 2 regions and less commonly in exon 3, 6, 7, 10 of CYP21A2 gene.

**Results:** .

**Conclusions:** The genotype and phenotype relation in CAH is well defined. The genetic analysis of patients was compared with clinical findings and laboratory values. There were similarities shown in other studies from Turkey.

P3-103

### EFFECT OF ANASTRAZOLE ON BONE MINERAL DENSITY AND BODY COMPOSITION IN CHILDREN WITH CONGENITAL ADRENAL HYPERPLASIA

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**Objectives:** To evaluate the effect of anastrozole, an aromatase inhibitor, on bone mineral density (BMD) and body composition in patients with congenital adrenal hyperplasia (CAH).

**Methods:** In a cross-sectional fashion, 25 CAH patients treated with anastrozole (mean age  $11.3 \pm 3.0$  years, 56% males) were compared to 31 untreated CAH patients (mean age  $13.5 \pm 4.6$  years, 29% males). Participants had height and weight measurements, a pubertal exam, and a dual energy absorptiometry (DXA) scan. Total BMD and L2-L4 BMD were adjusted for height-for-age Z-scores (TBMD<sub>HAZ</sub> and L2-L4<sub>HAZ</sub>). An average hydrocortisone dose (mg/m<sup>2</sup>/day) over the past year was obtained for each patient.

**Results:** After adjustment for pubertal status, type of CAH, years on hydrocortisone, years on anastrozole, and BMI Z-score, CAH patients treated with anastrozole did not differ from untreated patients for any measures of BMD ( $p=0.64$  for total BMD, estimated effect of anastrozole  $-0.15$  [SE 0.33];  $p=0.25$  for TBMD<sub>HAZ</sub>, estimated effect of anastrozole  $-0.35$  [SE 0.30];  $p=0.74$  for L2-L4, estimated effect of anastrozole  $-0.11$  [SE 0.32]; and  $p=0.53$  for L2-L4<sub>HAZ</sub> Z-scores, estimated effect of anastrozole  $-0.21$  [SE 0.34]). Visceral adipose tissue and the android:gynoid ratio did not differ between anastrozole treated and untreated patients after adjusting for pubertal status, type of CAH, years on hydrocortisone, years on anastrozole, and BMI Z-score ( $p=0.065$  for visceral adipose tissue, estimated effect of anastrozole  $0.21$  [SE 0.11]; and  $p=0.12$  android:gynoid ratio, estimated effect of anastrozole  $0.018$  [SE 0.011]).

**Conclusions:** Anastrozole use in children with CAH does not appear to significantly impact BMD or visceral adipose tissue. This provides preliminary data supporting the safety profile of anastrozole, an adjunct therapy to improve final adult height in children with CAH and advanced bone age. More long-term safety and efficacy data with respect to height outcomes should remain a focus of study in children with CAH.

P3-104

### THE INCIDENCE AND CHARACTERISTICS OF ADRENAL CRISIS IN CHILDREN YOUNGER THAN 7 YEARS WITH 21-HYDROXYLASE DEFICIENCY: A NATIONWIDE SURVEY IN JAPAN

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**Objectives:** Adrenal crisis is a life-threatening condition for patients with adrenal insufficiency. The aim of study was to evaluate the incidence and characteristics of adrenal crisis in children with 21-hydroxylase deficiency (21-OHD) that were hitherto undescribed comprehensively in Japan.

**Methods:** The Committee on Mass Screening, Japanese Society for Pediatric Endocrinology (JSPE) conducted a nationwide survey for the Councilors of JSPE to collect detailed information regarding adrenal crisis in children younger than 7 years with 21-OHD who were admitted to hospitals from April, 2011 through March, 2016. We defined adrenal crisis as acute impairment of general health condition due to glucocorticoid deficiency and clinical improvement after glucocorticoid administration with at least two of the following features: severe fatigue, nausea or vomiting, somnolence, hypotension, hyponatremia or hyperkalemia, and hypoglycemia.

**Results:** The Councilors of JSPE in 83 institutions responded this survey (response rate, 60.1%). Data analyses of 378 patients with follow-up time of 1,101.4 person-years (PY) revealed that 67 patients (17.7%) experienced at least one episode of hospital admission for adrenal crisis. The calculated incidence of adrenal crisis was determined as 10.9 per 100 PY [95% confidence interval (CI), 9.6-12.2], which was significantly higher than the recent study of German children (N=102) (6.5 per 100 PY; 95% CI, 4.6-8.8) (Eur J Endocrinol 2016; 174: 177-186). The mean age at adrenal crisis was 2.2 years (SD, 1.7). Female to male ratio was 51.0% to 49.0%, and 96.9% of crisis events were observed in patients with salt wasting form, whereas 3.1% in those with simple virilizing form. Upper and lower airway infections (40.6%) and gastroenteritis (33.3%) were popular precipitating factors. In 59.0% of crisis events, hyponatremia, hyperkalemia, or hypoglycemia was noticed concomitantly. One patient died from intractable seizure due to severe hypoglycemia, resulting in the mortality of adrenal crisis as 0.09 per 100 PY (95% CI, 0.0-0.2).

**Conclusions:** Adrenal crisis is not rare, mostly precipitated by infections, and often accompanied by electrolyte imbalance or hypoglycemia in children under 7 years with 21-OHD. It still remains challenging to prevent adrenal crisis and to avoid unnecessary death.

**Objectives:** 17- $\alpha$ -hydroxylase / 17,20 lyase deficiency (17-OHD) is one of the rare causes of congenital adrenal hyperplasia (CAH). The classical type is associated with bi-allelic mutations in the *CYP17A1* gene located on chromosome 10q24.3 and is characterized by hypertension and varying degrees of ambiguous genitalia and pubertal delay in both genders. We aimed to identify clinical, genetic findings and follow-up and treatment of 17-OHD cases.

**Methods:** Clinical findings, genetic testing, treatment and follow-up of 6 patients diagnosed with 17-OHE, two being from the same family, were evaluated.

**Results:** The mean age at presentation was  $14.6 \pm 4.2$  (6.2-17.8) years. The mean follow-up period was  $4.7 \pm 2.7$  (1.3-8.4) years. All the patients were born to consanguineous parents and raised as female. 5 patients presented with delayed puberty and primary amenorrhea, 3 cases had ambiguous genitalia, 4 had hypertension. Some clinical and laboratory features of the patients are summarized in Table 1. Karyotype was 46, XX in 3 and 46, XY in 3 patients. ACTH and progesterone levels were high, plasma renin activity was suppressed. Diagnosis was verified by molecular analyses. 4 novel mutations and one known mutation were found. The patients were started on steroid replacement therapy. 3 patients with 46, XY karyotype underwent gonadectomy. Estrogen replacement was initiated at puberty. Breast development reached an average Tanner stage of 4-5 at  $18.7 \pm 1.8$  years. Dual energy X-ray absorptometry (DEXA) revealed osteoporosis in 5 patients, who subsequently received treatment with calcium and vitamin D. Gonadal steroid replacement and supportive therapy were found to improve bone mineral density. 3 patients were treated for hypertension.

**Conclusions:** 17-OHE, which is a rare cause of CAH, should be kept in mind in patients with ambiguous genitalia, pubertal delay and / or hypertension. Gonadectomy at the appropriate age is necessary in phenotypic females with a male karyotype. Psychological problems resulting from delayed diagnosis, sexual identity selection, hypertension and osteoporosis are the principal health problems these patients endure.

PLEASE SEE TABLE ON FOLLOWING PAGE

P3-105

#### **A RARE CAUSE OF CONGENITAL ADRENAL HYPERPLASIA: CLINICAL AND GENETIC FINDINGS AND FOLLOW-UP OF SIX PATIENTS WITH 17 HYDROXYLASE DEFICIENCY**

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**Table 1** Some clinical, laboratory, treatment and follow-up features of the cases

	Case 1 R O	Case 2* F I	Case 3* H I	Case 4 D Y	Case 5 R K	Case 6 D A
<b>PRESENTATION</b>						
Age (year)	15,3 year	14,9 year	16,7 year	16,6 year	17,8 year	6,2 year
Height SDS	-3,1		-1,7	-2,1	-0,7	0,7
Hypertension	-	+	+	+	-	+
Pubertal stage (Tanner)	1	1	1	1	2	1
Bone age	10-11 age	8 10/12 age	11 6/12 age	13 age	14 age	5 9/12 age
Target height SDS	-1,5	1,0	1,0	-1,3	-1,6	-2,0
Karyotype	46,XX	46,XX	46,XY	46,XY	46,XX	46,XY
Molecular genetic result (Homozygous)	Exon 1-6 gene deletion (novel)	p.Y601fs*29 (novel)	p.Y601fs*29 (novel)	p.Pro409Leu (novel)	p.Arg362 His	p.G436R (novel)
Gonadectomy / time (age)			+	+		+
			(17 year)	(17 year)		(7 year)
<b>FOLLOW-UP</b>						
Follow-up	4 8/12 year	1 3/12 year	4 5/12 year	7 1/12 year	2 8/12 year	8 5/12 year
BMD (DEXA) L1-L4 Z score (Examination age)	-0,46 (15,3)	-5,3 (15,8)	-3,4 (16,9)	-4 (16,7)	-3,2 (18,3)	-2,6 (11,3)
Age (year)	19,2	16,2	21	23,7	20,4	14,6
Final Height SDS	-1,89	-1,28	-0,7	0,83	-0,02	-1,51
Puberty stage (Tanner)	5, mens+	2, mens -	4, mens-	5, mens-	5, mens+	2, mens-

\*sibling

P3-106

# **DIFFERENT WAYS LEAD TO DHT, A LC-MS/MS BASED METHOD FOR ANDROSTANEDIOL, ANDROSTERONE, DIHYDROTESTOSTERONE, ANDROSTENEDIONE, TESTOSTERONE, 17-HYDROXYPROGESTERONE AND ITS APPLICATION IN A COHORT OF 21-HDROXYLASE DEFICIENCY PATIENTS**

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**Objectives:** The backdoor pathway for biosynthesis of dihydrotestosterone (DHT) is known to exist in Tammar wallabies and suggested to exist in humans as well. Recently published molecular analysis identified pathologic mutations of genes involved in the backdoor pathway which leads to undermasculinization in these patients. In addition, urine steroid profiles of patients with 21- hydroxylase deficiency (21-OHD) demonstrated that the backdoor pathway is active postnatally in these cases. Our aim was to develop an LC-MS/MS based method to determine hormones of both pathways, the classical - and the backdoor pathway to DHT.

**Methods:** We developed an LC-MS/MS method for the determination of androstanediol (Adiol), androsterone (Asterone), DHT, androstenedione (Delta4), testosterone (T), 17-hydroxyprogesterone (17OHP) for plasma and serum. We compared the steroid profiles of 16 molecular proven treatment-naïve 21-OHD patients (10 females, 6 males, aged 0-7 years) and 16 matched control subjects.

**Results:** The method was linear from 0.01 nmol/L up to 200 nmol/L. The assay requires a sample volume of 0.1 mL. The lowest limit of quantification was 0.01 nmol/L . 21-OHD

patients had significant higher concentrations for 17OHP, Delta4 (p<0.0001, respectively). We also found higher concentrations for T and DHT (p <0.0001, p=0.0001, respectively). Moreover, we found higher values for Asterone in 21-OHD (p=0.003). We found a strong correlation of asterone (r= 0.75, p=0.0005) with the functional severity according to the underlying CYP21A2 genotype.

**Conclusions:** We developed a reliable LC-MS/MS assay for an “androgen profile” representing a snapshot of six steroids covering androgen biosynthesis of the classical and the backdoor pathway. In our cohort, we could demonstrate that backdoor pathway steroids are present and in part elevated in 21OHD patients.

P3-107

# **THE P.P222Q HOMOZYGOUS MUTATION IS THE MOST COMMON CAUSE OF 3-BETA-HYDROXYSTEROID DEHYDROGENASE DEFICIENCY (3BHSD) IN ALGERIAN PATIENTS.**

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**Objectives:** To estimate the prevalence, clinical and hormonal features, genetic findings and outcomes of patients with 3β-Hydroxysteroid dehydrogenase deficiency (3βHSD) deficiency in our population.

**Methods:** Clinical and hormonal data were collected from the medical records of patients attending a single centre between 2007 and 2017. Written informed consent was obtained from patients for genetic testing.

**Results:** In our cohort of classic CAH (165 families, 190 patients), 3βHSD was diagnosed and confirmed by molecular studies in 12 patients from 9 families (8 consanguinous), rendering it the commonest cause after 21-hydroxylase deficiency (150 families, 170 patients) and before 11-hydroxylase deficiency (6 families, 8 patients). In the absence of neonatal screening for CAH, all patients presented with severe salt-wasting during the neonatal period. All males were mildly undervirilized (mean EMS score 7±1.22), while 7 of the 8 girls presented with moderate clitoromegaly at diagnosis (regression after treatment for 5 girls).

17OHPprogesterone was mildly elevated, while 17OHPpregnenolone and/or DHEA-S were elevated in all patients.

Almost all patients (8 families, 88%) were homozygous for null mutation, p.R222Q (c.665C>A) of the *HSD3B2* gene coding the type II 3βHSD isoenzyme . The two sisters of the last family were homozygous for a 12bp deletion (c.453\_464del) leading a deletion of 4 amino acids (p.T152\_Pro155del). As these amino acids are located within the characteristic catalytic Y-X-X-X-K site, this mutation should be a null mutation, hence the good genotype/phenotype correlation observed. Three of the girls

(with both mutations) had their menarche at a normal age (12 and 14 years) but with irregular menses, and they all presented unilateral large adrenal masses of undetermined origin at the age of 13, 15 and 16 years.

**Conclusions:** In Algeria, 3 $\beta$ HSD appears more frequent than in another country. The p.P222Q mutation of the *HSD3B2* gene already described in patients of Algerian or South-American origin, seems to be the most common mutation and is associated with SW. Since few data regarding puberty and fertility are available in the literature, careful follow-up of our patients is indicated to see if the HSD3B1 isoenzyme could partially replace HSD3B2 for reproductive function.

P3-108

#### PERFORMING A SECOND NEWBORN SCREEN IMPROVES DETECTION OF NEWBORNS WITH NON-CLASSICAL CONGENITAL ADRENAL HYPERPLASIA

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**Objectives:** Newborn screening (NBS) for congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD) is mandatory in the U.S. The screen is based on detection of elevated 17-hydroxyprogesterone (17-OHP) on filter paper eluates. Most states, including California (CA), perform a single screen in the first 2-3 days of life, and a few, including Texas (TX), also perform a 2nd screen between 7-14 days of life. NBS was implemented to detect classical (severe) CAH; its efficacy in detecting milder, non-classical CAH (NCAH) is less clear. Our objectives were to determine how frequently NCAH is detected by the 1st and/or 2nd NBS, and whether NBS 17-OHP levels are higher in NCAH children than in unaffected newborns.

**Methods:** This retrospective observational study was performed at two centers, Texas Children's Hospital (TX) and Children's Hospital Los Angeles (CA). NCAH youth diagnosed clinically and/or biochemically between 1995 and 2016 were included, with genetic confirmation in 48%. We recorded the original NBS 17-OHP levels in TX from testing at birth. In CA, stored NBS filter paper cards were retrieved and tested (CA Department of Public Health) to derive NBS 17-OHP levels from pre-screen era samples. Two control populations were also tested in CA: classical CAH due to 21OHD (positive controls), and unaffected newborns (negative controls) whose NBS card had an adjacent accession number to a NCAH patient. Data are expressed as mean $\pm$  SD.

**Results:** 33 NCAH youth were studied (TX 14, CA 19). 21.2% (7/33) had an abnormal NBS, all on the 2nd NBS in TX (18.8  $\pm$  8.8 days). Older NCAH youth were diagnosed at 5.5  $\pm$  2.6 y in TX and 8.2  $\pm$  3.1 y in CA. NBS 17-OHP in TX: 1st NBS

1692.0  $\pm$  631.5, 2nd NBS 3189.7  $\pm$  1506.2 ng/dl. NBS 17-OHP in CA was on a continuum depending on severity of CAH: unaffected 56.2  $\pm$  102.1, NCAH 155.3  $\pm$  152, simple-virilizing 515.5  $\pm$  406.5, and salt-wasting 7693.3  $\pm$  5366.8 ng/dl.

**Conclusions:** A 2nd screen allowed detection of NCAH in 50% of TX newborns, which could reduce morbidity related to androgen excess in patients identified at birth. NCAH was not detected by 1st screen in either state. Additional studies are needed to evaluate a potential reduction in morbidity and cost associated with a second newborn screen in NCAH.

P3-109

#### CHILDHOOD METASTATIC ADRENOCORTICAL CARCINOMA: CASE PRESENTATION

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**Objectives:** Adrenocortical carcinoma is one of the rare malign tumors of childhood. It constitutes 0.2% of childhood tumors, 1.3% of carcinoma and 6% of adrenal tumors. Most of the patients refer to hospital with hormonal disorder, for example virilization findings of cushingoid findings.

##### Methods: Case

A 2.5 years-old female patient was presented to hospital with genital puberty, weight gain and abdominal distension. Her vital findings were: fever:36<sup>0</sup>C, respiration rate:26/min, heart rate: 145 pulse/min, blood pressure:165/105 mmHg. She had abdominal distension, umbilical hernia and a palpable solid mass leading to the inguinal channel on the left. The patient had Cushingoid appearance, axillary puberty, pubic stage of three and breast stage of 1. Her laboratory results were; Na:132 (130-145) mmol/L, K:3,3 (3.5-4.5) mmol/L, Total testosterone:330 (3-10) ng/dl, LH:0.58 mIU/ml, FSH:0.56 mIU/ml, ACTH:<5 pg/ml, cortisol:37.23 (3-21) mcg/dl, DHEA-S:>1000 (5-57) mcg/dl. In abdominal magnetic resonance imaging, there was a lesion intraperitoneally spreading from left surreal location with an axial dimension of 9x8.5cm and had an heterogeneous inner structure with a craniocaudal dimension of 11 cm. There were lesions in line with nodular metastasis, the biggest of which were 2 cm in liver parenchyma and lung parenchyma in cross-sectional levels. Adrenocortical tumor was considered for the patient with these findings. Surgery was considered to remove the abdominal mass. Although it was possible to remove some of liver and lung metastases, no surgical intervention was made, considering that it wouldn't be possible to completely remove all bilateral metastases since there are many of them. The abdominal mass was removed as a whole. Pathology report was in line with surreal cortical carcinoma. The patient who had a negative general condition in the follow-ups died due to ARDS and sepsis.

**Results:** In the imagings taken during diagnosis in our case, presence of multiple abdomen and thorax metastases (stage

IV) and cortisol hypersecretion in addition to a large mass is a sign of poor prognosis.

**Conclusions:** In conclusion, better results are achieved with early diagnosis and treatment.

P3-110

#### COMBINATION OF HIRSCHSPRUNG DISEASE AND A NOVEL DEFINED MUTATION RELATED CONGENITAL ADRENAL HYPERPLASIA IN CYP21A2 GENE: CASE PRESENTATION

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**Objectives:** Adrenal deficiency is a disease occurring due to congenital or acquired pathologies of hypothalamus, hypophysis or adrenal cortex hypophysis or adrenal cortex and progressing with life-threatening crises. All congenital adrenal hyperplasia types have an autosomal recessive inheritance. 21-Hydroxylase enzyme deficiency constitutes nearly 90% of all CAH cases.

**Methods: Case:** The infant was hospitalized in newborn unit due to postnatal respiratory problem. There was a mild hyperpigmentation in the genital area in the physical examination and bilateral testicles were in scrotum and the penis length was 4.8 cm. He was taken in OG drainage since post-feeding residues were present in the follow-ups. Gaita excretion was observed after enema. Metabolic acidosis was in the blood gas of the patient whose general condition got worse on the 14th day of hospitalization and had peripheral circulation and respiration problem. The results were as the following: Na:117 mmol/L, K:7.8 mmol/L, glucose:52 mg/dl. With these findings and results, the patient was evaluated to have adrenal crisis. 200mg/m<sup>2</sup>/day hydrocortisone and fludrocortisone treatment was started for the patient after taking blood. The values were: 17-OH Progesterone:>40 ng/ml, ACTH:>1250 pg/ml, cortisol:2,8 mcg/dl, T.Testosterone:12600 (75-400) ng/ml. The results were in line with CAH 21-OH enzyme deficiency. CYP21A2 was sent for complete gene serial analysis mutation. p.L8Afs\*72 (c.19\_20insT) homozygote mutation was detected in CYP21A2 gene. Dilated bowel loops were observed in erect abdominal radiograph. Rectal biopsy was taken from the patient who had findings to consider Hirschsprung disease in colon barium graphy. Hirschsprung disease diagnosis was confirmed since no ganglion cells were observed in histochemical examination.

**Results:** CYP21A2 was sent for complete gene serial analysis mutation. p.L8Afs\*72 (c.19\_20insT) homozygote mutation was detected in CYP21A2 gene.

**Conclusions:** Combination of congenital adrenal hyperplasia and Hirschburg disease was not detected before in literature. Although the mutation detected in the patient was a mutation undefined before, it was evaluated as a cause for the disease according to Mutation Taster evaluations and due to causing frameshift.

P3-111

#### MULTI-DISCIPLINARY EVALUATION OF A 5 MONTH OLD WITH HYPERTROPHIC CARDIOMYOPATHY RELATED TO A FUNCTIONAL ADRENOCORTICAL TUMOR

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**Objectives:** Hypertrophic cardiomyopathy in childhood is a rare diagnosis. There are isolated cases in the pediatric literature reporting adrenocortical tumors associated with hypertrophic cardiomyopathy. The patient unexpectedly clinically deteriorated, and we sought to understand the factors that could have contributed to his death.

**Methods:** We present a case of a five-month-old twin who presented with severe hypertrophic cardiomyopathy, hypertension, and Cushingoid appearance. He underwent laboratory workup and imaging studies to evaluate a cause for his clinical findings.

**Results:** Initial evaluation for hypertension revealed an adrenal mass. Labs demonstrated elevated glucocorticoids, mineralocorticoids, androgens, and urine metanephrines, and further diagnostic imaging confirmed an adrenocortical tumor (ACT). During preoperative planning, he developed profound vasoconstriction followed by cardiovascular collapse requiring mechanical circulatory support. Bowel ischemia ensued, and the patient passed away before surgical resection could be performed. Pathology revealed a benign, low risk adrenocortical tumor.

**Conclusions:** While the pathology suggested an ACT that was low risk, autonomous hormone secretion elevated his overall clinical risk and contributed to cardiovascular compromise. Cortisol causes hypertension by binding to both glucocorticoid and mineralocorticoid receptors. Glucocorticoids also enhance the action of the renin angiotensin system and inhibit vasodilators, including atrial natriuretic peptide, nitric oxide, prostacyclins and prostaglandins. In the case of this infant, high glucocorticoid production may have increased sensitivity to catecholamines, thus increasing blood pressure through increased systemic vascular resistance, worsening hypertension and cardiomyopathy. Mineralocorticoids increase blood volume and blood pressure, increasing afterload, and worsening hypertrophy. Androgens directly act on cardiac myocytes, causing hypertrophy. Some studies have also suggested a genomic role of increased susceptibility to hormonal causes of hypertrophic cardiomyopathy. This unusual case underscores the role of glucocorticoids, mineralocorticoids, and androgens in the development of secondary hypertrophic cardiomyopathy.

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Table 1. Laboratory Findings.

Lab	Values	Reference Range
ACTH (pg/ml)	<5	10-60
Cortisol (mcg/dl)	103	3-23
17-OH-Progesterone (ng/dl)	219	40-200
11-DOC (ng/dl)	1200	<150
Androstenedione (ng/dl)	693	<40
DHEA-S (mcg/dl)	32	70-170
Testosterone (ng/dl)	109	<10
Testosterone, Free (ng/dl)	2.3	0.1-1
Estrogens, Total Serum (pg/ml)	33	<40
Plasma Renin Activity (ng/ml/hr)	17	1.4-7.8
Aldosterone (ng/dl)	<4	6.5-86
<b>Fractionated Free Plasma Metanephrines</b>		
Normetanephrine, Free (nmol/L)	1.3	< 0.9
Metanephrine, Free (nmol/L)	0.38	< 0.5
<b>Urine Metanephrines</b>		
24 hour Urine Metanephrine (mcg/g Cr)	513	82-418
24 hour Urine Normetanephrine (mcg/g Cr)	3993	121-946
24 hour Urine Total Metanephrine (mcg/g Cr)	4506	241-1272

P3-113

### ADRENAL CRISIS IN METASTATIC ADRENAL CORTICAL CARCINOMA IN AN INFANT WITH NEUROFIBROMATOSIS TYPE 1

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**Objectives:** Adrenal Cortical Carcinoma (ACC) is a rare malignancy, and no definite association with Neurofibromatosis type 1 (NF 1) was observed. This is to describe an infant with NF 1, presented with adrenal crisis, diagnosed to have ACC of the Left suprarenal gland with distant metastasis to the liver.

**Methods:** A case report is presented with history, examination and investigations. There is detailed description of rare association and presentation of ACC.

**Results:** An infant with numerous café au lait patches and multiple Neurofibromas, presented with cardio respiratory arrest during General anaesthesia for Fibro-optic Laryngoscopy for Stridor. The investigations revealed severe hyperkalemia, hyponatremia and hypoglycaemia. CT abdomen revealed poorly enhancing hypodense mass in the region of left adrenal gland and numerous liver metastases. The patient succumbed due to aggressive metastatic ACC.

**Conclusions:** This case indicates ACC is a rare association in NF 1 and Unilateral ACC can present with adrenal crisis, due to suppression of contra lateral non affected adrenal gland with sub-clinical hypercortisolism of the affected gland.

P3-114

### LIPID CONGENITAL ADRENAL HYPERPLASIA (LCAH) FIRST PRESENTING AT 7 MONTHS WITH ACUTE SALT-WASTING CRISIS

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**Objectives:** Seven month old female admitted with profound hyponatremia consistent with adrenal salt wasting crisis found to have previously identified *StAR* gene mutation.

Despite genetic etiology, she had no prior episodes of adrenal crisis.

**Methods:** Female infant born to consanguineous Libyan parents, admitted with decreased oral intake and significant dehydration. Labs notable for profound hyponatremia and hyperkalemia. She had no history of prior episodes but her weight gain, linear growth and development stalled at 4-5 months. No family history of adrenal insufficiency. Physical exam significant for diffuse hyperpigmentation and normal female external genitalia with no clitoromegaly. Biochemical testing and gene sequencing for *CYP11A1*, *CYP17A1*, *NR5A1*, and *StAR* were pursued.

**Results:** Evaluation revealed low cortisol, elevated ACTH, elevated renin and inappropriately normal aldosterone in

P3-112

### ASYMPTOMATIC GANGLIONEUROMA IN A GIRL WITH NOONAN SYNDROME

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**Objectives:** Ganglioneuroma is a rare, benign tumour, which arises from neural crest tissue. It occurs in adolescence and early adulthood. We describe a patient with asymptomatic, bilateral suprarenal masses detected incidentally in routine imaging. Following the surgical excision of the tumours, histology confirmed the diagnosis of Ganglioneuroma

**Methods:** A case report is presented with history, examination, investigations, and elaboration regarding deferential diagnosis, confirmation, management and follow up.

**Results:** Thirteen year old girl with congenital hypothyroidism and Noonan Syndrome was found to have bilateral suprarenal masses in her routine Ultrasound abdomen done for screening of renal anomalies. However was asymptomatic and did not have evidence of excess hormones. MRI abdomen, pelvis, chest and neck revealed right side suprarenal mass and left para-spinal lesion extending from the left renal hilum superiorly and were extending towards thoracic cavity. Surgical excision was done for the tumours and histology was suggestive of ganglioneuromas.

**Conclusions:** Ganglioneuromas are asymptomatic, hormonally inactive tumours, The association of ganglioneuroma in Noonan is not known and we report a patient with ganglioneuroma and Noonan syndrome.

setting of hyponatremia, confirming primary adrenal insufficiency (Table 1). She was started on hydrocortisone and fludrocortisone. Sodium, potassium and renin levels normalized. DHEA-S, 17-OH pregnenolone, 17-OH progesterone, and pregnenolone were undetectable. Ultrasound imaging suggested normal appearing adrenal glands and present uterus. Chromosomes revealed 46,XX karyotype. Customized next-generation sequencing revealed homozygous *StAR* gene mutation in intron 1 (c.64 + 2T > G). This variant is predicted to significantly alter RNA splicing and has been previously reported in affected Libyan siblings. Loss of function mutations of *StAR* lead to lipoid congenital adrenal hyperplasia (LCAH). Although known to be pathogenic, this variant is not included in LCAH population databases. Affected patients demonstrate both glucocorticoid and mineralocorticoid deficiency, as well as androgen deficiency affecting pubertal development.

**Conclusions:** This case provides further evidence of the same pathogenic variant in children with LCAH of Libyan descent with unique feature of late presentation at 7 months of age. This finding confirms expansion of the previously described geographic distribution of LCAH. We suggest this variant should be included in the population databases such as 1000 Genomes, Exome Aggregation Consortium, and Exome Sequencing Project.

Lab	Value	Normal Range
Sodium	109	136-145 mmol/L
Potassium	8.2	3.4-5.0 mmol/L
Cortisol, random	1.4	3.4-16.8 ug/dL
Cortisol, 60 minute	2.6	>20 ug/dL
ACTH	>1999	<=45 pg/mL
Renin	738.0	2.35-37.0 ng/mL/hr
Aldosterone	10.9	7.0-99.0 ng/dL
DHEA-S	<1	<=29 mcg/dL
Pregnenolone	<5	13-327 ng/dL
17-OH pregnenolone	<25	<=917 ng/dL
17-OH progesterone	<10.0	<=148.0 ng/dL

P3-115

**LIPOID CONGENITAL ADRENAL HYPERPLASIA IN AN ITALIAN INFANT: AN UNCOMMON CAUSE OF ADRENAL INSUFFICIENCY**

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**Objectives:** Lipoid congenital adrenal hyperplasia (CAH) (OMIM n. 201710) is the most severe form of CAH. It is characterized by severe adrenal and gonadal steroidogenesis impairment due to a defect in the conversion of cholesterol to pregnenolone. Affected infants experience salt loss, but hormonal replacement therapy enables long-term survival. Lipoid congenital adrenal hyperplasia is relatively common in

Japan and Korea but extremely rare in Caucasian populations.

**Methods:** We report a new Italian case of lipoid congenital adrenal hyperplasia, presenting during infancy with a clinical phenotype of intermediate severity.

**Results:** She was born by caesarean section at the 33rd week of gestation due to maternal gestosis and rupture of membranes, from a twin pregnancy induced by in vitro fertilization and embryo transfer. Both parents were Caucasian of Italian ancestry, healthy and nonconsanguineous. Birth weight was 1960 g (0.17 SDS), length 43 cm (-0.06 SDS). Apgar scores at the 1st and the 5th min of life were 9 and 10, respectively. She had a normal weight gain up to about 7 months old, when she was admitted to a peripheral hospital for viral gastroenteritis, with significant weight loss, dehydration and mild hyponatremia (Na 128 mEq/L). One month later, she presented a new episode of gastroenteritis. Blood tests at admission showed severe hyponatremia (Na 110 mEq/L), hypochloraemia (Cl 74 mEq/L) and hyperkalemia (K 6.3 mEq/L). In both episodes blood glucose was in the normal range (61 mg/dl and 63 mg/dl, respectively). The study of karyotype showed a normal 46,XX female. The study of the *StAR* gene revealed two genomic variants c.562C> T and c.577C> T in compound heterozygosity. At the protein level the two mutations determine the p.Arg188Cys variant (rs104894090) and p.Arg193Ter variant (rs387907235), respectively. Sanger sequencing was used to confirm the identified variants and to perform familial study. The mother carried the p.Arg188Cys variant, while the father carried the p.Arg193Ter variant.

**Conclusions:** *StAR* mutations resulting in classical lipoid CAH should be considered all over the world in the differential diagnosis of newborn babies and infants presenting with primary adrenal insufficiency.

P3-116

**HIGH GRADE VON HIPPEL-LINDAU SYNDROME PRESENTING WITH BILATERAL PHEOCHROMOCYTOMA IN A CHILD**

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**Objectives:** Pheochromocytoma is a rare neuroendocrine tumor associated with several hereditary syndromes including VHL, multiple endocrine neoplasia type 2, and neurofibromatosis. We report a patient with bilateral pheochromocytoma and the necessity for further screening.

**Methods:** The patient is a 9-year-old previously healthy male presented with hypertension, increasing BMI despite decreased height and weight, last three years. He had headaches, blurry vision, night sweats, and pubic hair. His studies showed normal BMP and TSH. An abdominal ultrasound showed bilateral suprarenal masses. An abdominal MRI confirmed the finding of bilateral adrenal masses measuring 3 x 2.7 x 2.5 cm in the right and 3.6 x 3.5 x

2.7 cm in the left. Both his plasma and 24 hour urine showed markedly elevated norepinephrine and metanephrines. His blood pressure was controlled with Amlodipine. Upon completing Texas Children's Hospital protocol for alpha and beta blockade, bilateral adrenalectomy was performed due to no clear plane between the tumor and the adrenal gland. He was discharged home 10.9 mg/msq of hydrocortisone and Fludrocortisone.

**Results:** The pathology resulted as bilateral pheochromocytoma. Based on the scoring system of Kimura, et al. the tumor was scored 4 and is considered moderately differentiated.

Genetics testing showed p.V166F, a likely pathogenic variant in the VHL gene. The parents and siblings were negative for the gene mutation thus indicating that our patient has a de novo mutation.

**Conclusions:** VHL syndrome is characterized by the development of tumors throughout the body including hemangioblastomas, renal clear cell carcinoma, and pheochromocytoma. VHL is caused by mutations in the VHL gene, a tumor suppressor gene. VHL is inherited in an autosomal dominant pattern. About 20% of patients have a de novo mutation.

This case highlights the importance of early recognition of pheochromocytomas and genetic work-up for additional malignancies associated with VHL.

P3-117

#### **METYRAPONE TREATMENT IN AN INFANT WITH NEONATAL CUSHING AND MCCUNE-ALBRIGHT SYNDROME AD REVIEW OF THE LITERATURE**

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**Objectives:** We present this case to highlight a clinical presentation and the use of metyrapone in neonatal Cushing (CS) and McCune-Albright syndrome (MAS). MAS is caused by a postzygotic activating somatic mosaic mutation of the GNAS gene, encoding the alpha-subunit of the G-protein coupled membrane receptor involved in multiple hormonal signaling pathways. CS is a rare feature of MAS.

**Methods:** Chart data was reviewed from the EMR.

**Results:** The patient was born at 36 weeks gestation. He is now a 5 month old Caucasian male, found to have an abnormal pulse oximetry at birth, followed by cardiology. He developed hypertension and tachycardia and was found to have non-compaction cardiomyopathy at 7 weeks of age. At 2 months of age, during his routine cardiology follow up he was noted to have poor weight gain and feeding and was hospitalized for failure to thrive. Pediatric endocrinology evaluation noted hyperpigmented lesions on his anterior and posterior trunk, with full cheeks, and significant hypotonia. A skeletal survey showed polyostotic fibrous dysplasia and an abdominal ultrasound showed adrenal gland enlargement. A diagnosis of MAS was based on the café-au-lait lesions and bone findings. Further testing confirmed the presence of

ACTH independent Cushing syndrome. This included an elevated random cortisol 36 mcg/dL (2-24), an elevated 24 hour urine cortisol/creatinine ratio of 1100 mcg/g (7-25), and failure to suppress cortisol levels with a paradoxical rise (cortisol =60.1mcg/dl) following a high-dose dexamethasone suppression.

Clinical and biochemical improvement occurred after 2 months of treatment with metyrapone. Patient is now 5 months old and the hypertension and cardiac function are improving. On exam his tone and weight has been improving. His repeat cortisol level is now suppressed and he is now maintained on metyrapone with close monitoring of his cortisol and growth.

**Conclusions:** MAS is a heterogenous disorder.

The skin, skeletal and cardiac manifestations supported the diagnosis of neonatal CS and MAS. We hypothesize the cardiac involvement is due to an activating GNAS mutation in the cardiac muscle. Treatment with metyrapone has been useful in this case. Follow up of his cardiac manifestation and response to medical treatment will be essential as it may impact screenings for MAS.

P3-118

#### **CO-EXISTENCE OF PRIMARY CORTISOL DEFICIENCY AND GROWTH HORMONE DEFICIENCY IN AN INFANT WITH NEONATAL HYPOGLYCEMIA: COINCIDENCE OR CONSEQUENCE?**

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**Objectives:** Cortisol and growth hormone (GH) deficiencies are causes of neonatal hypoglycemia. When they coexist, a pituitary disorder is suspected. We present an infant with hypoglycemia in whom an ACTH receptor defect was associated with transient GH deficiency.

**Methods:** .

**Results:** Patient: A full term, AGA, African boy born to consanguineous parents presented with hypoglycemia (18 mg/dl) at 4 hours of life with undetectable serum cortisol (less than 1 ug/dl). On exam, he was diffusely hyperpigmented with normal male genitalia. Electrolytes were normal. GH concentration of 7.48 ng/ml (day 2-5: 33.5 +/- 4.2) during hypoglycemia and a peak GH level of 4 ng/ml with glucagon stimulation were consistent with GH deficiency. Thyroid function, prolactin and gonadotropins were normal. Serum cortisol remained undetectable with ACTH stimulation whereas endogenous ACTH was elevated at 4868 pg/ml (5– 46 pg/ml). Pituitary was normal on MRI. On physiologic hydrocortisone (HC) doses, blood glucose normalized but he then developed cholestasis at 3 weeks, so HC dose was increased to 50 mg/m2. At 7 weeks, ACTH declined to 300 pg/ml with resolution of cholestasis. GH therapy was not initiated given improvement in liver function



and maintenance of euglycemia. An ACTH receptor defect was suspected and molecular genetic testing revealed homozygosity for a known c.634del mutation of the Melanocortin 2 Receptor (MC2R) gene coding for the ACTH receptor. At 12 weeks, a random GH level was normal (10 ng/ml).

**Conclusions:** To our knowledge, this is the first report of cortisol deficiency owing to MC2R mutation associated with GH deficiency. We observed adequate GH secretion with HC replacement. A similar constellation of congenital cortisol deficiency and transient GH deficiency was reported in a patient with ACTH receptor deficiency and another with ACTH deficiency (JCEM, Sept 2011, 96(9):2670–2674). The authors hypothesized that physiologic glucocorticoid levels are required for the development and function of somatotrophs during fetal development and infancy. Our case is consistent with this hypothesis. We postulated corticotroph hypertrophy obstructing somatotroph function and its recovery with HC. Further studies are needed to elucidate this relationship.

P3-119

#### **GONADOTROPIN INDEPENDENT PRECOCIOUS PUBERTY AND ADRENAL INSUFFICIENCY: ATYPICAL CLINICAL PRESENTATION FOR TWO RARE GENETIC DISEASES**

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**Objectives:** Mutations of NR0B1 (DAX1) and CYP11B1 genes cause two rare diseases, both characterized by adrenal insufficiency. NR0B1 gene mutations typically determine congenital adrenal hypoplasia and hypogonadotropic hypogonadism; CYP11B1 gene mutations determine congenital adrenal hyperplasia, due to reduced or absent activity of 11 $\beta$ -hydroxylase enzyme, characterized by ambiguous genitalia, accelerated skeletal maturation, peripheral precocious puberty and hyporeninemic hypokalemic hypertension. We describe two patients with two different rare diseases presenting with the same atypical clinical manifestations.

**Methods:** Both patients presented with gonadotropin independent precocious puberty, with high levels of testosterone and advanced bone age, at the age of 1.7 and 2.9 years, respectively. Thereafter, they developed adrenal insufficiency presenting with adrenal crisis at the age of 5.9 and 3.0, respectively, and started treatment with hydrocortisone (HC). Parents of patient 2 were consanguineous. Molecular analysis of CYP21A2, HSD3B2, CYP11B1 and NR0B1 genes were performed in both patients and resulted normal. Measurement of VLCFA was also normal in both patients. Then, a panel of genes involved in disorders

of sex development (DSD) was studied with next generation sequencing (NGS).

**Results:** Testosterone concentrations returned to normal during HC treatment. In patient 1 we identified an hemizygous variant in the NR0B1 gene, c.1091T>G (p.Phe364Cys). The variant segregated from the mother and has not been reported so far. Pathogenicity prediction software define this variant as probably damaging. Molecular modelling confirmed its deleterious effect. Patient 2 had a previously unknown homozygous variant in CYP11B1 gene, c.1121+5G>A, that might affect the splicing mechanism.

**Conclusions:** NGS allowed the identification of the genetic variants associated with the disease. Sequencing of a large number of DSD genes permits characterization of particular clinical cases, like in this study, with the same clinical phenotype but with different molecular defects.

P3-120

#### **X-LINKED ADRENAL HYPOPLASIA CONGENITA WITH CHOLELITHIASIS AND ATYPICAL BIOCHEMICAL RESULTS**

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**Background:** X-linked adrenal hypoplasia congenita (X-linked AHC) caused by mutation in NR0B1, presents commonly in infancy with symptoms and signs of adrenal insufficiency.

**Methods:** N/A

**Results:** Case

A male infant born at term to healthy, non-consanguineous parents was admitted to hospital at 4 weeks of age for failure to thrive. On exam he had mild skin hyperpigmentation and normal male genitalia. Mother reported borderline low estradiol level on pre-natal screen. Newborn screening was negative.

Investigations revealed: hyponatremia (Na<sup>+</sup> nadir 125 mmol/L), hyperkalemia (K<sup>+</sup> peak 6.4 mmol/L), unconjugated hyperbilirubinemia and transaminitis. Abdominal ultrasound showed cholelithiasis with non-visualization of adrenal glands. Subsequent investigations included: baseline cortisol 232 nmol/L, ACTH 94 pmol/L, renin activity 104.9 (<14 ng/L/s), ACTH stimulated peak cortisol 323 nmol/L, 17-OHP 4.2 (3.2-22 nmol/L), 11-deoxycortisol 99.1 (< 4.5 nmol/L), DHEAS 0.4 (0.1-8.7  $\mu$ mol/L), and total testosterone 4.2 (0.3-9.9 nmol/L). At 5.5 weeks of age, he was started on hydrocortisone, fludrocortisone and sodium chloride. Feeding and weight gain improved. Repeat abdominal ultrasound at 8 weeks of age showed cholelithiasis had resolved. Bilateral adrenal glands were visualized but small. By 9 weeks of age, liver enzymes normalized. Molecular testing confirmed he was hemizygous in the NR0B1 gene for a missense mutation (p.Leu262Pro) previously described in two other patients presenting with typical signs of adrenal insufficiency.

**Conclusions:** This case demonstrates the phenotypic heterogeneity of the condition, even in those with the same genotype. Our case also highlights the following: isolated cortisol deficiency may be a rare cause of neonatal

cholestasis, low maternal estriol should raise concern for adrenal insufficiency if fetal karyotype is normal, and elevated 11-deoxycortisol level seen usually in 11 $\beta$ -hydroxylase deficiency, could also raise concern for X-linked AHC.

P3-121

#### **CHANGES IN CORTISOL KINETICS FOLLOWING BARIATRIC SURGERY IN A PATIENT WITH CLASSIC CONGENITAL ADRENAL HYPERPLASIA AND MORBID OBESITY**

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**Background:** Management of adult patients with classic congenital adrenal hyperplasia (CAH) is challenging and often complicated by obesity, metabolic syndrome and adverse cardiovascular risk. Alterations in weight can influence cortisol pharmacokinetics (PK). A 19 y/o female with classic CAH and morbid obesity suffered from persistent elevations of androgen levels while on oral glucocorticoid therapy. Improved control of adrenal androgens was achieved with continuous subcutaneous hydrocortisone infusion (CSHI) therapy, but obesity-related comorbidities persisted. The patient underwent sleeve gastrectomy, and experienced dramatic weight loss with improvement in insulin sensitivity and fatty liver in the post-bariatric period.

**Objective:** Evaluate changes in hydrocortisone PK pre- and post-bariatric surgery.

**Methods:** Cortisol clearance studies were performed to evaluate changes in hydrocortisone dose requirements and abdominal MRI with magnetic resonance spectroscopy (MRS) was performed to quantify liver fat. Clearance studies were performed 9 months pre-surgery, and at 9 and 15 months post-surgery. Liver MRS was performed 9 months pre-surgery on prednisone (pre-CSHI therapy initiation), 3 months pre-surgery (on CSHI therapy) and 9 months post-surgery.

**Results:** Patient's BMI dropped from 52.6 kg/m<sup>2</sup> pre-surgery to 27.1 kg/m<sup>2</sup> 15 months post-surgery. Cortisol clearance study performed 15 months post-surgery showed marked alterations with a 27% decrease in volume of distribution, a 74% increase in the area-under-the-curve and a 43% decrease in clearance as compared to pre-surgery cortisol PK measures. Hydrocortisone dose requirements subsequently decreased by 34% 15 months post-surgery. Effective control

of androgen excess was achieved on this lower hydrocortisone dose. Improvement in insulin resistance was also observed and liver fat decreased from 32% pre-surgery to 5.3% 9 months post-surgery.

**Conclusions:** This case highlights the impact of obesity-related comorbidities on glucocorticoid PK, which, in turn, affects the clinical management of CAH. Bariatric surgery was a safe and effective treatment for obesity in this patient with CAH and should be considered for patients with CAH and multiple obesity-related co-morbidities.

P3-122

#### **XP21 DELETION SYNDROME IN A BOY WITH MENTAL RETARDATION: DELAYED DIAGNOSIS OF DUCHENE MUSCLE DYSTROPHY AND CONGENITAL ADRENAL INSUFFICIENCY**

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**Objectives:** Xp21 contiguous deletion syndrome is a rare inherited disorder characterized by Duchene muscle dystrophy (DMD), congenital adrenal hypoplasia (NROB1), glycerol kinase deficiency (GK) and mental retardation. About 100 patients with this syndrome have been described to date. We report a case of delayed diagnosis of adrenal insufficiency and Duchene muscle dystrophy.

**Methods:** Urine glycerol was measured by gas chromatography-mass spectrometry.

**Results:** The boy was born at term from non-consanguineous parents with normal length and weight, and had unilateral cryptorchidism. He developed seizures at the age of 18 days. Liver enzymes were permanently elevated (150-200 U/l) suggestive for chronic hepatitis, viral hepatitis was excluded. The boy had psychomotor development delay since birth, nausea and muscle weakness, and he was misdiagnosed with infantile cerebral paralysis. At the age of three the boy manifested with severe vomiting, unconsciousness and mild pigmentation. High ACTH (380 pg/ml), hyperpotassemia (6.3 mmol/l), hyponatremia (129 mmol/l) proved adrenal insufficiency, and glucocorticoids and mineralocorticoid treatment was initiated with partial effect. He stopped vomiting but muscle weakness has progressed. He was admitted to our clinic at six yrs of age. At the examination we observed protruding ears, micrognathia, small distance between eyes, gait abnormality, severe muscle weakness and hypertrophy of calf muscles. Duchene muscle dystrophy was suspected. High levels of transaminases (AST 154 U/l, ALT 218 U/l), lactic dehydrogenase (811 U/l), creatinine phosphokinase (21725 U/l) and tricylglycerols (5.29 mmol/l)

were found. High levels of glycerol in urine indicated glycerol kinase deficiency. Taking into account association of primary adrenal insufficiency, progressive muscle dystrophy, mental development delay, glycerol kinase deficiency Xp21 deletion was suspected. Microarray analysis showed hemizygous Xp21.3p21.1(27242551\_32110378) deletion. The mother had the same gene deletion but no clinical symptoms.

**Conclusions:** Xp21 deletion should be suspected in male with mental retardation and severe muscle weakness. Congenital adrenal hypoplasia could be underdiagnosed in infancy. Urine glycerol measurements is a simple and valuable diagnostic method for glycerol kinase deficiency.

P3-123

#### **A NOVEL HOMOZYGOUS NONSENSE MUTATION IN THE HSD3B2 GENE IN AN APPARENT NON-CONSANGUINEOUS PATIENT OF ROMA DESCENT**

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**Objectives:** Two isoforms of 3 $\beta$ -hydroxysteroid dehydrogenase (3 $\beta$ HSD) have been reported and its deficiency, caused by recessive loss-of-function mutations, is a rare cause of congenital adrenal hyperplasia (CAH).

**Methods:** We report a 8.5 yr old 46,XY Roma boy born to non-consanguineous parents presenting with marked premature pubarche. After birth (term, 3720g) it was noticed that he had ambiguous genitalia (scrotal hypospadias, bifid scrotum, palpable gonads in the inguinal canal bilaterally). At the age of 15 days he was admitted with salt wasting crisis, diagnosed with CAH and replacement treatment was initiated (hydrocortisone and fludrocortisone). The patient did not show up for regular follow ups. At the age of 5 years he was admitted again with salt wasting crisis due to his low hydrocortisone dose, bilateral gynecomastia and pubarche (Tanner stage: G1P2A1, 1-2ml testicles in the inguinal canal). Again the patient did not show up for regular controls until a year ago. His bone age was by 4yrs ahead but he was prepubertal (Tanner stage: G1P3A2, 2ml testicles in the inguinal canal) and had very high testosterone and DHEA levels.

**Results:** A GC-MS urinary steroid profile showed the typical constellation of 3 $\beta$ HSD deficiency with excessive amounts of 5-ene unsaturated steroids (e.g. DHEA) and markedly reduced excretion of cortisol metabolites. Direct sequencing of HSD3B2 gene identified in homozygosity the novel p.Lys36Ter

nonsense mutation. This mutation, results in a premature stop codon in the transcribed mRNA, and hence in the production of a truncated or incomplete protein which is non-functional or has very little function. Furthermore, this patient was found to be heterozygous for p.Val281Leu in the CYP21A2 gene. Both parents of the patient were identified as carriers of the p.Lys36Ter.

**Conclusions:** GC-MS urinary steroid metabolome analysis presents an excellent non-invasive and non-selective means in the delineation of disorders in steroid metabolism. A novel nonsense p.Lys36Ter mutation in the HSD3B2 gene was identified in a patient with hypospadias of Roma descent. A multidisciplinary approach is highly recommended in solving most complex disorders such as DSD.

P3-124

#### **ADRENAL INSUFFICIENCY DUE TO COMBINED INHALED CORTICOSTEROID AND AZOLE AGENT**

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**Objectives:** Make prescribers aware that the combination between azole agents and medium dose inhaled corticosteroids may result in exogenous hypercortisolism and adrenal suppression (AS) increasing the risk of life-threatening adrenal crisis.

**Methods:** 9 year 10 month old F with history of Job syndrome and multiple complications including coccidiomycosis meningitis and cavitary lung lesions who was on chronic fluticasone; an inhaled corticosteroid (ICS) for several years. She had also been on antifungal therapy with fluconazole which was switched to posaconazole 200mg daily due to multiple side effects.

**Results:** Her initial endocrine visit was for evaluation of low bone mineral density (BMD) after suffering a pathological right distal femur fracture. A DEXA scan showed a Z score of -4.9 at the spine, consistent with osteoporosis. A few months later, the patient complained of fatigue, "puffiness" of the face, and hair loss. A morning cortisol was <0.3mcg/dl. A low dose ACTH stimulation test was performed showing values for baseline, 30 and 60 minutes post-cosyntropin less than 1mcg/dL.

She was started on hydrocortisone replacement (~9mg/m<sup>2</sup>/day), which was slowly weaned over a 7-month period and fluticasone was also completely discontinued over that same period. After the wean, the patient underwent a second low dose ACTH stimulation test that showed a cortisol peak response of 21.8 mcg/dL. In addition, Cushingoid features resolved and growth velocity normalized to 6 cm/year annualized (up from 3 cm/year while on the combined ICS and azole treatment).

**Conclusions:** Our patient developed Cushingoid features, growth failure, diminished BMD, and adrenal insufficiency as

a result of the interaction between ICS and an azole agent. These symptoms resolved after discontinuation of ICS which allowed recovery of her adrenal function. It is important to recognize that this combination of medications can result in exogenous hypercortisolism and adrenal suppression (AS).

P3-125

#### IATROGENIC CUSHING'S SYNDROME CAUSED BY OCULAR GLUCOCORTICOIDS IN AN INFANT WITH SALT-WASTING CONGENITAL ADRENAL HYPERPLASIA

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**Objectives:** Iatrogenic Cushing's syndrome is a well-known complication of oral and parenteral corticosteroid therapy whereas glucocorticoid-containing eye drops as a cause have rarely been reported. We observed a girl with congenital adrenal hyperplasia (CAH) who developed Cushing's syndrome after repeated treatment with dexamethasone-containing eye drops during early infancy.

**Methods:** Retrospective chart review

**Results:** Salt wasting CAH (I2A/con) was diagnosed neonatal because of a positive 17-OHP newborn screening and ambiguous genitalia (Prader score 4).

Therapy with hydrocortisone (25mg/sqm), fludrocortisone and salt was initiated. According to suppressed androgen and renin levels, therapy was subsequently weaned down to 15mg/sqm of hydrocortisone and 0,05mg of fludrocortisone per day. During the first 6 months, growth remained normal (50th pc) but weight increased above the 97th pc. In addition, she gradually developed a cushingoid facies. As came to light retrospectively, the girl had been prescribed repeated courses of dexamethasone-/gentamycin-containing eye drops (0,7mg of dexamethasone per day) because of recurrent conjunctivitis due to nasolacrimal duct obstruction. Together with ongoing hydrocortisone treatment, she had received a daily equivalent dose of 65-70mg/sqm of hydrocortisone over almost 6 weeks. Concomitantly, height subsequently dropped to the 3rd pc and blood pressure rose above the 97th pc, necessitating transient antihypertensive therapy (atenolol) for 6 months. By the age of 21 months, the girl's growth velocity had normalized and the Cushing facies disappeared. ACTH was still undetectable pointing to persistent secondary adrenal insufficiency that had not resolved so far.

**Conclusions:** Our rare case of an infant with CAH and a secondary iatrogenic Cushing's syndrome due to repeated use of dexamethasone-containing eye drops illustrates the need to be aware of substantial systemic side effects caused by topical steroids.

P3-126

#### THERAPEUTIC OBJECTIVES OF EPLERENONE TREATMENT IN APPARENT MINERALOCORTICOID EXCESS SYNDROME

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**Background:** Eplerenone selective binds to the mineralocorticoid receptor (MR), with minimum binding capacity to androgen receptors. Its effects had not been studied in hypertensive patients less than 4 years old. Apparent Mineralocorticoids Excess syndrome (AME) is due to a decrease 11 $\beta$ -hydroxysteroid dehydrogenase type 2 activity allowing cortisol to bind MR, generating hypertension, nephrocalcinosis, hypokalemia and high plasma cortisol/cortisone relation (F/E).

**Objective:** We report 2 cases with AME syndrome treated with Eplerenone.

**Methods:** N/A

**Results:** Case 1: A 5 year 3-month-old boy derivated for hypertension study. Full term newborn adequate for gestational age. First son of non-consanguineous parents. He has bilateral nephrocalcinosis. Aldosterone: 1.02 ng/dL (reference value (RV): 5-80) and PRA: 11BHSD2 molecular study in process. Eplerenone 50 mg started at 5 years 11-months, in association with hidrocolotiazide/triamterene. Normalized blood pressure was observed 1 month later, and oral potassium was finished 2 months later. His PRA suppression persists.

Case 2: A 2-year old girl with severe hypertension. Full term newborn, small for gestational age. Second daughter of normotensive parents who are first degree cousins. She has bilateral nephrocalcinosis, high urine calcium/creatinine index. Aldosterone: <1ng/dL and PRA:<0,2 ng/mL/hr ACTH: 33 pg/ml F/E relation: 175,5. Molecular study shows a pathological variance in 11BHSD2: R213C on exon 3. Eplerenone began at 2 years 3 months. Dose adjusted to 25 mg. Potassium levels were normalized 1 month after starting treatment. A decrease from 4 to 3 antihypertensive drugs was achieved.

In both cases, no adverse effects were observed.

**Conclusions:** Eplerenone dose in AME should be titrated based on the response of plasma electrolytes, PRA and blood pressure. Objectives of treatment are: achieving normokalemia and normotension, normalize PRA, avoid renal damage due to hypercalciuria, maintain adequate growth and development, and avoid other adverse effects. For hypertension management, monotherapy with eplerenone may not be sufficient and requires the addition of more antihypertensives.

### IATROGENIC CUSHING SYNDROME: A CASE OF ERRONEOUS COMPOUNDING OF HYDROCORTISONE

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**Objectives:** A 20-month-old girl with classic salt wasting congenital adrenal hyperplasia (CAH) had iatrogenic Cushing syndrome as a result of erroneously compounded hydrocortisone.

**Methods:** Chart review and liquid chromatography coupled with tandem mass spectrometry for steroid analysis.

**Results:** Case Report: The diagnosis of 21-hydroxylase deficiency CAH was suspected due to atypical genitalia, confirmed by hormone tests and genotype. Treatment began on DOL #2 with hydrocortisone 2.5 mg tid (~31mg/m<sup>2</sup>/day), fludrocortisone 0.1 mg bid, and sodium chloride 250 mg qid. Serum 17- hydroxyprogesterone, testosterone, androstenedione and plasma renin activity were measured and medications were tapered. By 6 weeks, hydrocortisone total daily dose was 5 mg qd, 17.8 mg/m<sup>2</sup>/day, as crushed, weighed tablets prepared by a compounding pharmacy. The infant's length had been 90% for the first months of life. Growth deceleration began after 6 months, such that by 15 months length was ~1% with excessive weight for length (90%). Examination showed irritability, increased facial fat and excess body hair. At a hydrocortisone dose of 1 mg three times daily (7.5 mg/m<sup>2</sup>/day), her adrenal profile showed persistent suppression of all analytes. Tumor markers and imaging for an androgen or cortisol-producing adrenal tumor were negative. Due to strong suspicion of iatrogenic Cushing Syndrome the prescribed hydrocortisone capsules were analyzed by the Sports Medicine Research & Testing Laboratory in Salt Lake City, Utah. Liquid chromatography coupled with tandem mass spectrometry revealed that each hydrocortisone capsule contained 5 to 10 times what was indicated on the label, thus delivering a supra-physiologic dose of hydrocortisone. No anabolic steroids were detected. Once compounded hydrocortisone was substituted from another pharmacy, the child's growth rate improved, and Cushingoid features gradually began to resolve. This case has been reported to the FDA.

**Conclusions:** Infants with CAH require small hydrocortisone doses unavailable as standard tablets. Clinicians frequently prescribe crushed, weighed packets or capsules from compounding pharmacies. Providers should be alert to errors in medications evidenced by signs of glucocorticoid excess.

### AUTOIMMUNE POLYENDOCRINE SYNDROME TYPE II (APS-II) IN A 9 YEAR OLD BOY PRESENTING WITH HYPONATRAEMIC ENCEPHALOPATHY

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**Objectives:** Presenting a rare and dramatic manifestation of APS-II in a young boy with neurological complications due to severe hyponatraemia and highlighting the importance of differential diagnosis and management to optimize the neurological outcome.

**Methods:** Case report

**Results:** A previously healthy 9 year old boy presented after a generalized seizure at home and continuing impaired consciousness. He had been unwell for 2 weeks with lethargy, muscle ache after exercise, unsteady gait and eventually vomiting. On arrival he was still unresponsive to pain with an increased muscle tone. Further physical examination including skin was unremarkable but he had tachycardia (140 bpm) and a blood pressure of 129/40 mmHG. His blood sugar level was 117 mg/dl. Anti-epileptic treatment proved ineffective. An emergency cranial MRI scan was normal. A blood test revealed a severe hyponatraemia of 107 mmol/l (134-145 mmol/l) and a potassium of 6,8 mmol/l (3,5-5,5 mmol/l). Full blood count, renal and liver function tests were within normal limits. In view of these results he was given boluses of 3% saline aiming for a rapid rise of serum sodium (10-12 mmol/l in the first 24 hours) and hydrocortisone. He needed intubation and ventilation over 12 hours. His conscious level remained impaired until his sodium levels returned to near normal on day 3. An EEG during this period had nonspecific changes. Subsequent investigations showed an inappropriate low normal aldosterone with a markedly elevated renin, a very high ACTH and positive anti-adrenal antibodies confirming the suspected diagnosis of Addison's disease. In addition he was found to have anti-thyroid antibodies fulfilling the criteria for Schmidt's syndrome. The boy made a good recovery without obvious neurological sequelae. He was continued on hydrocortisone and fludrocortisone replacement therapy. Interestingly the boy's grandmother was said to have died of hyponatraemia in her eighties.

**Conclusions:** APS-II can occur in non-diabetic prepubescent boys. Hyponatraemic encephalopathy is a very serious complication demanding a careful management. A recovery with intact neurological outcome is possible.

### ALLGROVE SYNDROME : A CASE SERIES

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**Objectives:** Allgrove syndrome (AAA) is characterized by three specific features: alacrima, achalasia and adrenal insufficiency with mutations in AAAS gene (12q13) that codes for ALADIN protein. It may also be called 4A syndrome because of the presence of autonomic disturbances associated with the original three characteristics. The alacrima is the earliest though the most neglected symptom, and the achalasia and adrenal insufficiency develop over the first two decades. 60% of patients develop progressive neurologic symptoms.

**Methods:** We report herein four cases of Allgrove syndrome being treated at Sir Ganga Ram Hospital, a tertiary care hospital in Northern India.

Cases are summarized as follows:

Case 1: 3.5y/male born of consanguineous marriage presented with multiple episodes of hypoglycemic seizures, hyperpigmentation, absent tears and developmental delay. Younger sibling died at 2year6months of age unexpectedly. By whole exome sequencing, homozygous variant in the AAAS gene, c.889\_901delinsTCT (p.Ser300\_Leu546delinsIle) was detected.

Case 2: 12.25y/female born of consanguineous marriage with dysphagia since birth, hyperpigmentation and inability to walk. Younger sibling died at 7years of age due to adrenal crisis. Molecular genetic analysis for AAAS gene was homozygous for c.762delC (p.Ser255Valfs35) in exon 8.

Case 3: 1.6y/female born of consanguineous marriage presented with dysphagia, hyperpigmentation, hypotension, hyponatremia and delayed milestones. CT chest revealed achalasia cardia, Heller's myotomy was done at 4.5y of age.

Case 4: 8y/male born of non consanguineous marriage presented with hyperpigmentation, hypoglycemic seizures, alacrima. Child was operated for achalasia cardia at 14years of age. Elder sibling 13y/ male was operated for achalasia cardia & had absent tears, however no symptoms of adrenal insufficiency have appeared till date.

**Results:** Genetic testing done in two patients.

**Conclusions:** AAA, though rare, should be kept in mind while evaluating a child with adrenal insufficiency. A family history of early unexplained infant deaths and familial consanguinity provides important clues. Evaluate siblings for early signs, particularly alacrimia because this defect is frequently present from birth.

P3-131

### LOW LEVEL SUPPRESSION OF HPA AXIS FROM CICLESONIDE

*Jaime Haidet , MD, Akron Children's Hospital, Northeast Ohio Medical University, Akron, OH, United States; Luigi Garibaldi,*

*MD, Children's Hospital of UPMC, Pittsburgh, PA, United States*

**Objectives:** Background: Inhaled corticosteroids (ICS) are routinely used as effective medical therapy for chronic respiratory illnesses. Hypothalamic pituitary adrenal (HPA) axis suppression is possible with ICS. ICS formulations have differing pharmacodynamics and pharmacokinetics. Newer ICS molecules such as ciclesonide may be more beneficial in reducing systemic complications and some studies have concluded ciclesonide does not affect HPA axis function. One would anticipate ciclesonide to have clinical effect at the lungs with lower systemic effect given it is converted to a metabolite that has high first-pass metabolism rate, is highly protein bound, and is rapidly cleared. Experience with ciclesonide is not as widespread nor as long standing as other inhaled corticosteroids, thus its unknown if the anticipated lower systemic effect will hold true.

**Methods:** Methods: N/A

**Results:** Clinical case: 4 yo with asthma was referred to endocrinology for cushingoid features. These signs and symptoms became evident after starting ICS (fluticasone). Her 24hour urinary free cortisol was undetectable. She underwent high dose ACTH stimulation testing with undetectable ACTH and cortisol levels at baseline and low cortisol at 60 minutes. Adrenal insufficiency (AI) was suspected secondary to her ICS. Her ICS was changed to ciclesonide at which time she started oral hydrocortisone (HC) which was gradually weaned off. After being off maintenance HC for 17months, she passed a high dose ACTH stimulation test. She continued to have evidence of AI with illness requiring stress dosing thus a low dose ACTH stimulation test was subsequently pursued. She had a low dose ACTH stimulation test 23 months after being off maintenance HC indicating low level suppression, thus she remained on stress dosing. Her asthma was doing well and she eventually stopped taking ciclesonide. About 18 months after stopping ciclesonide, she had low dose ACTH stimulation test which she passed. She no longer had evidence of AI with illness without stress dosing.

**Conclusions:** Newer ICS molecules such as ciclesonide may be more beneficial in reducing systemic complications but low level suppression of the HPA axis may be seen in some individuals.

P3-132

### VIRILIZING ADRENAL ADENOMA IN A TEN YEAR OLD GIRL

*Juyoung Yoon, MD, Gyeongsang National University Changwon Hospital, Changwon, Korea, Republic Of*

**Objectives:** A 10 year old girl suffered from hirsutism, voice deepening, and acne. These symptoms started 1 year before she visited our clinic. At physical exam she had severe hirsutism (25 points by Ferriman-Gallaway score), and showed no breast budding.

Laboratory exam was as follows: DHEA-S >1000 µg/dL, testosterone >15 ng/mL, 17 OHP 3.86 ng/mL. Abdominal CT

revealed about 9x8.5x8.9cm sized mass at right adrenal gland with heterogeneous enhancement. Surgery was performed and the right adrenal gland was excised. The histopathologic report was consistent with a benign cortical adenoma. Six months after surgery, the patient's virilizing signs regressed and she had menarche. Her DHEA-S level dropped to normal range (52.5 µg/dL). Follow-up CT showed no residual tumor. Adrenal cortical neoplasm can manifest as virilization in females. Virilization can impair their quality of life. And although most of childhood adrenal cortical neoplasm is benign adenoma, malignant adrenal cortical neoplasm can occur. Therefore, adrenal neoplasm should be suspected in girls with excessive virilization

**Methods:** .

**Results:** .

**Conclusions:** .

## POSTER SESSION 3

**Saturday, September 16, 2017, 12:00-1:00pm**

### **P3 - Bone and mineral metabolism**

#### **P3-200 – P3-238**

P3-200

#### **THE BONE METABOLISM IN PEDIATRIC PATIENTS WITH CEREBRAL PALSY**

*Giorgiana f Brad, MD; Tamara Marcovici, MD; Oana Belei, MD; Raluca Tamasanu, MD; Teofana Bizerea, MD; Niculina Mang, MD; Ioana Bota, MD; Otilia Margineanu, Assist. Prof., University of Medicine and Pharmacy, "Victor Babes", Timisoara, Timisoara, Romania*

**Objectives:** Evaluation of the bone metabolism in patients with cerebral palsy (CP) and their response to the prescribed treatment.

**Methods:** Patients (0-18years old) with CP hospitalized in the 1<sup>st</sup> Pediatric Clinic of Children Hospital, Timisoara were studied between January 2012 and December 2016. They were evaluated anthropometric (weight, height, BMI), clinical (including Tanner stage), biological (in serum and urine phospho-calcium metabolism, serum levels of 25OH vitamin D, intact PTH and bone remodeling markers), and imagistic (DXA and X-rays).

**Results:** The studied sample consisted in 16 patients (7.1±1.9 years old) diagnosed with CP (37.5% male). 75% of patients were underweight, 50% had short stature and the majority was stage II-IV Tanner. Clinically, dental dystrophy (81.25 %), kyphoscoliosis (80%), and fragility fractures (86.66%) were found. They had chronic epilepsy treatment with more than two anticonvulsants (68.75%) and deglutition disorders (56.25%). Vitamin D deficiency associated with secondary hyperparathyroidism (87.5%), hypophosphatemic rickets (6.25%) and osteoporosis (56.25%, mean z-score= -2.2) were diagnosed, for which bisphosphonates, calcium and vitamin D were prescribed. There was a trend in time of normalization of the biological parameters, with the decreasing of the bone

remodeling markers and z-score, with the reducing of pain and the number of fractures.

**Conclusions:** The bone metabolism abnormalities in patients with CP are secondary to many causes. 2. The treatment with bisphosphonates, calcium and vitamin D is very important in these patients with great beneficial, increasing the quality of life of these patients.

P3-201

#### **UNEXPLAINED FRACTURES IN INFANTS AND YOUNG CHILDREN: (IR)RELEVANCE OF SERUM VITAMIN D**

*Jaya Sujatha Gopal-Kothandapani, MRCPCH, University of Sheffield, Sheffield, United Kingdom; Elaine Pang, MBBS, Sheffield Medical School, Sheffield, United Kingdom; Alan Sprigg, FRCR, Sheffield Children's Hospital, Sheffield, United Kingdom; Amaka C Offiah, PhD, University of Sheffield, Sheffield, United Kingdom*

**Objectives:** To test the hypothesis that in the absence of rachitic features on radiographs, vitamin D insufficiency increases fracture risk in children younger than two years of age.

**Methods:**

A retrospective single centre study. The hospital database was interrogated for children ≤2years who had serum 25OHD measured between 01/01/10 and 12/31/14 AND at least 1 skeletal radiograph within 2 weeks of this. Blinded to 25OHD levels, 2 observers independently scored the anonymised full skeletal surveys (SS) and individual radiographs (XR) for fracture (yes/no), bone density (reduced/normal) and rickets (Thacher score 0/≥1). Discrepancies were arbitrated by a third observer in a final consensus read. Analyses (SPSS V22.0 for Mac, p ≤ 0.05) included descriptive statistics (prevalence of clinical and radiographic parameters), Cohen's kappa (interobserver reliability for radiographic parameters) and binomial logistic regression (likelihood of fracture based on 25OHD levels, bone density or Thacher score). Research and Development approval was granted; Ethics Committee approval was waived.

**Results:** 388 children, mean age 9 months (0-24) and 184 (47%) full skeletal surveys were included. Mean 25OHD was 67nmol/L (<6-778nmol/L); 77 children (20%) were Vitamin D deficient (≤25nmol/L); 78 (20%) insufficient (25.1-50nmol/L); 69 (18%) had at least one fracture; 39 (10%) reduced bone density; 22 (6%) Thacher ≥1. Interobserver kappa was very high for fracture (0.915) and Thacher score (0.842) and good for bone density (0.706). Logistic regression (table) showed that radiographic bone density was the only statistically significant variable predictive of presence of fracture, with an odds ratio of 4.61 (95%CI 2.05-10.38). The odds ratio for 25OHD level was 1.02 (0.99-1.06).

**Conclusions:**

Inter-observer reliability for diagnosing reduced bone density and rickets from radiographs ranges from good to very high. Our data provides objective evidence to support mainstream thinking that in the absence of radiographic evidence of reduced bone density and/or rickets, a low serum 25OHD



level should not be interpreted as the cause of unexplained fractures in children less than 2 years of age.

Table: Logistic Regression

Parameter	B	SE	Wald	df	p	Odds Ratio (OR)	95% CI for OR	
Bone Density	1.53	0.41	13.60	1	0.000	4.61	2.05	10.38
Thacher Score	-0.52	0.63	0.69	1	0.405	0.59	0.17	2.03
Vitamin D Level	0.02	0.02	1.36	1	0.244	1.02	0.99	1.06
Vit D by Ln Vit D	-0.00	0.03	0.72	1	0.397	1.00	0.99	1.00
Constant	-2.39	0.41	34.15	1	0.000	0.09		

P3-202

BONE MINERAL DENSITY ADJUSTMENT IN KIDNEY-TRANSPLANT RECIPIENT CHILDREN

Regina Ambrosi, MS/MA, Hospital Infantil de Mexico Federico Gómez, Mexico City, Mexico; Miguel Angel Guagnelli, MD, Hospital Infantil de Mexico, Mexico City, Mexico; Ana Maria Hernandez, MS/MA; Mara Medeiros, MD; Patricia Clark, PhD, Hospital Infantil de Mexico Federico Gómez, Mexico City, Mexico

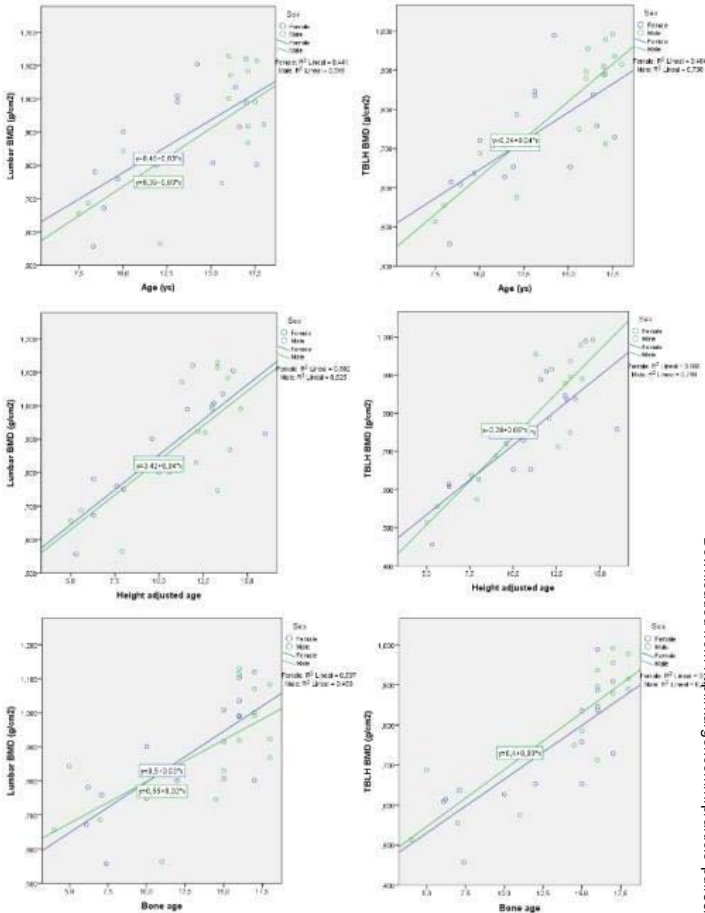
**Objectives:** Chronic kidney disease in children causes multiple bone alterations, particularly renal osteodystrophy, which affects both bone quality and size, in turn causing short stature, bone deformities and brittleness. Once they get a transplant, this process starts to revert, and although mineral alterations improve, short stature often requires growth hormone supplementation but bone fragility requires evaluations in order to revert the disease’s effects. DXA is a valuable tool for its measurement in children affected with chronic diseases but it requires adjustment for their proper evaluation since it is size-dependent. Our objective was to evaluate height adjusted age (according to 50th percentile in CDC growth charts) and bone age (according to Greulich and Pyle charts) correlation to bone mineral density in kidney transplant recipient children.

**Methods:** DXA measurements were made for 31 (16 girls) pediatric kidney transplant recipients. Lumbar and total body less head (TBLH) bone mineral density (BMD) were obtained. Within the same measurement, non-dominant hand image was obtained to evaluate bone age. BMD for chronological age was obtained directly, height adjusted age and bone age were calculated and the results graphed into a scatterplot, R square values were obtained.

**Results:** R square correlation of lumbar and TBLH were higher both for bone age and height adjusted age than for chronological age. Height adjusted age shows the best correlation in both boys and girls with values up to 0.76 in girls for TBLH and 0.68 for girls in lumbar region.

**Conclusions:** Height adjusted age seems to show a better correlation with BMD in children recipient of kidney transplant. Follow up of these patients is in progress to evaluate long term evolution of bone mineral density, response to transplant and long term fracture risk.

PLEASE SEE TABLES IN NEXT COLUMN



P3-203

TOTAL 25-HYDROXYVITAMIN D MEASUREMENT MAY NOT BE A SENSITIVE SCREENING METHOD TO DETECT VITAMIN D DEFICIENCY IN SOME ETHNIC PEDIATRIC POPULATIONS

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**Objectives:** Total 25-dihydroxyvitamin D (T25OHD) is frequently low in African Americans who exhibit no clinical or biochemical manifestation of deficiency, though it is universally accepted as a sensitive screening tool. New evidence cast doubts on its usefulness in detecting true cases of vitamin D deficiency in some African children

**Methods:** We measured T25OHD and other vitamin D metabolites by mass spectrometry, parathyroid hormone [PTH] by immunoassay, and serum albumin and calcium by bichromatic end point method in 3 groups of well children age  $\leq 7$ : white Caucasian Minnesotans (n=14), Minnesotans of Somali descent (n=55), and Ugandans in Africa (n=99, equatorial latitude).

**Results:** Vitamin D levels  $<30$  ng/ml were found in 64% of Caucasians, 91% of Somalis and 49% of Ugandans. Of those,

89% of Caucasians, 52% of Somalis and 12% of Ugandans were hypocalcemic (corrected total serum Ca<9.1 mg/dl for age≥11 months, and 8.5 for age<11 months). For vitamin D levels <20 ng/ml, 100% of Caucasians, 38% of Somalis and 0% of Ugandans were hypocalcemic. PTH and ALK means (SD) for the groups are 35.75 (18), 302.48 (119.04) for Caucasians, 44.64 (21.12), 287 (110.93) for Somalis, and 47.48 (18.91), 262.81 (62.57) for Ugandans, respectively. Across all groups, higher PTH was associated with hypocalcemia ( $r = -0.32$ ,  $P = <0.0001$ ) but not with T25OHD status ( $D < 30$ ,  $r = -0.07$ ,  $p = 0.6$ ). Assuming hypocalcemia represents true vitamin D deficiency status, T25OHD<30 ng/ml (ENDO insufficiency guidelines), had an overall sensitivity of 74% (72%, 92%, 40%, for White, Somali, and Ugandan groups respectively). We have found a positive correlation between a promising new biomarker, the ratio of inactivated vitamin D (24,25(OH)2D3) to T25OHD [24/25D ratio], and serum calcium ( $r = 0.35$ ,  $p = <0.0001$ )

**Conclusions:** Measurement of T25OHD may neither be sufficient to evaluate significance of underlying metabolic derangements related to vitamin D status nor inform clinical decision about therapy in African children. Future work will test participants' vitamin D binding protein levels, its haplotype, and calculate free and bioavailable 25OHD to better explore the observed correlation of 24/25D ratio with calcium levels and whether it can serve as a better indicator of vitamin D status and mineral metabolism.

P3-204

#### THE EFFECT OF WHOLE BODY VIBRATION TRAINING ON BONE AND MUSCLE FUNCTION IN CHILDREN WITH OSTEOPENIA IMPERFECTA

Wolfgang Hogler, MD; Janis Scott, BSN, Birmingham Children's Hospital, Birmingham, United Kingdom; Nick J Bishop, MD, Sheffield Children's Hospital, University of Sheffield, Sheffield, United Kingdom; Paul Arundel, MD, Sheffield Children's Hospital, Sheffield, United Kingdom; Peter Nightingale, BSN, Queen Elizabeth Hospital, Birmingham, United Kingdom; Zulf Mughal, MD; Raja Padidela, MD, Royal Manchester Children's Hospital, Manchester, United Kingdom; Nick J Shaw, MBBS; Nicola Crabtree, PhD, Birmingham Children's Hospital, Birmingham, United Kingdom

**Objectives:** Osteopenia imperfecta (OI) is a bone fragility disorder associated with reduced muscle size, dynamic muscle function and mobility. This randomised controlled pilot study (NCT03029312) assessed the effect of whole body vibration (WBV) training on bone density and geometry, muscle size and function, mobility, and balance in children with OI.

**Methods:** Twenty-four children (5-16 years) with OI types 1,4 and limited mobility (CHAQ score =0.13) were recruited in gender- and pubertal stage-matched pairs. Children randomised to intervention received 5 months of WBV training (3x3min twice daily) or regular care. Incident fractures in two boys (WBV arm) led to exclusion of two prepubertal male pairs.

Main Outcome Measures were bone and muscle variables as measured by dual-energy X-ray absorptiometry (lumbar spine, hip, total body) and peripheral quantitative computed tomography (distal and proximal tibia). Mobility was assessed by six-minute walk tests and CHAQ; dynamic muscle function and balance were measured by mechanography.

**Results:** All participants had reduced walking distances and dynamic muscle function ( $p < 0.001$ ). BMI Z-score was associated with higher CHAQ scores ( $\rho = +0.552$ ;  $p = 0.005$ ) and lower walking and two-leg jumping performance ( $\rho = -0.405$  to  $-0.654$ ,  $p < 0.05$ ). The WBV and control groups did not differ in the 5-month changes in bone density or geometry. Total lean mass increased more in the WBV group (+1119g [+224 to +1744]) compared to controls (+635g [-951 to +1006]),  $p = 0.01$ , without improvements in mobility, muscle function or balance.

**Conclusions:** The increase in lean mass without changes in muscle function or bone mass suggests reduced biomechanical responsiveness of the muscle-bone unit in children with OI. The association of overweight with impaired mobility highlights the need for active weight management in children with OI.

P3-205

#### FRACTURE PREVALENCE IN RELATION TO LOW WEIGHT PARAMETERS AND MENSTRUAL STATUS IN ADOLESCENT GIRLS WITH ANOREXIA NERVOSA

Nurgun Kandemir, MD, Hacettepe University, Ankara, Turkey; Kendra R Becker, PhD; Meghan Slattery, NP; Shreya Tulsiani, BS/BA; Vibha Singhal, MD; Alex Faje, MD; Jennifer J Thomas, PhD; Kathryn Coniglio, BS/BA; Karen K Miller, MD; Kamryn T Eddy, PhD; Anne Klibanski, MD; Madhusmita Misra, MD, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

**Objectives:** Diagnostic criteria for anorexia nervosa (AN) (specifically weight and menstrual status) are less rigid in DSM-5 compared with DSM-IV. Data are lacking regarding the impact of the various weight cut-offs used to diagnose AN on bone outcomes. The purpose of this study was to evaluate the clinical utility of existing weight cut-offs by determining which of these are most strongly associated with fractures. We also determined the impact of amenorrhea on fracture outcomes.

**Methods:** 350 females (222 with AN and 128 normal-weight controls) 12-21 yo were included. BMI, BMI percentile, percentage of median BMI (%mBMI) and percentage of expected body weight for height (%EBW-Ht) were calculated. Fracture history was recorded and height adjusted BMD Z-scores were calculated for the lumbar spine, whole body less head, and total hip.

**Results:** Females with AN did not differ from controls for age and height z-scores. Compared to controls, they had significantly lower body weight and aBMD z-scores at all sites, and a significantly higher fracture rate. For most cut-offs used to define low weight (BMI ≤17.5 or ≤18.5 kg/m<sup>2</sup>, ≤5<sup>th</sup> or ≤10<sup>th</sup> percentile, %mBMI ≤85% or ≤90% and %EBW-Ht of

### DENOSUMAB IN OSTEOGENESIS IMPERFECTA – INDIVIDUALIZED TREATMENT AFTER A PILOT TRIAL

Oliver Semler, MD; Mirko Rehberg, MD; Lisa Neuburg, MD; Eckhard Schoenau, PhD; Heike Hoyer-Kuhn, MD, University Cologne, Cologne, Germany

**Background:** Osteogenesis imperfecta is a rare skeletal disease causing bone fragility and reduced bone mass. Most patients are affected by mutations in *COL1A1/A2* impairing quantity and quality of collagen. In severe cases a treatment with bisphosphonates is frequently used but not approved in children. Recently antiresorptive treatment with the Rankl antibody Denosumab has been investigated in children with OI, showing an increase of aBMD after a treatment with 1mg/kg body weight every 3 months for 48 weeks (Hoyer-Kuhn H et al: Safety and efficacy of denosumab in children with osteogenesis imperfecta—a first prospective trial. JMNI 2016, 16(1):24-32).

**Objective and hypotheses:** After completing a prospective trial (NCT01799798) treatment cycles of the ten patients were individualized depending on bone resorption markers.

**Methods:** 10 children (male n=7, mean age 8.63 years) with genetically confirmed OI (*COL1A1*: 7 patients) were followed up after completing of the pilot trial. Denosumab was administered when deoxypyridinoline (DPD) measured in the urine bi-weekly increased to the baseline limits showing a vanishing effect of the antibody. Dose of the antibody and substitution of Calcium and vitamin D was administered according to the original trial protocol. Change of areal bone mineral density at the lumbar spine and whole body was assessed by GE lunar iDXA

**Results:** After end of trial the individualized treatment led to prolonged treatment intervals determined by bone resorption markers measured in the urine. Only 8 patients required a continuation of the treatment with a mean interval of 4.8 months (range: 3.9 – 6.1). Mean aBMD z-scores decreased after 1 year by -0.85 SD at the lumbar spine and by -0.56 SD at the whole body measurement.

**Conclusions:** Denosumab has shown to be an effective treatment to increase aBMD in children with OI. The individual treatment interval determined by bone resorption markers was longer than the previously chosen 3 months. During individualized treatment aBMD decreased without any subjective deteriorations. More severely affected children needed the antiresorptive treatment more frequently than children with OI type I.

P3-208

### QUANTITY AND QUALITY OF AXIAL AND APPENDICULAR MARROW ADIPOSE TISSUE IN ADOLESCENTS AND YOUNG ADULTS WITH SEVERE OBESITY

Vibha Singhal, MD, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States; Charumathi Baskaran, MD; Stanford C Fatima, MD; Karen J Campoverde, MD; Alexander Toth, BS/BA, Massachusetts General Hospital,

≤85% or ≤90%), AN were almost twice as likely to have fractures as controls. Further, AN with BMI >17.5 kg/m<sup>2</sup> or >5<sup>th</sup> percentile had a significantly higher fracture rate than controls. However, AN girls with BMI >18.5 kg/m<sup>2</sup> or >10<sup>th</sup> percentile, those at >85% mBMI or >85% or >90% of EBW-Ht did not differ for fracture rate from controls. The effect of low weight parameters on fracture rate was more marked in the AN group older than 16 years. AN both with and without a recent history of amenorrhea were twice as likely to have fractures as controls.

**Conclusions:** Low weight parameters of BMI ≤18.5 kg/m<sup>2</sup> or ≤10<sup>th</sup> percentile, ≤85% mBMI, and ≤85% EBW-Ht differentiated AN girls with a history of fracture from those who did not differ from controls for a history of fracture. Further, AN girls with or without amenorrhea had a similar increase in risk for fractures. Thus clinicians should discuss fracture risk in these patients regardless of the history of amenorrhea.

P3-206

### FROM RESEARCH TO CLINIC: TRANSLATION OF VITAMIN D STATUS IN CHILDHOOD

Ana Cristina Rodríguez-Dehli, PhD, San Agustín Hospital, Avilés, Spain; Isolina Riaño-Galán, PhD, Central University Hospital of Asturias, Oviedo, Spain; Ana Fernández-Somoano, PhD, CIBERESP and Oviedo University, Oviedo, Spain; Inés Olaya Velázquez, MD; Mercedes Candenas, PhD, San Agustín Hospital, Avilés, Spain; Adonina Tardon, PhD, CIBERESP and Oviedo University, Oviedo, Spain

**Objectives:** To analyze the effect of the translation of a research study on vitamin status on vitamin D in childhood.

**Methods:** 494 pregnant mothers recruited between 2003 and 2008 from the Spanish population-based cohort study Environment and Childhood [Infancia y Medio Ambiente] Project (INMA). Research protocol was approved by the Ethics Committee. We analyzed circulating 25OH vitamin D3 in pregnancy (n 243) and at 4 years (n 194) and at 8 years (n 255) in offspring. A workshop was organized to promote an adequate intake of vitamin D and effective exposure to sunlight after analyzing data at 4 years. The children with severe deficiency were derived to pediatric endocrinology.

**Results:** Mean vitamin D in pregnancy was 28.15 ng/dl (11.04 SD), at 4 years 20.9 ng/ml (7.33 SD) and, after intervention, at 8 years 26.1 (8.70 SD). The median estimated vitamin D intake was 4.63 g/day (range 0.71-22.52) at pregnancy and 2.74 g/day (range 0.81-12.66) at 4 years.

Table 1. Levels of circulating 25OHvitaminD3 (ng/dl) in pregnancy, at 4 years and 8 years.

**Conclusions:** High prevalence of hypovitaminosis D in pregnancy and infancy was detected. Translation of a research study let improve vitamin D status.

	N	Mean	SD	Min	P25	P50	P75	Max
In pregnancy	243	28.15	11.04	6.40	19.50	27.40	35.30	66.90
At 4 years	194	20.09	7.33	2.77	15.49	19.88	24.44	49.80
At 8 years	255	26.10	8.70	.00	20.00	25.10	31.60	53.00

# COLLECTIVE STUDY OF FAMILIAL HYPOMAGNEAEMIA WITH HYPERCALCIURIA AND NEPHROCALCINOSIS DUE TO CLDN16 MUTATIONS IN JAPAN

Yusuke Tanahashi, MD, PhD; Hironori Takahashi, MD, Asahikawa Medical University, Asahikawa, Japan; Toshihiro Tajima, MD, Jichi Children's Medical Center, Tochigi, Japan; Hiroshi Azuma, MD, PhD, Asahikawa Medical University, Asahikawa, Japan

**Objectives:** Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC) is a rare autosomal recessive tubular disorder exhibiting a high risk for progressive chronic kidney disease (CKD). The disorder is caused by mutations mainly in the CLDN16 gene encoding the tight junction protein claudin-16 which plays a crucial role in the paracellular reabsorption of magnesium and calcium in the thick ascending limb (TAL) of Henle's loop. Although a few reports about FHHNC from Europe and America reveal this disease becomes established, in Japan it has been limited, only a case report.

The aim in this study is to clear clinical and genetic information about FHHNC in Japan.

**Methods:** Based on questionnaire sending to related doctors throughout Japan, we gathered Japanese patients with FHHNC. Clinical informations from the patients were collected and mutational analysis of CLDN16 was also performed under informed consent.

**Results:** We identified 8 male patients with FHHNC (7 families / 1 sibling). All patients had CLDN16 mutations. Nephrocalcinosis/nephrolithiasis, polyuria/polydipsia were frequent symptoms. Almost patients presented hypomagnesaemia, hypercalciuria, and increased serum intact parathyroid hormone (iPTH). In mutation analysis of CLDN16, 9 different mutations among 7 patients were identified. These missense and nonsense mutations existed within the extracellular loop and transmembrane domain regions of claudin-16 protein. the extracellular loop and transmembrane domain.

We could find not a few patients with FHHNC in Japan. Compared with Europe or America, clinical feature and mutations of CLDN16 have their own some features in Japanese patient. Additionally urinary screening programs for school children has been executed nationwide from 1974 in Japan. We think that we could find more FHHNC patients by using the screening program. To confirm the diagnosis of FHHNC, genetic analysis of CLDN16 would be a very useful tool.

**Conclusions:** We presented the first collective study of FHHNC in Japan. Not a few patients with FHHNC could be identified in Japan as well as Europe or America.

Boston, MA, United States; Madhusmita Misra, MD, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States; Miriam A Bredella, MD, Massachusetts General Hospital, Boston, MA, United States

**Objectives:** Adults with abdominal obesity have higher marrow adipose tissue (MAT) and MAT is positively associated with hemoglobin A1C (HbA1C). Moreover, adults with type 2 diabetes mellitus have a lower proportion of unsaturated fatty acid estimates within MAT. These findings suggest that MAT may have metabolic implications in obesity. Adolescence is the period of physiologic increases in MAT however the effect of obesity on MAT content and composition in adolescents is not known.

We aimed to compare the quantity and composition of MAT in adolescent females with obesity and normal weight healthy controls and assess associations with HbA1C.

**Methods:** We recruited 35 adolescent females: 21 with severe obesity (OB) and 14 normal weight healthy controls (HC). MAT content of the L4 vertebra and femoral diaphysis was quantified by 1H-MR spectroscopy. Unsaturation index (UI) was calculated at the femoral diaphysis.

**Results:** OB were younger and as expected had higher BMI, total lean and fat mass as compared with HC. OB had lower MAT at the L4 vertebra ( $0.38 \pm 0.18$  vs.  $0.58 \pm 0.27$ ;  $p=0.01$ ) and femoral diaphysis ( $2.65 \pm 1.88$  vs.  $6.22 \pm 2.41$ ;  $p=0.0001$ ) which remained significant after controlling for age. However, the groups did not differ after controlling for BMI. There was no interaction between age and the subject grouping on MAT. There was no association between MAT and HbA1C. Unsaturation index of MAT at the femoral diaphysis did not differ between OB and HC even after controlling for age and BMI. However, in OB, UI was positively associated with HbA1C ( $R=0.64$ ,  $p=0.01$ ).

**Conclusions:** Contrary to adult data, adolescents with obesity have lower MAT at the lumbar vertebra (axial) and femoral diaphysis (appendicular site) as compared with normal weight controls. The degree of unsaturation of MAT is not affected by weight. In adolescents with obesity, increasing HbA1C is associated with greater unsaturation of MAT and warrants further studies to evaluate its clinical and pathophysiologic implications.

Table 1: Characteristics of the groups with severe obesity (OB) and normal weight controls (HC)

	OB (N= 21)	HC (N= 14)	P
Age (years)	16.90 ± 2.32	21.56 ± 2.11	< 0.0001
Weight (kg)	120.26 ± 21.19	59.53 ± 11.03	< 0.0001
Height (cm)	165.08 ± 4.83	163.62 ± 8.39	0.52
BMI (kg/m <sup>2</sup> )	43.98 ± 6.43	22.08 ± 2.36	< 0.0001
Visceral Fat (cm <sup>2</sup> )	96.82 ± 47.1	41.22 ± 24.07	0.0003
Subcutaneous Fat (cm <sup>2</sup> )	669.53 ± 166.99	164.39 ± 87.53	< 0.0001
Femur Diaphysis MAT (Lipid/Water Ratio)	2.65 ± 1.88	6.22 ± 2.41	0.0001
L4 MAT (Lipid/Water Ratio)	0.38 ± 0.18	0.58 ± 0.27	0.01
Unsat/Total Femoral Dia Lipids (UI)	0.08 ± 0.02 (n=19)	0.076 ± 0.02 (n=14)	0.4215

### BONE MINERAL DENSITY IN FEMALE SURVIVORS OF CHILDHOOD CANCER: WHO NEEDS EVALUATION?

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**Objectives:** Osteopenia is a potential complication of childhood cancer therapy, particularly after treatment for leukemia or brain tumors but the magnitude of this problem in survivors of other types of cancer is not well known. We examined the bone mineral density (BMD) status in long-term female survivors of childhood cancer.

**Methods:** This prospective cross-sectional study involved 44 female adults survivors of common types of childhood cancer (4 leukemia, 21 lymphoma, 14 sarcoma and 5 neuroblastoma and others), except brain tumors. Patients had a median age at diagnosis of 9.8 years (range 0.4-17.4), a median age at evaluation of 24.8 years (18.8-40.7) and a median follow-up time of 16.5 years (5.9-35.7). BMD of the lumbar spine (BMDLS) and femoral neck (BMDFN) were measured by dual X-ray absorptiometry. Osteopenia and osteoporosis were defined as BMD Z-score below -1 and -2.5 SDS respectively.

**Results:** Osteopenia or osteoporosis (BMDLS and/or BMDFN) was present in 11/44 (25%) of survivors, mainly in leukemia and lymphoma survivors. Three out of those 11 who had osteopenia had fractures. Cancer treatment before puberty, older age at first menses, treatment with Methotrexate or Prednisone were associated with lower BMD. Markers of ovarian function (AMH, Estradiol, FSH, LH, Inhibin B, follicular count and ovarian volume) had no influence on BMD.

**Conclusions:** In this cohort of female childhood cancer survivors, 25% had osteopenia and/or osteoporosis, mainly after treatment for leukemia or lymphoma including Methotrexate and/or Prednisone. These results indicate that greater awareness is warranted in this subpopulation of childhood survivors.

P3-211

### BONE MASS AND BODY COMPOSITION POST HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR CHILDHOOD MALIGNANCIES

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**Objectives:** There are many factors leading to poor bone health and imbalanced body composition in bone marrow transplant (BMT) recipients. We aimed to report our patients' profile and to correlate it with clinical parameters.

**Methods:** Cross-sectional study of paediatric BMT patients. Assessment of growth (height, weight, BMI) and dual-energy X-ray absorptiometry (DXA) for evaluation of bone mineral density (BMD) and geometry, muscle and fat mass. All results were converted to Z-scores. Also, lean tissue mass and fat mass indexes were calculated (LTMI and FMI, respectively) and BMD was corrected for height, where indicated. Comparisons were made with 57 Greek controls and between patient subgroups.

**Results:** 34 patients, aged  $14.6 \pm 3$  years were studied (of which 15 girls, 27 adolescents and 12 with a previous diagnosis of acute lymphoblastic leukaemia). Six patients (17%) sustained a total of 12 fractures (1 vertebral) and three had osteonecrosis. 85% were on vitamin D and calcium supplements and 41% were exercising regularly. 35% were on hormone replacement therapy for hypogonadism and 23% had low vitamin D. Compared to controls, our population had impaired growth, lower lumbar BMD Z-score (mean:  $-0.5 \pm 1.3$ ,  $p < 0.01$ ) lighter and smaller bones, with lower strength and less muscle mass (LTMI Z-score:  $-1.7 \pm 1.3$ ,  $p < 0.01$ ). Within-group analysis revealed that female sex, prepubertal status, hypogonadism and lack of regular exercise adversely affected both total body (less head) BMD and LTMI. History of graft-versus host disease led to lower Z-score for bone strength (bone mineral content/lean tissue mass ratio), mean value  $0.2 \pm 1.1$ ,  $p = 0.03$ ). Of note, BMD and body composition were not affected by inadequate calcium intake, history of bone pain, radiotherapy or corticosteroid treatment ( $p > 0.05$ ). Finally, strong and positive correlations were found between BMI, bone width and BMD at both sites of measurement, LTMI and FMI ( $p < 0.01$ ).

**Conclusions:** In our cohort, and despite proper dietary supplementation and hypogonadism treatment, growth, bone and muscle mass were adversely affected, whereas fat mass was comparable to controls.

P3-212

### BONE MINERAL DENSITY (BMD) & CALCIUM METABOLISM PARAMETERS IN POORLY TRANSFUSED PATIENTS WITH THALASSEMIA MAJOR (TM): EFFECT OF INTRAMUSCULAR (IM) HIGH DOSE VITAMIN D.

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**Objectives:** We examined BMD and calcium metabolism parameters in poorly transfused TM patients. We also

evaluated the effect of high-dose vitamin D on BMD & calcium homeostasis.

**Methods:** Thirty pubertal TM patients aged 15-35 years completed a prospective study where patients received IM 600,000 IU vitamin D at baseline. Calcium metabolism parameters were measured initially, at 6, & at 12 months (mo). Lumbar spine (LS) & femoral neck (FN) BMD were measured initially & at 12 mo. Pretransfusion hemoglobin range was 6-8 g/dl. Patients with suboptimal calcium intake (Daily calcium intake < 50 % of the recommended dietary intake) received oral calcium carbonate 1000 mg/day. Vitamin D deficiency (VDD) was defined as (<30ng/ml).

**Results:** The number of patients with a biochemical abnormality is listed in the table below:

	VDD	Hypocalcemia
Baseline	17	10
6 mo	4	4
12 mo	7	1

Among the 10 patients with hypocalcemia, 5 had VDD. There was a significant increase in vitamin D level at 6 & 12 mo ( $p<0.001$ ). There was a significant increase in serum calcium at 12 mo ( $p=0.036$ ). There was a significant decrease in serum ALP at 6 mo ( $p=0.009$ ) & 12 mo ( $p=0.006$ ). There was no significant change in parathyroid hormone at 6 mo and 12 mo.

At baseline, 24 patients had low LS BMD (Z-score= $\leq -2$ SD, mean  $-3.1$  SD). Among these patients, 12 patients had VDD, 2 patients had hypoparathyroidism, & 3 patients had isolated hypocalcemia. In the subgroup of patients who had low LS BMD & VDD at baseline, there was a significant improvement in LS BMD Z-score at 12 mo ( $n=12$ ,  $p=0.047$ ). There was no significant change in LS BMD Z-score in the subgroup of patients who had low LS BMD along with normal vitamin D level at baseline ( $n=12$ ,  $p=0.4$ ). At baseline, the mean FN BMD Z-score was  $-0.3$ , with 2 patients had Z-score  $\leq -2$ SD. There was no significant change in FN BMD at 12 mo.

**Conclusions:** Patients with TM have significantly low LS BMD (80%). Calcium profile was normal in 33% of TM patients with low LS BMD. The etiology of bone disease in TM patients is multifactorial including VDD, nutritional hypocalcemia, and hypoparathyroidism. Single yearly IM vitamin D 600,000 IU is an effective treatment for VDD in TM patients and improves bone mineralization.

P3-213

**UTILIZATION OF FUROSEMIDE/HYDROCHLOROTHIAZIDE LOADING TEST TO DIFFERENTIATE BARTTER SYNDROME AND GITELMAN SYNDROME IN CHILDREN**

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**Objectives:** To summarize the clinical features, furosemide / hydrochlorothiazide loading test and genotype of the children with Bartter syndrome and Gitelman syndrome; To guide the

clinical classification and selection of the target gene examination of Bartter and Gitelman syndrome through furosemide / hydrochlorothiazide loading test.

**Methods:** Retrospective analysis of clinical and biochemical characteristics, furosemide / hydrochlorothiazide loading test and genetic testing results of five cases of Bartter syndrome and Gitelman syndrome in the period from 2012 to 2014 in our department.

**Results:** These 5 patients came from 5 families, newly diagnosed at the age of 0.91-15.72 years old, median age 2.46 years. All patients had hypokalemic alkalosis with the normotensive, hyperreninemic hyperaldosteronism. Most of them had polydipsia, polyuria, and various degrees of growth retardation. All of the gene-diagnosis was coincided with the clinical diagnosis which were made depending on the results of furosemide / hydrochlorothiazide loading test.

**Conclusions:** The preliminary diagnosis of Bartter and/or Gitelman syndrome can be better carried out according to the results of furosemide / hydrochlorothiazide loading test. The preliminary diagnosis can guide the selection of a target gene detection.

P3-214

**PATHOLOGIC RIB FRACTURES WITHIN 4 MONTHS OF ETIDRONATE TREATMENT IN GENERALIZED ARTERIAL CALCIFICATION OF INFANCY DUE TO ABCC6 MUTATION**

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**Objectives:** Generalized Arterial Calcification of infancy (GACI) is a rare autosomal recessive disorder that features mineral deposition within arteries and fibrointimal hyperplasia, resulting in stenosis and decreased elasticity of vessel walls. It is often lethal in the neonatal period; bisphosphonate treatment is associated with survival beyond infancy. Patients with GACI due to *ENPP1* mutations who survive beyond infancy often develop hypophosphatemic rickets. The presented case highlights possible side effects of etidronate therapy in the absence of hypophosphatemia.

**Methods:** Diagnosis of GACI was made in a baby at 2 months of age upon 1 month of progressive multi-drug resistant hypertension when generalized calcification was noted on CT scan. Genetic analysis revealed a homozygous c.3940C>T mutation in exon 28 of the *ABCC6* gene.

**Results:** Because of feeding intolerance, baby started on sodium thiosulfate intravenously, then successfully switched to oral etidronate at a dose of 20 mg/kg/day by 2½ months of age. Two weeks later, hyperphosphatemia followed by hypercalcemia developed with suppressed PTH and hypercalciuria. Oral feedings switched to low calcium formula with resolution of hypercalcemia and hypercalciuria, normalization of PTH and improvement but not resolution of hyperphosphatemia. At 6 months of age, baby developed new feeding intolerance and inconsolability with rising

alkaline phosphatase, bilateral rib deformity and difficulty breathing. A repeat CT scan showed mild-moderate improvement of arterial calcifications, generalized bone demineralization, and 8 rib fractures with significant atelectasis. Incidental right radius fracture was discovered on surveillance without evidence of a callous. Hypertension is controlled with multiple agents, and cardiac function has stabilized. Etidronate therapy is on hold to allow healing of fractures, rib remodeling, and improve respiration.

**Conclusions:** This case indicates the difference in disease course in GACI due to *ABCC6* versus the more common *ENPP1* mutation. This case also exemplifies the known side effect of etidronate to increase renal tubular phosphate reabsorption, and demonstrates a direct effect of etidronate on bone mineralization leading to pathologic fractures despite normal-high serum calcium and phosphorus.

P3-215

#### **VDR MUTATION IN TWO SISTERS: PHENOTYPE VARIABILITY AND CLINICAL OUTCOME**

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**Objectives:** Hereditary vitamin D-resistant rickets (HVDRR) is an autosomal recessive disease secondary to the mutation of vitamin D receptor (VDR) gene. These children show an early onset of rickets and in some of them alopecia is associated.

**Methods:** We describe clinical features and laboratory findings in two sisters affected by HVDRR, as well as their response to treatment.

**Results:** The first born is now 4 years old and had a severe and resistant hypocalcaemia, with low response to high doses of calcium per os, the requirement of intravenous infusion of calcium for a prolonged period, hypocalcaemic seizures resolved with high doses of intravenous calcium and high doses of vitamin D. Clinical features were characterized by a typical rickets phenotype associated to alopecia and axial hypotonus. She presented hypocalcaemia, hypophosphatemia and high levels of PTH: 829 pg/ml. Genetic study of VDR revealed a homozygous novel mutation in the VDR gene (c.462+1G>A in the splicing locus of exon 6). The younger sister, 11 months old, was screened at birth, in the neonatal care unit, for hypocalcaemia, showing however normal values.

She was called in our centre to further investigate her genetic status, showing the same mutation of the sister. At the age of 7 months she was further investigated and showed asymptomatic hypocalcaemia (6.7 mg/dl), low Ca<sup>++</sup> (3.67 mg/dl), hypophosphatemia (3.2 mg/dl), high PTH (559 pg/ml). She was treated with calcium per os, and vitamin D, with a rapid normalization of calcaemia (Ca<sup>++</sup>: 4.31 mg/dl). She did not show skeletal manifestations of rickets, however she developed a mild alopecia.

**Conclusions:** The two sisters showed a different clinical phenotype, probably in part linked to the precocious diagnosis of the younger sister.

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#### **HYPOPHOSPHATASIA: NONLETHAL DISEASE WITH PRENATAL SKELETAL PRESENTATION AND SEVERE SHORT STATURE**

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**Objectives:** Hypophosphatasia (HPP) is a rare inherited disorder caused by desactivating mutations within the gene of the tissue non-specific alkaline phosphatase (TNSALP). HPP skeletal disease in utero was thought to predict a lethal outcome. However, several reports emphasized a Benign Prenatal form with a mild postnatal course. Although more than 300 mutations have been analyzed to explain the wide range of severity of the disease, the variability of clinical behavior is discussed. The aim is describe a patient with HPP caused by previously not described mutation.

**Methods:** We described a girl with prenatal bowing of the long bones suggestive of a severe dysplasia.

**Results:** She was a product of non-consanguineous healthy parents. Screening US in the second gestational trimester showed femoral and humeral shortness and bowing. She was born at term, BW 2.650 g, -1.2 SD, length 44 cm, -2.7 SD. Radiographs at 4 months of life showed severe symmetrical bowing and shortening of the long tubular bones, flared front end of ribs. At 2y she showed height 71.5 cm, -4.6 SD, Weight 6.760g, -3.4 SD, hypotony, delayed psychomotor development, pectus carinatum, bilateral limb bowing, and clubfeet. Normal serum levels of calcium and phosphorus, low ALP 44UI/L with elevated level of B6 vitamin 25.3 ng/ml (HPLC). Rx scan showed signs of rickets, chest deformity, lower limbs with symmetrical bowing and shortening with metaphyseal widening, less deformity of tibiae and fibulae and bowler spurs of the radius. At 3.6 y, she showed height 81.2cm, -4.38 SD, with less limb bowing with disappearance of the radius spurs and premature exfoliation of one teeth with intact roots. Genomic DNA analysis confirmed a compound heterozygous mutations in the TNSALP gene: in exon 6, c.542C>T (p.Ser181Leu) and in the exon 12, c.1400T>C (p.Met467Thr). The first variant has been described as pathogenic in heterozygosis in a patient with Infantile HPP(1). The other mutation previously not described was reported as pathogenic in the specific database, with a frequency of 0.0000085 in the total population.

**Conclusions:** In addition to the reported, the phenotype in this patient would be explained by the existence of both mutations, one of which was not described. Other additional



epigenetic factors could explain the clinical behavior observed in this case.

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#### IMPROVEMENT IN SPINAL INVOLVEMENT WITH ZOLEDRONIC ACID IN PEDIATRIC PATIENTS WITH CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS: A CASE SERIES.

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**Objectives:** To report a case series of 3 patients seen at a tertiary pediatric center between March 2014 and January 2016 with Chronic Recurrent Multifocal Osteomyelitis (CRMO) and vertebral spine involvement, treated with Zoledronic Acid.

**Methods:** We treated three patients with CRMO and vertebral spine involvement with intravenous Zoledronic Acid 0.025mg/kg every 3 months for a duration of at least 6 months. We performed full body MRI before and 6 to 12 months after Zoledronic Acid.

**Results:** A 14-year-old girl had hyperintense vertebral lesions which completely resolved after 6 months, while a 10-year-old girl with a diagnosis of William syndrome also had hyperintense vertebral lesions which significantly improved within one year. Both patients reported back pain before initiating Zoledronic Acid, which completely resolved within 3 months with concomitant use of NSAIDs. The third case, a 4 ½ year old girl, did not have hyperintense vertebral lesions or back pain, but rather a Genant grade 3 vertebral compression fracture. Her fracture did not progress further after 6 months of treatment. Zoledronic Acid was well tolerated with no significant adverse effects in all patients.

**Conclusions:** This case series is the first to document the effect of Zoledronic Acid on spinal involvement in pediatric CRMO patients. The positive effect of Zoledronic Acid in our patients is concordant with the reported effect of Pamidronate in CRMO patients treated for spinal involvement and back pain. One of our patient had a severe vertebral compression fracture, possibly due to a previous and inactive spinal lesion from CRMO. Follow-up imaging in this patient only 6 months after treatment might explain the absence of improvement in her vertebral fracture. Our data shows that Zoledronic Acid can be useful in treating vertebral hyperintensities and back pain in pediatric CRMO. Further experience with the use of Zoledronic Acid in this context is needed to confirm these findings.

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#### A RARE CAUSE OF RICKETS.

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**Objectives:** The development of hypophosphatemic rickets in infants fed with the elemental formula Neocate® has been recently reported. We present 7 cases of exclusively Neocate-fed babies who developed hypophosphatemic rickets.

**Methods:** Three patients (P1,3,4) had incidental findings of rickets on chest X-rays, two (P2,6) developed leg deformities and rickets was confirmed on X-rays, and two (P5,6) presented with femur fractures. Patient 7 was found to have low phosphate concentrations on routine blood testing and was further investigated. All patients (age 5months-3.2 years) were exclusively fed on Neocate® at presentation and had normal serum calcium and parathyroid hormone concentrations, raised alkaline phosphatase and hypophosphatemia. Vitamin D deficiency and renal phosphate wasting were excluded (Table 1).

**Results:** Following exclusion of other causes of rickets, reduced intestinal phosphate absorption due to EF was considered. Patients 1 - 6 were treated with phosphate supplements after diagnosis of rickets. Patient 6 was previously on long term steroids and received one course of bisphosphonates after the fracture. Formula was changed eventually in all patients and phosphate concentrations normalized after 1 week-4 months. Clinical and/or radiological improvement of rickets was noted in P2,3,4. No X-ray confirmation of improvement is available so far in the others.

**Conclusions:** The fact that serum phosphate improved following weaning of Neocate supports its role in the causation of hypophosphatemia; poor intestinal absorption of phosphate is the assumed mechanism in infants exclusively fed with Neocate. Clinicians should exercise caution in the use of EF in the absence of clear clinical indications. Infants on Neocate should have close clinical and biochemical monitoring of bone profile, in accordance with existing guidance.

PLEASE SEE TABLE ON THE FOLLOWING PAGE

Table 1. Clinical and biochemical characteristics of patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Gestational age	31w	27w	33w	39w+3	31w	term	34w+4
Diagnosis	Presumed cow's milk allergy	GORD, cow's milk intolerance	Pierre-Robin Syndrome, cleft palate, CP, GORD, NJ fed	CHARGE syndrome, GORD, PEG fed	FTT, GORD, PEG-NJ fed	SCID, BMT, GVHD on steroids, refusing feed	SOD, GORD, 8q12.3del, tectal plate glioma, NJ fed
Age at presentation	6 months	10months	11 months	18 months	9 months	3y 2m	5 months
Exclusively on Neocate before presentation (duration)	3 months	10 months	>8months	>6months	5 months	15 months	5 months
Ca (mmol/L)	2.48	2.52	2.6	2.49	2.57	2.47	2.38
Phosphate (mmol/L)	1.23	0.68	0.83	1.04	0.84	1.34	0.63
ALP (IU/L)	1000	1000	3469	431	1653	419	2206
PTH (ng/L)	24	19.8	17	5.6	21	31	Normal
25-OH-VitaminD (nmol/L)	59.7	86	88	347	76	131	110
TRP (%)	99.5	-	99.8	>91, >97	NA	NA	NA

successfully to guide a need for further removal of possibly involved other parathyroid glands. Hungry bone syndrome is a risk, occasionally requiring postoperative calcium supplements.

**Conclusions:** Parathyroid adenomas are uncommon in children. Intraoperative PTH level may indicate a successful complete removal of the adenoma.

P3-220

### SEVERE HYPERCALCEMIA DUE TO SUBCUTANEOUS FAT NECROSIS SUCCESSFULLY TREATED WITH PAMIDRONATE IN AN INFANT WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY

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**Objectives:** Subcutaneous fat necrosis (SCFN) of the newborn is an uncommon form of panniculitis that occurs after fetal distress and involves fatty areas during the first weeks of life. This rare disorder is generally self-limiting and undergoes complete regression. However, it can be complicated with a potentially lifethreatening hypercalcemia

**Methods:** -

**Results:** A 35 day old male infant admitted to our clinic for persistent vomiting. His medical history revealed a severe hypoxic-ischemic encephalopathy which was treated with hypothermia. His physical examination showed erythematous subcutaneous nodules over the back. Serum calcium level was 19.7 mg/dL (N: 8.5-10.5 mg/dl), ionized calcium 2.6 mmol/L (N:1,13-1,32), phosphorus 3.3 mg/dL, parathyroid hormone 4.4 pg/mL (N: 10-65 pg/ml) and 25-OH vitamin D 42,6 ng/ml (N: 20-100 ng/mL). Renal ultrasonography showed bilateral nephrocalcinosis. Intravenous hyperhydration and furosemide therapy did not decrease serum calcium. Therefore intravenous pamidronate therapy initiated and serum calcium level significantly decreased after the first dose of pamidronate and returned within the normal range after the second dose. A diagnosis of subcutaneous fat necrosis (SCFN) of the newborn confirmed by skin biopsy.

**Conclusions:** We report a case of severe hypercalcemia due to SCFN occurring after serious perinatal hypoxic injury, which resolved by intravenous administration of pamidronate. This treatment was rapidly effective and well tolerated. We suggest that pamidronate could be the first line therapy for severe hypercalcemia in SCFN.

P3-221

### ASFOTASE ALFA THERAPY IN A 16 YEAR-OLD MALE WITH HYPOPHOSPHATASIA

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### PERI-OPERATIVE MANAGEMENT OF A CHILD WITH PRIMARY HYPERPARATHYROIDISM

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**Background:** Childhood primary hyperparathyroidism (PHPT) is a rare disease (Incidence 1 in 200-300,000), mainly due to single benign adenoma. The presentation can be delayed after 10 years of age due to non-specific symptoms and hypercalcemia may be found incidentally. A special peri-operative monitoring of serum calcium (Ca) may be needed to avoid associated complications.

**Methods: Case Report:** An 11 years old boy previously healthy presented with right flank pain for a week. Renal functions were normal but adjusted Ca was 3.1mmol/l, phosphorus 1.28 mmol/l, PTH 25.98 pmol/l, urine Ca 5.19, and a vitamin D level 12.7. The abdominal x-ray revealed a right ureteric stone and renal ultrasound showed hydronephrosis. The patient was treated by laser fragmentation of the stone and stent. The parathyroid US showed a teardrop-shaped hypoechoic lesion, (0.6 x 1.5 cm) with hyperemia. The parathyroid (99 mTc) scan revealed a focus of more tracer retention in the lower pole of the right thyroid lobe. The patient received hyperhydration and furosemide preoperatively followed by partial Parathyroidectomy. Intra operative PTH dramatically dropped (from 22.3 – 5.18 pmol/l) suggesting a complete removal of the adenoma. Serum Ca level was monitored carefully post-surgery to avoid acute consequences of hungry bone syndrome.

**Results: Discussion:** PHPT is rare in childhood, commonly due to isolated parathyroid adenoma. It usually presents late with complications, which mainly involve the kidneys. Preoperative hydration and the use of diuretics help to adjust serum Ca level and reduce ongoing renal damage but surgery is the definitive treatment. We used intraoperative PTH level

**Objectives:** We report growth and clinical outcome of enzyme replacement therapy in a 16 year-old male with childhood hypophosphatasia (HPP) who was started on asfotase alfa at age 15 years.

**Methods:** Case report

**Results:** The patient was diagnosed with HPP at age 2 years when he presented with premature loss of primary teeth and genu varum. He had a history of multiple fractures requiring 16 orthopaedic surgeries with rod and pin placement in his lower extremities. He had chronic skeletal pain and used cane to ambulate with great difficulty. He presented to Endocrine Clinic at age 15 years with height of 126.4 cm (Z score -4.7, height age 7.5 years), arm span 139 cm, weight 25.2 kg (Z -5.78), Tanner stage 3 for pubertal development. He had severe scoliosis and deformity of both legs. Serum alkaline phosphatase level was undetectable (<20 U/L; normal 55-360), with elevated serum pyridoxal 5'-phosphate (836.8 nmol/L; normal 20-125) and urine phosphoethanolamine (622 nmol/mgCr; normal 0-35). Bone age was delayed at 12.5 years with marked metaphyseal fraying and lucency in distal radius and ulna. He was started on asfotase alfa at the dosage of 2 mg/kg given subcutaneously 3 times per week. He had marked clinical improvement in growth and mobility with no report of pain after 3 months of treatment. At 6 month follow up, he walked without cane and became more sociable and liked to play outdoor with peers. Bone radiograph at 6 months showed striking improvement in previous lucency areas. At 9 months, height was 133.5 cm (growth velocity of 9.5 cm/year), while arm span increased to 148 cm (growth velocity of 12 cm/year). However, at 12 months, he was noted to have worsening scoliosis from 70 degrees before therapy to 110 degrees, with slightly decreased height at 129.5 cm, necessitating a scoliosis surgery. His lumbar bone density improved from baseline of 0.319 gram/cm<sup>2</sup> to 0.381 gram/cm<sup>2</sup> at 1 year (height-adjusted Z score decreased from -2.7 to -3.1).

**Conclusions:** Treatment with asfotase alfa for 1 year significantly improved growth, physical function, pain, overall quality of life and skeletal radiographic findings in this patient.

P3-222

#### **HYPERCALCEMIA DEVELOPING IN THREE CASES FOLLOWING DISCONTINUATION OF DENOSUMAB TREATMENT**

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**Objectives:** Denosumab, a human monoclonal antibody against the receptor activator of nuclear factor kappa-B (RANK) ligand binds RANKL and blocks interaction with RANK, thereby inhibiting activation of osteoclasts and osteoclast-like giant cells which reduces bone remodeling and increases bone mineral density. However, following treatment, hypercalcemia may develop as a result of increased bone

resorption by reactivation of osteoclasts. Herein, we report three patients who developed hypercalcemia after discontinuation of long-term denosumab treatment.

**Methods:** Laboratory analysis was carried out using autoanalyzer (Beckman Coulter, inc.)

**Results:** Case 1, a 6-year-old girl with aneurysmal bone cysts at cervical vertebrae was treated with denosumab for an 11-month course. She developed vomiting and nausea 4 months after the last dose. Laboratory showed an elevated serum Ca of 18.9 mg/dl (**N:8.8-10.8**), phosphorus 5.09 mg/dl (**N:3.3-5.6**), alkaline phosphatase 215 U/L, parathyroid hormone(N:12-88).

Case 2, a 13.5-year-old boy with Noonan syndrome, pulmonary stenosis, UP, and giant cell tumor of the mandible was admitted for vomiting, stomach ache 2.5 months after discontinuation of a 10 month course of treatment with denosumab. On admission, serum Ca was 14.7 mg/dl, phosphorus 5.5 mg/dl, alkaline phosphatase 120 U/L, parathyroid hormone < 6 pg/ml.

Case 3 was a 14.5 year-old boy with aneurysmal bone cyst in right acetabulum. He was admitted for nausea, vomiting and constipation three months after discontinuation of denosumab treatment lasting nine months. On admission, serum Ca was 14.2 mg/dl, phosphorus 5 mg/dl, alkaline phosphatase 237 U/L, parathyroid hormone < 6 pg/ml. Hypercalcemia was treated with saline, furosemide and one or more doses of pamidronate in all cases. Hypercalcemia was attributed to osteoclastic hyperactivity that developed after discontinuation of denosumab.

**Conclusions:** Denosumab is an effective treatment in adults as well as children for fibrous dysplasia, juvenile Paget disease, aneurysmal bone cyst, and giant cell tumor of bone. Although hypercalcemia is rarely reported in adults after cessation of treatment, it may occur more often in children after discontinuation of treatment which may be due to a faster rate of remodelling.

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#### **OSTEOGENESIS IMPERFECTA TYPE V: CLINICO-RADIOLOGICAL DIAGNOSIS OF TWO CASES IN A LIMITED RESOURCE SETTING**

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**Objectives:** To inculcate awareness amongst physicians especially those from resource limited countries regarding the clinico-radiological diagnosis of a rare form of Osteogenesis Imperfecta –Type V (OI-V)

**Methods:** Proband, 13-year-old boy, referred to the endocrine clinic for familial short stature. Height was 126.5cm (z score -3.7). He also had severe back pain since the last 2 years. He sustained a fall 9 years back, resulting in fracture of proximal third of shaft of left femur after which a swelling appeared at the site 6 months later, associated with

### SEVERE HYPERCALCEMIA FOLLOWING DENOSUMAB CESSATION IN A SKELETALLY MATURE 18 YEAR OLD WITH MCCUNE ALBRIGHT SYNDROME AND POLYOSTOTIC FIBROUS DYSPLASIA

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**Objectives:** Denosumab (DMAB) is a human monoclonal antibody that binds to and neutralizes RANKL, a cell-surface protein involved in many cellular processes, including osteoclastogenesis. Therapeutically, DMAB inhibits osteoclast function and decreases bone resorption. It has been used in pediatrics to treat giant cell tumor of the bone, fibrous dysplasia (FD), juvenile Pagets and osteogenesis imperfecta but its safety profile remains uncertain.

**Methods:** Herein we report the case of severe rebound hypercalcemia and worsening FD in a skeletally mature 18 year old female with McCune Albright Syndrome and FD 5 mos after cessation of DMAB.

**Results:** YM has pan-skeletal FD with urinary phosphate wasting, scoliosis, restrictive lung disease, and hypothyroidism. She began DMAB for expanding craniofacial lesions and chronic pain after serial pamidronate and zoledronate (ZOL) treatments failed. She received DMAB subcutaneously (1mg/kg) every 6-8 wks over 3 mos. Subsequent treatments were postponed due to hypocalcemia, hypophosphatemia and secondary hyperPTH. Increased Ca supplementation and calcitriol normalized her serum Ca and PTH, but hypophosphatemia continued. Four mos after DMAB cessation, increasing nausea, decreased oral intake and weight loss were noted. Endoscopy pointed to non-specific esophagitis. Five mos after DMAB, she was admitted with profound hypercalcemia (20.1 mg/dl) with suppressed PTH (12 pg/ml). Standard hypercalcemia treatment plus ZOL (4 mg IV) was effective; she was discharged 6 days later with serum Ca 9.6 mg/dl. At 7 mos, she received a second dose of ZOL (2 mg IV) due to worsening craniofacial FD confirmed on MRI and increasing Ca levels up to 11.4 mg/dl. One week after ZOL, serum Ca was 9.2 mg/dl.

**Conclusions:** We are not aware of previous reports of hypercalcemia after DMAB cessation in *skeletally mature* patients. Several groups have reported cases in *skeletally immature* patients aged 8-10 years with FD, GCTB and juvenile Pagets. The timing of transition from inhibition to excessive bone resorption appears variable, and it is difficult to identify at-risk patients. For patients with high disease burden treated with DMAB, we propose a 12-mos monitoring protocol starting 4 wks post-DMAB including serum Ca, phos, PTH and c-telopeptide as well as patient/provider education.

excruciating pain. Radiography revealed periosteal thickening at the site (**Fig. 1**). Biopsy was done at the age of 8 years, suggested a hyperplastic callus (HPC). We noticed distinct forearm deformities bilaterally, with restricted supination and pronation. Father noticed to have the same deformities (**Fig. 2**). Detailed questioning revealed that the father had sustained multiple fractures since the age of 5 years.

Forearm Xray showed calcification of interosseus membrane between radius and ulna, and radiodense metaphyseal band adjacent to the growth plate. (Fig 1 & 2)

Chest Xray showed thin, gracile ribs. Irregular contour and osteoporotic long bones were also observed. Lateral view xrays of the spine showed Grade-2 (moderate) and Grade-3 (severe) deformities of the vertebrae. Father showed Grade-3 vertebral deformities.

The proband has been started on bisphosphonates and is on follow up.

**Results:** Calcification of interosseus membrane as seen in our cases has been found to be present in 80-100% in literature. Characteristic finding of HPC predilection for the femur has been shown in our cases as is periosteal new bone formation being attributed to the exuberant bone formation seen in OI-V.

A metaphyseal dense line was seen adjacent to the growth plate. Thin and gracile ribs were noted in both. The biochemical parameters were normal, except for a slightly raised total alkaline phosphatase which could be attributed to the HPC formation.

**Conclusions:** A molecular diagnosis could not be made as it is extremely expensive and has limited availability, underscoring the importance of a detailed history and clinical examination to diagnose OI-V.



Fig.1 Proband

a- Calcified interosseous membrane of the forearm; Metaphyseal band

b- Bilateral forearm deformity

c- Thin, obliquely positioned ribs. Lateral radiograph of spine showing Grade 2 (moderate) and Grade 3 (severe) vertebral biconcave and wedge deformity fractures

d-Localized periosteal thickening

# SEVERE HYPERCALCEMIA AS FIRST MANIFESTATION OF ACUTE UNSPECIFIC MYOSITIS IN A 11 YEARS OLD GIRL.

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**Objectives:** Objektivesto present a case of severe hypercalcemia in an adolescent with severe weakness and no previous diagnosis.

**Methods:** review clinical report

**Results:** Case report; 11 years old hispanic female with 6-month history of fatigue, weakness and anorexia, without physical exam findings, being admitted to the ICU for severe hypercalcemia and acute renal failure.Laboratory show calcium 13.8 mg/dl (8,5-10,5), ionic calcium of 6.89 mg/dl, creatinine of 1.2 mg/dl, ureic nitrogen 33 mg/dl with urine calcium/creatinine ratio 0.58 (nv < 0.2) Magnesium and phosphorus were within normal range, blood count, liver profile, chest X-ray, and abdominal ultrasound were normal. Intact parathyroid hormone (iPTH) was 3.0 pg/ml (8-72) and vitamin D of 21 ng/ml.(20 – 100) Hyperhydration and furosemide was begun and calcium gradually normalize. iPTH independent hypercalcemia was suspect. BM biopsy was negative for malignance, osseous scintigraphy was normal and PTHrp was 1pmol/l (nv< 2).PETCT scan revealed an intense axial and lower limb musculature uptake of FDG (fluorodeoxyglucose). MRI of the lower limbs showed a diffuse, bilateral,symmetrical myofascitis and joint effusion associated with knee synovitis. Muscle biopsy demonstrated nonspecific myositis,immunohistochemistry show T lymphocytes predominant CD8 - CD3 positive,suggesting polymyositis and skin biopsy conclude moderate perivascular interface dermatitis, no granulomas were found. Lactate dehydrogenase was 412 U/L, creatinkinasa was in the normal range and angiotensin converting enzyme (ACE) was elevated in 183 U/l(8-52) Serum immunologyc markers were normal,only ANA antibodies were positive by 1/320. C3 was normal and C4 low.Dilated eye exam did not demonstrate uveitis.Prednisone start at dose of 1mg/kg\*d.

**Conclusions:** Hypercalcemia can be a serious manifestation associated to myositis in adolescents. A rational study allowed to get the diagnosis, rarely describe in children and adolescents.

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**Objectives:** Hypophosphatasia (HPP) is an inherited metabolic disease characterized by impaired bone mineralization due to decreased activity of tissue nonspecific alkaline phosphatase (TNSALP). HPP is caused by loss-of-function mutations in the gene *ALPL* encoding TNSALP. Severe patients have been perinatally lethal, though since enzyme replacement therapy (ERT) with Asfotase alfa was approved in 2015, they came to be saved. Genotype-phenotype correlation of HPP in relation to ERT has not been fully evaluated.

**Methods:** 6 patients with HPP (3 females) were enrolled. Information on the clinical characteristics were extracted, including HPP type, height, and bone mineral density, as well as the presence of calcified defectiveness by bone X-ray and low ALP. All 12 exons and flanking sequences of *ALPL* were amplified by PCR and analyzed by direct sequencing. We evaluated the association between gene mutations and clinical characteristics, including the efficacy of ERT.

**Results:** The ages of diagnosis were 0-8 years (median:1.8).None of the patients belonged to a consanguineous family. Serum ALP levels at the diagnosis were 16-255 IU/l (median:121). Sequencing analysis of *ALPL* revealed that homozygous mutations in 1 patient, compound heterozygous mutations in 3, and heterozygous mutation in 1 . Case 1 was the homozygote of c.1559delT mutation, but he presented much milder without respiratory distress compared to those with the same mutation previously reported. Severity of the clinical symptom of the patients of the compound heterozygous mutations with c.1559delT and other mutation were various (cases 2, 3 and 4). Even in the siblings who have same mutations, there was difference of the phenotype(cases 2 and 3). F310L were found in patients with relatively mild form (case 4). Case 5 was heterozygote with M62I mutation and showed skeletal symptoms probably because the M62I mutant almost completely lost its activity. Cases 1 and 2 were treated with Asfotase Alfa from 12 days and 5 months after birth, respectively. ERT effectively mineralized the HPP skeleton in the patients and no serious adverse events were observed.

**Conclusions:** The symptoms of HPP are various, and examination about the adaptation of HRT would be necessary.

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# TREATMENT OPTIONS IN HYPOPHOSPHATEMIC RICKETS, CASE STUDY.

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**Objectives:** Hypophosphatemic rickets is a rare genetic disease associated with overproduction of FGF-23, which

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# GENOTYPE-PHENOTYPE CORRELATION IN SIX CASES OF HYPOPHOSPHATASIA. -C. 1559DELT MUTATION IN ALPL PRESENTS HETEROGENEOUS PHENOTYPES -

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leads to impaired resorption of phosphorus in the kidneys and reduced conversion of vitamin D3 to active forms with numerous consequences for the phosphate-calcium metabolism and the skeletal system.

**Methods:** We present a patient with hypophosphatemic rickets with diagnosed mutation in the PHEX gene inherited from his mother. This is an example of a rare disease in a patient who does not comply with the treatment recommendations. In his early childhood, the therapy was applied in an appropriate manner. In the pre-school period, the mother gradually took over the therapy by introducing slight modifications. After a few years, she gave up follow-up visits to the endocrinologist and independently determined the dosage of drugs, which resulted in administration of the drugs. She assumed the concentration of serum calcium, phosphate, and vitamin D3 to be the indicator of correct compensation of phosphate-calcium metabolism. About a year ago, she brought the boy, aged 15, to the Department of Endocrinology. The patient was diagnosed with distinct shank deformities and complications caused by the improper treatment. Further diagnostics indicated somatotropin hypopituitarism.

**Results:** The current therapy with oral intake of phosphates and analogues of the active forms of vitamin D3 fails to restore the physiological conditions of phosphate-calcium metabolism but should make metabolism closer to the physiological condition; hence, the chance for the implementation of recommendations is reduced. Failure to take phosphate mixes contributes to phosphate leaching from bones, bone loss, and development of accompanying complications. Intake of excess doses results in secondary hyperparathyroidism and "phosphoric" bolus followed by parathyroid hyperplasia as well as tissue calcification and arterial hypertension.

**Conclusions:** Therapy should be personalised and based on mutual trust between the doctor and patient. In determination of the dosage, besides the clinical and laboratory indicators of applied therapy, patient's abilities as well as limitations associated with the nature of the disease should be considered.

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#### **A UNIQUE CASE OF PARATHYROID ADENOMA WITH NEPHROLITHIASIS AND LOW FRACTIONAL CALCIUM EXCRETION**

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**Objectives:** Primary hyperparathyroidism (PHPT) is rare in children. When it does occur, it is generally associated with significantly increased urinary calcium excretion. We aim to describe a case of pediatric PHPT presenting with nephrolithiasis in setting of low fractional calcium excretion

to highlight variability in presentation and emphasize importance of reassessment.

**Methods:** Literature review and retrospective chart review

**Results:** 14 year old previously healthy male presented with renal colic. Renal ultrasound demonstrated two 3 mm calculi in right kidney and 1 in left kidney. Work-up revealed hypercalcemia (11.4 mg/dl) with low normal phosphorus 3.8 mg/dL and elevated PTH 76. Fractional excretion of calcium (FeCa) was low (0.9%). Repeat FeCa was equivocal at 1.6%. 25-Hydroxy Vitamin D was 27 pg/mL, Magnesium 2.11mg/dL, alkaline phosphatase 510U/L. Thyroid ultrasound and sestamibi scan did not reveal parathyroid adenoma. Preliminary diagnosis of familial hypocalciuric hypercalcemia (FHH) was made and treatment initiated with cinacalcet 7.5 mg daily (0.19 mg/kg/day) while awaiting genetic confirmation. CASR gene analysis was normal prompting re-evaluation. Repeat thyroid U/S showed hypoechoic extra-thyroidal mass slightly posterior to left inferior thyroid suggestive of parathyroid adenoma. Parathyroid adenoma was surgically resected without complication and hyperparathyroidism resolved. Genetic testing was negative for CASR, CDC73, CDKN1B, MEN1 and RET mutations.

**Conclusions:** FHH and PHPT can be difficult to distinguish clinically. FeCa is frequently used to differentiate these disorders with FeCa in FHH <1% and FeCa in PHPT >2%.

However, rarely FeCa can be elevated in some FHH kindreds and low in PHPT. Definitive diagnosis is imperative as FHH is observed/treated medically whereas PHPT requires surgical intervention. Initial low FeCa in our case was likely due to comorbid Vitamin D insufficiency. High index for suspicion was maintained due to end organ effects from hypercalcemia (nephrolithiasis) which is atypical in FHH and negative CASR analysis prompted reassessment ultimately leading to correct diagnosis. This case emphasizes the importance of ongoing reassessment to guide clinical management, especially in atypical cases.

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#### **2,6-YEAR-OLD GIRL WITH OSSIFICATIONS, PHP, HYPOTHYROIDISM**

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**Objectives:** 2y9m girl with a bony prominence in the area of the right hand. At the age of 19 days was a blood sample in the right elbow. Then, formed a distinct hematoma in the area of the injection site and also in places of physical impact at the time of taking blood samples. At the age of 6 months there was a bony prominence in the area of the right wrist with marked limitation of movement. In the area of the elbow there was a further ossification and further spread to the right shoulder and right clavicle. The girl also has problems with motor function of the right hand.

**Methods: On physical examination,** a mild facial dysmorphism, deep depression of the root of the nose, upward nostrils, epicanthus. Skin is partially dry, with scattered pale-reddish macules. There is a scar on the right elbow; clearly defined



ossifications that are palpable from the right hand to the right clavicle. Condition of the joints: clavicle palpable with thickened bony prominence. Significant limitation of movement of the right arm. Other joints are unremarkable. Her height is 88 cm (50), weight is 15 kg (50 percentile). **X-ray** of the chest, right shoulder and forearm: a massive heterotopic ossification.

**MRI:** signs of mass lesion in the soft tissues of the right hand.

**Histology** - progressive osseous heteroplasia. **Genetic diagnosis:** No mutations in the gene ACVR1; FOP is excluded. **Genetic testing on GNAS** (endocrinology lab exam in Lübeck, prof. O.Hiort): heterozygous mutations in GNAS, EXON 13, c.1128-1129delGT, therefore early termination p.F377Qfs5 (NM\_001077488.2).

**Results:** The patient has subcutaneous deeply progressive heterotopic ossifications. And was diagnosed with POH. This was confirmed at the molecular genetic level (GNAS gene). Here was found heterozygous replacement in Exon 13, which leads to the stop-codon and thus, to the loss of the protein chain. POH is associated with autosomal dominant inherited mutations in the gene GNAS.

**Conclusions:** These genetic changes are often described with hormonal resistance, so the endocrine function was also investigated. Hypocalcemia, hyperphosphatemia, increased level of PTH was found, so pseudohypoparathyroidism was diagnosed. Moreover, level of TSH was elevated, and fT4 was low, so hypothyroidism was diagnosed. Levels of ACTH and cortisol were normal.



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## SEVERE HYPERCALCEMIA IN AN INFANT DUE TO TOXIC DOSES OF HIGHLY CONCENTRATED VITAMIN D SOLUTION.

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**Objectives:** Vitamin D supplementation of 400 IU is recommended in all breastfed infants and non-breastfed infants who do not drink 1L of vitamin D fortified milk per day (AAP/PES). Vitamin D liquid formulations are available over the counter as cholecalciferol (400 to 150000 IU/ml) and by prescription ergocalciferol (8000 IU/ml) in US. Confusion about formulations may lead to toxicity and hypercalcemia in infants.

**Methods:** A 6 week old male infant presented to the hospital with failure to thrive, below birth weight. He had poor

feeding, emesis and had wet diapers with physical exam showing hypotonia and dehydration. Blood tests showed a high calcium (17 mg/dL), normal serum phosphorus (5.1 mg/dL), low PTH (5 pg/mL), and high 25 OH Vitamin D (> 96 ng/dL) and 1,25 dihydroxy vitamin D (> 600 pg/mL), with elevated urine calcium:creatinine ratio of 2.1 (normal up to 0.86). The parents gave 1-1.5 mL of a highly concentrated over the counter vitamin D liquid with 5000 IU/drop and 150000 IU/mL daily for 3.5 weeks. Vitamin D toxicity was the cause of hypercalcemia. The patient was treated with IV normal saline bolus, IV hydration at 1.5 times maintenance with a dose of calcitonin IM and pamidronate infusion (Table 1). In 12 hours, calcium level was 14.1 mg/dL. Subsequently, hydrocortisone, furosemide and repeat doses of calcitonin and pamidronate were given to bring calcium to < 11 mg/dL. Renal ultrasound showed nephrocalcinosis. Breast milk was supplemented with low calcium formula Calcilo (2.9 mg/5 oz). **Results:** Calcium levels were 10-11 mg/dL by day 5. The baby had improved oral intake, weight gain and tone. Infant was discharged on oral hydrocortisone, breastmilk and Calcilo formula. Serial calcium levels and repeat renal ultrasound will be done.

## Conclusions:

1. Different vitamin D solutions available in the US over the counter can lead to toxicity, hence pediatricians should prescribe a specific formulation.
2. Hypercalcemia due to vitamin D toxicity should be managed aggressively with hydration, calcitonin, bisphosphonates, furosemide and steroids. Close monitoring of calcium is needed as vitamin D may take 2-3 months to clear from the body.
3. Nephrocalcinosis can occur with a short duration of exposure to toxic doses of vitamin D.

Table 1

Day of treatment	Serum calcium (mg/dL)	Other laboratory studies	Weight (kg)	Intervention
1	17 → 16.6 → 15.5 → 14.2	25 OH vitamin D > 96 ng/dL 1, 25 (OH) <sub>2</sub> vitamin D > 600 pg/mL PTHrP 3.4 pmol/L BUN 33 mg/dL Creatinine 0.6 mg/dL Magnesium 2.2 mg/dL Phosphorus 5.1 mg/dL	3.79 (Birth weight 4.15)	<ul style="list-style-type: none"> <li>• Calcitonin 4 U/kg IM X 2</li> <li>• Pamidronate 0.5mg/kg</li> </ul>
2	13.1 → 14.1 → 13	BUN 9 mg/dL Creatinine 0.5 mg/dL	4.1	<ul style="list-style-type: none"> <li>• Hydrocortisone 1 mg/kg/dose q6h</li> <li>• Furosemide 1 mg/kg q24h</li> </ul>
3	13.1 → 13.5			<ul style="list-style-type: none"> <li>• Pamidronate 1mg/kg X 1</li> <li>• Furosemide 1 mg/kg q24h</li> <li>• Hydrocortisone 1mg/kg/dose q6h</li> <li>• Calcitonin 4 U/kg X 1</li> </ul>
4	12.5 → 12.3	BUN 7 mg/dL Creatinine 0.4 mg/dL Magnesium 1.2 mg/dL Phosphorus 2.6 mg/dL		<ul style="list-style-type: none"> <li>• Hydrocortisone 1mg/kg/dose q6h</li> <li>• Furosemide 1mg/kg/dose q12h</li> <li>• Magnesium sulfate 50 mg/kg X 1</li> <li>• Sodium phosphate 0.3 mmol/kg X 1</li> </ul>
5	10.7 → 11.6	Magnesium 2.4 mg/dL Phosphorus 3.5 mg/dL	4.245	<ul style="list-style-type: none"> <li>• Hydrocortisone 1mg/kg/dose q8h</li> <li>• Discontinued Furosemide</li> <li>• Calcitonin 4 U/kg X 1</li> </ul>
6	10.1 → 10.6	25 OH vitamin D > 96 ng/mL	4.315	<ul style="list-style-type: none"> <li>• Hydrocortisone 1mg/kg/dose q8h</li> </ul>
7	10 → 10.7	1, 25 (OH) <sub>2</sub> vitamin D 495 pg/mL	4.61	<ul style="list-style-type: none"> <li>• Hydrocortisone 1mg/kg/dose q8h</li> </ul>
8	10.3	Magnesium 1.9 mg/dL Phosphorus 3.9 mg/dL		<ul style="list-style-type: none"> <li>• Hydrocortisone 1mg/kg/dose q8h</li> <li>• Discharged</li> </ul>
10	10.2	BUN 12 mg/dL Creatinine 0.17 mg/dL		<ul style="list-style-type: none"> <li>• Hydrocortisone 1mg/kg/dose q8h</li> </ul>

Calcitonin: Intramuscular, Pamidronate: IV infusion over 4 hours, 25 OH vitamin D (normal 30-80 ng/mL), 1, 25 (OH)<sub>2</sub> vitamin D (normal 20-79 pg/mL), PTH – Parathyroid hormone (15-75 pg/mL), PTHrP – Parathyroid hormone related peptide, BUN – Blood urea nitrogen (normal 10-26 mg/dL), Creatinine (normal 0.2-0.4 mg/dL), Calcium (normal 9-11 mg/dL), Magnesium (normal 1.6-2.3 mg/dL), Phosphorus (normal 4.5-6.7 mg/dL).



## TWO NOVEL CYP19A1 GENE MUTATIONS IN AN ADOLESCENT MALE PRESENTING WITH AN UNUSUAL FRACTURE

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**Objectives:** The aim of this case report is to describe a male athlete who was diagnosed with aromatase deficiency in adolescence.

**Methods:** A literature review was completed to write this case report.

**Results:** A 17-year-old male athlete was referred to pediatric endocrinology for low bone mineral density (BMD). He had initially presented to sports medicine with unilateral knee pain. When his magnetic resonance imaging (MRI) showed a contusion of the medial femoral condyle, he had a dual-energy x-ray absorptiometry (DEXA) scan that showed an anterior-posterior (AP) spine L1-L4 BMD z-score of -3.3. His history was positive for inadequate calcium intake but negative for steroid use and gastrointestinal symptoms. On exam, his height was at the 42%ile with midparental height at the 56%ile. He was Tanner V with 20mL testes bilaterally and normal secondary sexual characteristics including facial hair. Laboratory evaluations showed normal calcium, phosphorus, and vitamin D levels. His testosterone level was at the upper limits of normal (898ng/dL) with undetectable estradiol (<2pg/mL) and estrone (<1pg/mL) levels. At chronological age 17-3/12 years, his bone age was 14 years with unfused epiphyses. His genetic evaluation revealed two heterozygous CYP19A1 gene mutations, c.230 A>G and c.380 T>C. Neither mutation has previously been reported. The mutations are likely pathogenic as the variants are on opposite alleles.

**Conclusions:** Aromatase is an enzyme that converts androgens to estrogens. Its deficiency results in low estrogen levels. Estrogen is needed to accrue and maintain bone mass in both males and females. Aromatase deficiency is a rare condition in males that is usually found by screening labs after other family members are diagnosed or in adulthood when the affected individual continues to grow in height. Our case is unique because the patient was identified in adolescence after he presented with an unusual sports-related injury and was found to have low bone mineral density. At presentation, he did not have tall stature and was actually below his mid-parental height. He was found to have two novel CYP19A1 mutations. This case reiterates that it is important for all physicians to consider this rare diagnosis in young patients with repeated injuries or unusual fractures, especially of the long bones.

## CASE REPORT: A RARE HETEROZYGOUS ACTIVATING MUTATION IN CASR GENE, CAUSING FAMILIAL HYPOCALCEMIA

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**Objectives:** Calcium-sensing receptor (CaSR) is a key regulator of calcium (Ca) homeostasis. CaSR loss of function mutations have been described in the literature more frequently than gain of function mutations. CaSR activity is increased in CaSR gain-of-function mutations leading to the development of hypercalciuric hypocalcemia. We report one of the youngest cases of CaSR gain-of-function mutation described.

**Methods:** We report the case of a 1-month-old boy, who was referred for asymptomatic hypocalcemia detected since day 1 of life, in the context of familial hypocalcemia.

**Results:** The patient's maternal grandmother had a history of hypocalcemia and his mother suffered from seizures due to severe hypocalcemia. At day 1 of life, the patient presented with hypocalcemia and inappropriate PTH level (Ca 1.73 mmol/L (N 2.13-2.55), Phosphorus 1.90 mmol/L (N: 1-2.60), PTH 7.48 µg/mL (N 15-65)). Treatment was immediately initiated (Alfacalcidol and Ca gluconate) and Ca levels gradually increased. At day 4 of life, Urinary Calcium/Creatinine was elevated (1.8 mmol/mmol) with persistent hypocalcemia. Renal ultrasound revealed hyperechogenicity of the left fornix of the left kidney. Genetic screening identified a previously undescribed heterozygous mutation of the CaSR gene in exon 7 (pGly685Ala, c.2054G>C).

The review of the literature showed phenotypic variability in the clinical presentation of activating mutations of CaSR. Most patients are asymptomatic. One of the goals of the treatment is to avoid nephrocalcinosis.

**Conclusions:** We describe a rare gain-of-function mutation of CaSR, leading to familial hypocalcemia. Early screening for hypocalcemia in our patient prevented the onset of seizures, unlike his mother. Our case and the review of literature illustrate the importance of genetic testing and early diagnosis. Early management can prevent the complications of hypocalcemia.

## LONG TERM USE OF PARATHYROID HORMONE (PTH 1-34, AND RECENTLY, PTH 1-84) IN 3 YOUNG WOMEN WITH ACTIVATING MUTATIONS OF THE CALCIUM-SENSING RECEPTOR (CASR)

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**Objectives:** 3 women (21-23 yrs) with activating mutations of CASR have been treated with PTH for a total of 7-15 years. All did poorly on therapy with calcitriol and calcium, and had nephrocalcinosis. All were treated at the NIH since ages 6, 13

and 15 years receiving PTH<sup>1-34</sup> (200 mcg/mL) injections BID or TID. During a 6 month protocol using PTH<sup>1-34</sup> delivered via a pump, all had normalization of urinary calcium. The patients have subsequently been followed at USF for 4 years and received PTH<sup>1-34</sup> (Forteo;250 mcg/mL) via an insulin pump for 1-4 years.

**Methods:** Pt 1 has remained on a pump for 4 years (13 mcg/d;continuous basal infusion). Pt 2 was on a pump for 3.5 years (30 mcg/d) but resumed TID injections (32 mcg/d) due to insurance denial. Pt 3 was on a pump for a year (21 mcg/d), but had recurrent problems with infusion sites prompting resumption of BID injections of Forteo for 3 years (32 mcg/d); she recently started PTH<sup>1-84</sup> (Natpara) 25 mcg sc BID.

**Results:** While on pump therapy 24 hr urinary ca/creat ratio was normal or near normal in all subjects. Since resuming injections this has increased slightly in Pt 2, but not in Pt 3. eGFR and bone density have remained in the normal range. All 3 women feel that health and well being have substantially improved on PTH.

	Ca (mg/dL)	urine ca/creat ratio (mg/mg)
Pt 1	8.4 ± 0.6*	0.14±
0.04		pump X 4 yrs
Pt 2	7.6 ± 0.9	0.21 ±0.07
pump X 3.5 yrs		
Pt 2	7.8 ± 0.5	0.23 ±0.01
TID inj X 6 mos		
Pt 3	8.2 ± 1.1	0.18 ±0.05
pump X 1 yr		
Pt 3	8.4 ± 0.6	0.14 ±0.04
BID inj X 3 years		
*mean ± SD		

**Conclusions:** 3 young women have been treated with sc PTH for a total of 7-15 years with overall improved quality of life, normal bone density, and stable kidney function. Pump therapy appears to normalize urinary calcium most consistently, but for some patients, injection therapy may accomplish this as well. Insurance coverage remains an obstacle as is lack of a home blood calcium monitor.

P3-234

**A CASE WITH INFANTILE HYPOPHOSPHATASIA PRESENTING WITH SEVERE HYPERCALCEMIA AND PSEUDOTUMOR CEREBRI**

Filiz Tutunculer, MD; Kibar Mutlu, MD; Ayse Uguz, MD; Raif Yildiz, MD; Nese Ozkayin, MD, Trakya University Faculty of Medicine, Edirne, Turkey

**Objectives:** Hypophosphatasia is a rare inherited disorder characterized by poor bone mineralization and deficiency of tissue nonspecific alkaline phosphatase (TNAP) activity. We report a case of infantile hypophosphatasia who developed severe hypercalcemia and pseudotumor cerebri.

**Methods:** A five month-old boy was hospitalized to pediatric infection diseases clinic as he was suspected acute meningitis due to bulging anterior fontanelle, vomiting and lethargy for 4 days. His clinical findings did not resolve

despite antibiotic therapy. During this time, his biochemical analysis revealed severe hypercalcemia. He was a second child of unrelated healthy parents and was born by normal delivery at term, weighing 3.8 kg. On physical examination he had bulging and widened anterior fontanelle, sign of rickets including soft skull bone and chest deformity as well as generalized muscle weakness and delayed motor development. His weight SDS was -3.07, height SDS was -4.4. Laboratory findings were calcium 18 mg /dl (NR: 8.5-10.5), phosphorus 4.6 mg /dl (NR:3.5-5.5), alkaline phosphatase 30 IU /L (NR:40-150), parathyroid hormone 0.1 pg /ml (NR:15-65) and 25 hydroxyvitamin D 32 ng /ml (NR:10-60). Skeletal X-rays demonstrated impaired mineralization and rachitic changes in the metaphyses. Optic fundus examination showed bilateral papilledema. Cranial MRI findings were consistent with pseudotumor cerebri. Renal ultrasonography showed bilateral medullary nephrocalcinosis. Based on these findings the patient was diagnosed as infantile hypophosphatasia. Sequencing analysis of TNAP gene revealed two heterozygous variants. The p.Glu191Lys variant had previously been reported while the p.Arg184Gln variant was novel.

**Results:** The patient was treated with fluid hydration and calcium restricted formula followed by asfotase alpha with a dose of 2 mg /kg 3 times a week. After 3 months of asfotase alpha therapy, his calcium level returned to normal ranges and motor development improved.

**Conclusions:** Hypophosphatasia should be considered in the differential diagnosis of any patient presenting with increased intracranial pressure or hypercalcemia. Alkaline phosphatase level should be measured.

P3-235

**CRANIOSYNOSTOSIS AS THE PRESENTING FEATURE OF X-LINKED HYPOPHOSPHATEMIC RICKETS IN AN INFANT**

Janaki D Vakharia, MD, Brown University, Providence, RI, United States; Helena OB Taylor, MD, PhD, FACS, Mount Auburn Hospital, Cambridge, MA, United States; Lisa Swartz Topor, MD, MMSc, Brown University, Providence, RI, United States

**Objectives:** Describe the earliest case of craniosynostosis in an infant with x-linked hypophosphatemic rickets.

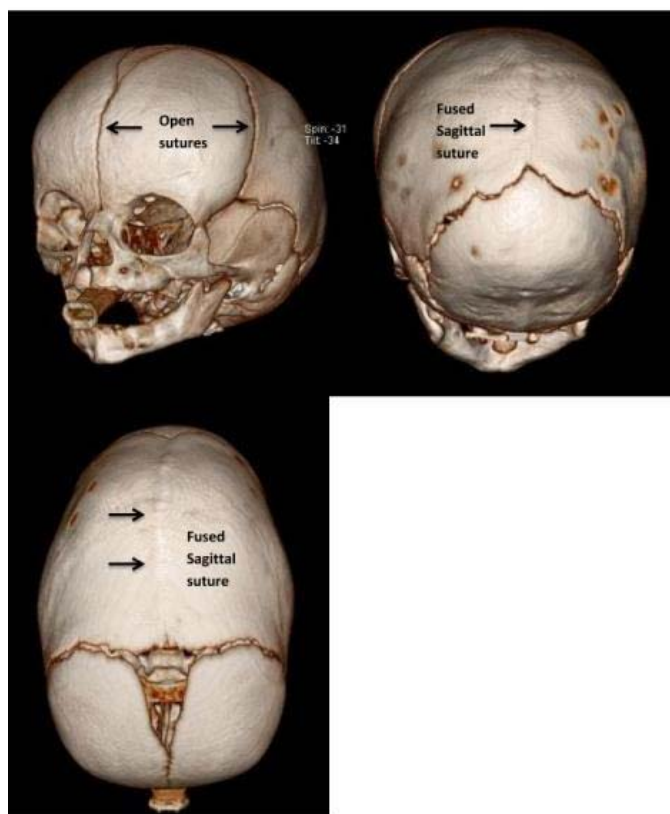
**Methods:** Retrospective chart review

**Results:** Craniosynostosis is the premature closure of cranial sutures. It typically causes head shape deformity, and may cause elevated intracranial pressure with developmental delays. Primary, or congenital, craniosynostosis is most often sporadic, but may be associated with specific syndromes or chromosomal abnormalities. Secondary craniosynostosis is less common, and can occur in metabolic bone diseases, including rickets. We describe the earliest reported case of primary craniosynostosis in a full term infant with x-linked hypophosphatemic rickets (XLH). Born with an abnormally long cranium, at 3 months of age, she was diagnosed with scaphocephaly secondary to sagittal synostosis, confirmed on 3-dimensional computerized tomography scan (Figure 1). The

patient otherwise had normal growth and no features of rickets. Family history was notable for XLH in her mother, maternal grandmother, and maternal cousins. Serum laboratory studies showed low phosphorus (4.0mg/dl [range 4.8-8.1mg/dl]) and elevated alkaline phosphatase (590 IU/L [range 110-320 IU/L]). Serum calcium, parathyroid hormone, vitamin D, and urine calcium were normal. Urine phosphorus was 3 mg/dL. Treatment with phosphate and calcitriol replacement began at 4 months, and she had cranial vault reconstruction at 5.5 months without complication. The XLH diagnosis was confirmed by genetic testing, identifying the same PHEX mutation as her mother. At 10 months of age she was noted to have mild lower extremity bowing which improved after continued treatment with phosphorous and calcitriol replacement. Growth and development has been normal, and at 2 years of age her height Z-score was -0.34.

**Conclusions:** Prior case reports and series have described craniosynostosis in XLH during childhood, more typically occurring after treatment initiation. This is the earliest report of primary craniosynostosis in XLH, and indicates that craniosynostosis may be a presenting feature of XLH.

Figure 1. Primary sagittal synostosis in an infant with x-linked hypophosphatemic rickets



Lyon, Lyon, France; Sylviane Ailloud, Physician's Assistant; Herve Lejeune, MD; Rolland Chapurlat, MD, Hospices Civils de Lyon,, Lyon, France; Stephanie Boutroy, MD, Université de Lyon,, Lyon, France; Cyrille Confavreux, MD, Hospices Civils de Lyon,, Lyon, France

**Objectives:** Klinefelter syndrome (KS) is a frequent disease due to the karyotype disorder XXY (1/660 male births). Patients with KS have an increased incidence of hip fracture and a prevalence of osteoporosis of about 40%. Data on bone microarchitecture are scarce in KS patients and we aimed to analyze it in vivo by high resolution peripheral quantitative tomography (HRpQCT).

**Methods:** Non-mosaic KS patients included in the French Research Fertility Program ( [NCT01918280](#).) were included before introduction of androgen therapy. They underwent assessment of areal BMD at lumbar spine and hip as well as whole body composition by DXA (DiscoveryA, Hologic®) and bone microarchitecture at distal tibia and distal radius by HR-pQCT (XtremeCT, Scanco Medical AG®). Each patient was age-matched with three healthy men from the STRAMBO cohort for the patients more than 18 years olds and vitados cohort study when they are <1\_ years old.. Statistical analyses were adjusted for height and body weight.

**Results:** Twenty-four patients with KS and 66 healthy controls were included in this analysis. Mean ( $\pm$ SD) age and body mass index of KS patients were  $22.5 \pm 1.1$  years and  $24.8 \pm 0.4$  kg/m<sup>2</sup>. None of the subjects had fracture history. 36% of KS patients had low serum total testosterone (<10nmol/L). Relative appendicular lean mass was lower in KS than controls ( $7.5 \pm 1.3$  vs  $8.9 \pm 1.0$  kg/m<sup>2</sup>;  $p < 0.001$ ). Lumbar spine and total hip areal BMD were significantly lower in KS patients than controls:  $0.94 \pm 0.16$  vs  $1.08 \pm 0.14$  g/cm<sup>2</sup> and  $0.83 \pm 0.16$  vs  $0.98 \pm 0.14$  g/cm<sup>2</sup> respectively ( $p < 0.01$ ). At the tibia, trabecular bone was impaired as reflected by a lower volumetric density:  $193 \pm 39$  vs  $225 \pm 34$  mg/cm<sup>3</sup> ( $p < 0.001$ ) and trabecular number:  $1.86 \pm 0.25$  vs  $2.03 \pm 0.29$  ( $p < 0.05$ ). KS patients also had a 24% thinner cortex at the tibia compared to healthy controls (cortical thickness:  $1.13 \pm 0.30$  vs  $1.48 \pm 0.27$   $\mu$ m;  $p < 0.001$ ). By contrast, distal radius microarchitecture was not significantly different between KS patients and controls.

**Conclusions:** In young KS patients, naïve of androgen therapy, we observed lower areal and volumetric BMD and severely impaired trabecular and cortical bone microarchitecture at the weight-bearing distal tibia. This study will allow for the analysis of bone microarchitecture impairment according to testosterone serum levels in KS patients.

P3-238

#### OSTEONECROSIS OF THE JAW AND HYPERCALCAEMIA: SERIOUS ADVERSE EFFECTS OF DENOSUMAB USE IN ADOLESCENTS

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P3-237

#### PATIENTS WITH KLINEFELTER SYNDROME HAVE PRECOCE BONE MICROARCHITECTURE IMPAIRMENT: PRELIMINARY RESULT OF THE KLINOS STUDY

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FRCS, Royal Orthopaedic Hospital, Birmingham, United Kingdom; Luke Rogers, MBBS, Calderdale & Huddersfield NHS Foundation Trust, Halifax, United Kingdom; Wolfgang Hoegler, MD, Birmingham Women's and Children's Hospital NHS Trust, Birmingham, United Kingdom

**Objectives:** Giant cell tumour of bone (GCTB) is a benign, locally aggressive tumour whose neoplastic stromal cells express receptor activator of nuclear factor kappa-B ligand (RANKL) and activate its receptor RANK on osteoclast-like giant cells. Denosumab (RANKL inhibitor) is an FDA/EMA approved treatment for GCTB in adults and ‘skeletally mature’ adolescents. Safety concerns include oversuppression of bone remodelling, with risk of osteonecrosis of the jaw [ONJ] and atypical femur fractures during treatment, and rebound hypercalcaemia after treatment cessation. To date, ONJ has never been reported in children or adolescents. We report serious adverse effects of ONJ and rebound hypercalcaemia secondary to denosumab use in 2 adolescents.

**Methods:** Two adolescents with sacral GTCB received denosumab as per trial protocol (Table 1).

**Results:** Following 4 years of therapy (age 19years), P1 developed ONJ after a dental extraction necessitating surgical debridement and sequestration of exposed jaw bone. P2 completed GCTB treatment without complications. Both patients presented unwell with hypercalcaemia and acute kidney injury 6-7 months after denosumab cessation. Other causes of hypercalcaemia were excluded. Since hypercalcaemia was unresponsive to hyperhydration, P1 received repeated doses of calcitonin. P2 received low dose pamidronate and despite prophylactic oral calcium developed symptomatic hypocalcaemia requiring intravenous calcium. Both patients received treatment for vitamin D deficiency.

**Conclusions:** Here, we report the first case of ONJ in an adolescent. Both adolescents were naïve to chemotherapy, radiotherapy, bisphosphonates, corticosteroids and metastases free; hence, denosumab therapy was confirmed as the cause of P1’s ONJ, and both patients’ rebound hypercalcaemia. Over-suppression of bone remodelling due to this potent, high-dose antiresorptive drug has to be weighed up against its effect on tumour shrinkage. These cases call for close monitoring for side-effects during and after therapy, for safety data to be collected in adolescents and consideration on weight-based dosing.

SEE TABLE IN NEXT COLUMN

Table 1: Patient characteristics, treatment indication, duration, dosing information and hypercalcaemia management

	Patient 1 (P1)	Patient 2 (P2)
Age at diagnosis	14 years 9 months	14 years 2 months
Gender	Male	Female
Weight (Kg)	56.5	45.6
Location of GCTB	Sacrum	Sacrum
Denosumab indication	Tumour recurrence following surgery and embolization	Large tumour not amenable to surgery
Denosumab regimen ClinicalTrials.gov Identifier: NCT00680992	120 mg subcutaneously on day 1, 8,15, 28 and then 4 weekly	120 mg subcutaneously on day 1, 8,15, 28 and then 4 weekly
Individual dose (mg/kg)	2.1	2.6
Total number of doses	46	18 (12 pre-, and 6 post-operative)
Cumulative dose over treatment duration (total, and mg/kg)	5,520 mg 98 mg/kg	2,160 mg 47 mg/kg
Total treatment duration	3.6 years	1.3 years
Reason for treatment cessation	Osteonecrosis of the jaw (ONJ)	End of treatment
<b>Rebound hypercalcaemia</b>		
Time from last denosumab dose	7 months	6 months
Calcium at presentation	3.1 mmol/L (nL 2.2-2.7)	3.4 mmol/L (nL 2.2-2.7)
Creatinine at presentation	180 µmol/L (nL 80-120)	137 µmol/L (nL 37-70)
Parathyroid hormone	3.7 ng/L (nL 11-29)	< 3 ng/L (nL 11-29)
25 hydroxy-vitamin D	10.5 nmol/L (nL >50)	17 nmol/L (nL >50)
Treatment	Hyperhydration + calcitonin (400IU in 500 mls 0.9% NaCl over 6 hours)	Hyperhydration + pamidronate (0.6 mg/kg, over 8 hours, for 2 days)
Recurrent hypercalcaemia	Yes x2, requiring repeat calcitonin	No

POSTER SESSION 3  
Saturday, September 16, 2017, 12:00-1:00pm  
P3 - Endocrine care transition  
P3-300 – P3-304

P3-300

**USE OF BIO-SIMILAR GROWTH HORMONE IN INDIA**  
Vaman V Khadilkar, MD,DNB, MRCP, DCH; Veena H Ekbote, PhD, Hirabai Cowasji Jehangir Medical Research Institute, Pune, India; Ankita Maheshwari, MD, BHARATI VIDYAPEETH MEDICAL COLLEGE UNIVERSITY, PUNE, India; Anuradha V Khadilkar, MD, DCH, Hirabai Cowasji Jehangir Medical Research Institute, Pune, India

**Objectives:** To study efficacy and safety of use of Biosimilar growth hormone (GH) in Indian children with growth disorders.

**Methods:** We studied (retrospectively) 107 patients (from January 2008-2017) treated with Biosimilar growth hormone (GH) (Headon [Somatropin], Sun Pharmaceutical Industries Ltd, Mumbai, India) -dose 30 mcg/kg/day, subcutaneously, 7 injections/week. Height, stimulated GH and insulin like

growth factor -1(IGF-1) concentrations were assessed as indicated. Height for age z-scores (HAZ) were calculated.

**Results:** 48% children were growth hormone deficient (GHD), 17% had Multiple Pituitary Hormone Deficiencies (MPHD), 14% had Idiopathic short stature (ISS), 5% were Small for gestational Age (SGA), 10% had Skeletal Dysplasia (SD), 6% children had Turner Syndrome (TS).

Mean stimulated GH was  $1.74 \pm 1.6$ ,  $0.62 \pm 0.6$ ,  $8.3 \pm 1.5$  and  $12.4 \pm 5.9$  ng/ml in GHD, MPHD, ISS and SGA children, respectively. Mean IGF-1 concentrations at baseline were  $63.5 \pm 37.2$ ,  $24 \pm 5.6$ ,  $119.6 \pm 65.9$ ,  $73.7 \pm 81.9$ ,  $94.5 \pm 22.8$  in GHD, MPHD, ISS, SGA and SD children.

There were no serious adverse reactions; 9 instances of headaches, 2 of local reaction at injection site, 1 each of hives and facial oedema were reported. Reactions were mild and were treated symptomatically.

Mean baseline HAZ was  $-4.4 \pm 1.3$ ,  $-4.8 \pm 1.3$ ,  $-2.8 \pm 1.1$ ,  $-4.2 \pm 2.1$ ,  $-4.1 \pm 1.6$  and  $-3.7 \pm 1.2$  in children with GHD, MPHD, ISS, SGA, SD and Turner syndrome. The mean duration of treatment was  $2.0 \pm 1.6$  years. Further, at the end of GH therapy, the HAZ was significantly ( $p < 0.05$  for all) improved in all children with the mean HAZ of  $-2.9 \pm 1.2$ ,  $-2.4 \pm 1.8$ ,  $-1.8 \pm 1.2$ ,  $-2.7 \pm 2.2$ ,  $-3.3 \pm 1.4$  in GHD, MPHD, ISS, SGA, SD respectively and was marginally significant ( $p = 0.057$ ) in children with Turner syndrome. The mean HV during the first year of treatment and after the first year was  $10.6 \pm 2.7$ ,  $7.6 \pm 2.2$  in GHD,  $11.3 \pm 3.6$ ,  $6.8 \pm 1.9$  in MPHD,  $8.8 \pm 1.8$ ,  $7.8 \pm 1.6$  in ISS,  $10.6 \pm 2.9$ ,  $6.7 \pm 0.7$  in SGA,  $8.8 \pm 2.0$ ,  $7.05 \pm 0.8$  in SD and  $7.9 \pm 1.6$ ,  $6.1 \pm 0.8$  cm in Turner syndrome respectively.

**Conclusions:** A biosimilar growth hormone such as the one used in the present study was effective and safe for treatment in children where growth hormone use is indicated.

P3-301

#### PARTIAL RECOVERY OF PITUITARY FUNCTION AFTER LINEAR GROWTH IN PATIENTS WITH CONGENITAL COMBINED PITUITARY HORMONE DEFICIENCY (CPHD)

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**Objectives:** To evaluate pituitary function in patients with CPHD after linear growth.

**Methods:** Forty-six patients with CPHD (28 male) underwent stimulation test after the end of linear growth. Recovery of GH axis was considered when both GH peak to the insulin tolerance test (ITT) was higher than 5ug/L and IGF1 higher

than -2 standard deviations (SD) for age and sex. Other axes were evaluated in all CPHD patients along their follow-up.

**Results:** Two patients presented transient recovery of GH axis. The first presented GH deficiency (GHD) and diabetes insipidus, besides asthma. GHD diagnosis was done at 2yrs and 2mo with height of 73 cm (Z -4.4), target height (TH) 165cm (Z -1.4), bone age (BA) 6mo and GH peak of 1.5 and 0.5ug/L in two clonidine tests (CT). Pituitary magnetic resonance imaging (MRI) showed anterior lobe (AL) of normal dimensions, centered pituitary stalk and non-visualized posterior lobe (PL). He was treated with GH up to 18 yrs, final height (FH) 167 cm, -1.2 SD. At 18 yrs presented GH peak of 10.6ug/L in ITT. The second patient harbored GH, TSH and ACTH deficiencies. He was diagnosed with GHD at 8yrs and 2mo with height of 111cm (Z -2.7), TH 166cm (Z -1.2), BA 5 yrs and GH peak to CT and glucagon test of 1.7 and 1.6ug/L, respectively. He took GH up to 16 yrs, FH 174cm, -0.1SD. At age 17, GH peak to ITT was 14.7ug/L. MRI showed hypoplastic AL and non-visualized PL. In the follow up both patients maintained IGF1 > -2SD and sustained bone mass for at least 1.5yr, but IGF1 decreased after that period. ITT was repeated, GHD was confirmed and GH replacement was resumed. Only one patient recovered gonadotropic axis. This was a female patient harboring the *GLI2* mutation c.2353\_2368del p.Leu788Serfs\*7 in heterozygous state. She presented GH, TSH, LH/FSH deficiencies with hypoplastic AL and ectopic PL. She had spontaneous menarche at 16 yrs, but evolved with secondary amenorrhea and low LH/FSH levels. At 26 yrs she delivered a healthy baby after ovarian stimulation. Two years after delivery she presented regular menses and spontaneously got pregnant.

**Conclusions:** The recovery of at least one pituitary axis in CPHD is rare but possible, highlighting the importance of clinical follow-up.

P3-302

#### ASSESSMENT OF TRANSITION CARE IN LATIN AMERICA.

Magdalena Mira, MD, Universidad de Chile, Santiago, Chile; Hamilton R Cassinelli, MD, Centro de Investigaciones Endocrinológicas "Dr. César Bergadá" /CEDIE), CONICET - FEI - División de Endocrinología, Hospital de Niños "Ricardo Gutiérrez", Buenos Aires, Argentina; Ethel Codner, MD, University of Chile, Santiago, Chile

**Objectives:** Transitioning from pediatric to adult care is known to be a critical time in the care of patients with chronic diseases. A complete absence of information regarding the transition programs for adolescents in Latin America exists. The aim of this study was to evaluate the transitioning process in Latin America.

**Methods:** A survey to evaluate the transition experience of Pediatric Endocrinologists in different countries (N:13) of South and Central America was sent by email or given personally to Pediatric Endocrinologists that attended SLEP 2015-2016 (N: 457).

**Results:** The total number of questionnaires that were answered was 194 (42%). Most of the physicians were Pediatric Endocrinologist (87%) and pediatricians (8%). A transition of patients to adult care was reported in 97% of the responders; the remaining 3% referred to see adult patients in their clinic. The methodology for transferring the patients to adult care is shown in the Table. The quality of the transition was perceived as regular, poor and as good by 44%, 7% and 38% of the physicians respectively. The most significant factor associated with a good quality of transition care was the presence of a program including a meeting with the adult team ( $p<0.05$ ).

**Conclusions:** This is the first study that has evaluated the transition of pediatric endocrine patients to adult care in Latin America. The transition quality is perceived as regular and done by writing a referral note or complete summary of clinical history in most of the cases. Few physicians report the presence of a transfer program in their center. This could be the first step to motivate the health systems to develop a more organized approach to the transition process in endocrine diseases.

**Table:** Method used for transferring patients to adult care in the different countries.

	Referral Note	Complete Summary of Clinical History	Transfer Program	Meeting with Adult Team
Chile (N: )	38% (17/45)	38% (17/45)	7% (3/45)	18% (8/45)
Argentina(N: )	11% (9/81)	49% (40/81)	2% (2/81)	37% (30/81)
Brazil (N: )	29% (4/14)	29% (4/14)	21% (3/14)	21% (3/14)
Mexico (N: )	24% (4/17)	65% (11/17)	12% (2/17)	0% (0/17)
Other (N: )	44% (14/32)	44% (14/32)	3% (1/32)	9% (3/32)
Total (N: )	25% (48/189)	46% (86/189)	6% (11/189)	23% (44/189)

P3-303

**COMMUNICATION IS THE KEY! FINDINGS FROM TRANSITION OF ADOLESCENTS WITH GROWTH HORMONE DEFICIENCY (GHD) IN GERMANY**

*Jakob Meinel, Medical Student, MVZ Dr. Eberhard & Partner Dortmund, Dortmund, Germany; Katharina Kühle, MD, University Children's Hospital Münster, Münster, Germany; Eva Jürgens, Academic assistant; Annette Richter-Unruh, PhD, University Children Hospital, Münster, Germany*

**Objectives:** Progress in GHD research has shown the necessity for some patients for GH-substitution, even after skeletal maturity is reached, thus requiring re-evaluation and therapy of GH-deficiency beyond paediatric care. We aim to identify the experiences and wishes of GHD Patients for the transition from paediatric to adult care.

**Methods:** Surveys were sent out to 1437 Patients that had been in therapy for GHD in our University Hospital and nearby ambulant medical centre. Their birth year ranged from 1967 to 1998. The Survey covered questions concerning the condition and therapy during childhood, adolescence and adulthood, the transition phase from paediatric to adult care. Further the patients' wellbeing and satisfaction was enquired into. The survey consisted largely of tick-boxes covering 8 pages, which were completed anonymously. 117 were returned for evaluation.

**Results:** Ordinal regression of independent variables (IV) on perceived success of the transition process showed that

patient information and awareness of continued care in adulthood is key ( $p=0,001$ ). The only other examined IV showing significance was patients transition willingness ( $p=0,025$ ). A joint appointment with the patient, as well as paediatric and adult physician also did not show to be significant ( $p=0,149$ ) for transition success. However, 50% of patients that did not participate in a joint appointment said it would have helped their transition.

23 (19.7%) patients remembered undergoing the GH stimulation test after skeletal maturity was reached. Of the others, 51,1% were interested in conducting a stimulation test to evaluate the current GH status. Fishers exact test and phi-coefficient showed a relationship between persistency of GHD in adulthood and existence of isolated GHD or GHD in combination with other pituitary hormone insufficiencies ( $p=0,005$ ,  $\phi=0,51$ ). GHD persisted in 75% of patients with combined pituitary hormone insufficiencies.

**Conclusions:** Physicians must adequately discuss transition to adult care and implications of GHD with patients due to high influence on transition success. For improving transition patients' most frequent wish was more information about transition (43,6%). 31.6% wished for more information on the disease.

P3-304

**QUALITY OF LIFE AND HEALTH NEEDS DURING TRANSITIONAL CARE FROM PAEDIATRIC TO ADULT AGE IN MCCUNE-ALBRIGHT SYNDROME**

*Daniele Tassarì, MD, Università di Torino, Torino, Italy; Patrizia Matarazzo, MD, University of Turin, Torino, Italy; Valter Dal Pos, Family Association, European Association of MAS, Torino, Italy; Roberto Lala, MD, University of Turin, Torino, Italy; Luisa De Sanctis, PhD, Regina Margherita Children's Hospital – Università di Torino, Turin, Italy*

**Objectives:** The McCune-Albright Syndrome (MAS) is a sporadic rare congenital disorder with an estimated prevalence ranging from 1:1,000,000 to 1:100,000. It is caused by a post-zygotic somatic activating mutation of GNAS gene resulting in an increased Gs $\alpha$  protein signaling responsible for scattered bone cells and endocrine tissues hyperfunctions, with wide phenotypic spectrum. This study analyzes the quality of life (QoL) and health needs during transitional care from paediatric to adult age in MAS patients.

**Methods:** An anonymous semi-structured questionnaires focused on the disease clinical manifestations, the comorbidities, the professional occupation, the emotional and sexual bonds, the clinical assistance and the need of social and psychological support has been distributed through the EAMAS (European Association of MAS) mailing list to MAS patients >18 years old.

**Results:** Data from 15 patients (2M and 13F, with an average age of 31.3 years old, ranging from 18 to 58) were collected. All of them display polyostotic fibrous dysplasia, 10 had peripheral precocious puberty, 3 hyperthyroidism, 1 GH-hypersecretion and 3 hypophosphatemic rickets; moreover, 13 patients disclose walking impairment, 3 visual defects, 1

hearing deficit, 4 aesthetic problems due to craniofacial fibrous dysplasia; 13/15 patients (86%) are still receiving health care, 8 from paediatric endocrinologists, 2 from paediatric orthopaedics, 3 from paediatric neurosurgeons, 3 only from adult endocrinologists. Pain was recorded from 13/15 patients (86%), with an average score of 6.9 (0-10 scale): 1 patients don't treat it, 10 utilize a pharmacological therapy, associated to non-conventional therapy in further 4 subjects.

The most compromised areas seem those regarding job activities (present in 9/15 patients) and emotional/sexual bonds (in 13/15 patients). The QoL was defined very good by 1 patient, good by 5, acceptable by 7, poor by the remaining 2. Only 8 (53%) declare to have relevant clinical and psychological support at evaluation-time.

**Conclusions:** Transitional cares from paediatric to adult age represent indeed a difficult moment, especially for rare diseases as MAS; thus, it would be desirable to strengthen management in this age, by expanding clinical and patient networks.

## POSTER SESSION 3

**Saturday, September 16, 2017, 12:00-1:00pm**

### **P3 - Fetal and neonatal endocrinology and metabolism, including hypoglycemia**

**P3-500 – P3-525**

P3-500

#### **EFFECTS OF LONG-ACTING RELEASE OCTREOTIDE IN TREATING 15 SAUDI CHILDREN WITH CONGENITAL HYPERINSULINISM: A CLINICAL TRIAL**

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**Objectives:** To simplify the daily treatment regimen of children with congenital hyperinsulinism (CHI), by replacing three-four daily s.c injection of octreotide with single and monthly intramuscular (i.m) injection of long-acting release (LAR) octreotide.

**Methods:** In this clinical trial 15 patients with CHI who are on s.c injections of octreotide were started on monthly i.m (LAR) octreotide injection. Families were instructed to continue monitoring the blood glucose and to give s.c octreotide as needed. The growth, glucose readings, CBC, LFT, IGF1, Ha1C were monitored before each i.m LAR octreotide injection. The patients were followed up for minimum of 6 months.

**Results:** Twelve of 15 patients (80%) were able to maintain their glucose level within the target and completely stopped the s.c octreotide injections (most of them were able to do so after the first i.m LAR octreotide injection), while 20% were clearly unable to stop or decrease their daily s.c octreotide injections. Apart from hyperglycemia in one patient, we did not encounter any serious complications.

**Conclusions:** LAR octreotide is effective and safe in treating most of our patients. Moreover, it is certainly simplified the medical care of those children.

P3-501

#### **AN IN VITRO MODEL OF CONGENITAL HYPERINSULINISM CAUSED BY MUTATIONS IN HNF-1A**

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**Objectives:** The pancreatic  $\beta$ -cell secretes insulin to coordinate nutrient flux and storage, a process that results in hyper- or hypoglycemia if not perfectly balanced. Congenital hyperinsulinism is caused by a number of  $\beta$ -cell defects that result in unregulated insulin secretion and ensuing hypoglycemia. Heterozygous mutations in the transcription factor HNF-1 $\alpha$  are an increasingly recognized cause of hyperinsulinism during infancy. Interestingly, mutations in HNF-1 $\alpha$  can also cause monogenic diabetes (MODY3) in adults and have been implicated in the pathogenesis of type 2 diabetes. However, the role that HNF-1 $\alpha$  plays in  $\beta$ -cell function, especially in hyperinsulinism, remains unknown.

**Methods:** The recent development of techniques to differentiate human pluripotent stem cells (hPSCs) into  $\beta$ -cells has opened up new avenues for research. In these studies, we use both  $\beta$ -cells derived from hPSCs and the EndoC- $\beta$ H cell line, a stable engineered human pancreatic  $\beta$ -cell line with glucose-responsive insulin secretion. Using both stable genomic knock-out by CRISPR/Cas9 and acute knockdown with siRNA technology, we have developed models of hyperinsulinism caused by HNF-1 $\alpha$  haploinsufficiency in order to better investigate the molecular mechanism behind this emerging cause of congenital hyperinsulinism.

**Results:**  $\beta$ -cells differentiated from hPSCs lacking one or both copies of HNF-1 $\alpha$  have increased basal insulin secretion along with impaired secretion upon stimulation with glucose. We are currently conducting experiments in the EndoC- $\beta$ H cell line following acute knockdown of HNF-1 $\alpha$  using siRNA technology.

**Conclusions:** hPSC-derived  $\beta$ -cells lacking one or both copies of HNF-1 $\alpha$  have increased basal insulin secretion, recapitulating the phenotype seen in patients who present with hyperinsulinism in infancy due to heterozygous HNF-1 $\alpha$  mutations. Based on the observation that diazoxide improves hyperinsulinism in these patients, we anticipate that HNF-1 $\alpha$ -deficiency will result in excessive insulin secretion due to dysregulation of the expression of key regulatory gene(s) within the insulin secretion pathway upstream of the K<sub>ATP</sub> channel. The development of this *in vitro* human model of congenital hyperinsulinism HNF-1 $\alpha$  haploinsufficiency will allow us to elucidate the molecular mechanism underlying this disease.



# ENDOCRINOLOGICAL DISORDERS IN CHILDREN WITH CONGENITAL INFECTION OF ZIKA VIRUS

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**Background:** Congenital infections are associated with endocrine disorders. The World Health Organization has declared an international health emergency over the spread of the Zika virus, now known to cause devastating birth defects. The Zika virus has been linked to microcephaly in children born to infected mothers, as well as blindness, deafness, seizures and other congenital defects.

**Objectives:** The aim of this study is to identify endocrine disorders in children born with Congenital Zika Syndrome.

**Methods:** children (43 girls and 34 boys) with clinical and molecular diagnosis of congenital Zika virus infection were enrolled and followed for their first year of life. Clinical and hormonal data were collected.

**Results:** Growth disorders - 29 children (17 girls and 12 boys) have short stature, 25 with prenatal origin (41- 46 cm of birth length), and all infants presented low first-year growth velocity (below percentile 3). IGF1 levels ranged from 14 to 132 ng/ml (medium 25ng/ml). Gonadal disorders: 12 children (9 boys and 3 girls) were affected. 4 boys with cryptorchidism, 3 boys with micropenis and 2 boys with hypospadias; 3 girls with coalescence of the labia minora. Puberty: 2 girls with telarca. Thyroid: 2 boys with hypothyroidism. Dyslipidemias: 8 children ( 4 boys and 4 girls) presented hypercholesterolemia and 3 hipertriglicerydemia.

**Conclusions:** Congenital Zika Syndrome has been linked to endocrine disorders, specially short stature.

P3-503

# SHORT AND LONG-TERM OUTCOME OF PATIENTS WITH CONGENITAL HYPERINSULINISM

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**Objectives:** Congenital hyperinsulinism (CHI) occurs in 1/25000 to 1/50000 birth and frequently becomes the cause of persistent hypoglycemia in neonates. Most of persistent hypoglycemia due to CHI is caused by genetic defects. The objective of this study is to evaluate the adequacy of treatment choice and long-term prognosis of CHI patients in one institute.

**Methods:** We retrospectively investigated clinical course, laboratory data, diagnosis, treatment modality, and short and long-term outcome in patients with hyperinsulinemic hypoglycemia through their medical records from 2002 to 2017.

**Results:** 44 patients from 4-month-old to 46-year-old (current age), diagnosed as hyperinsulinemic hypoglycemia were involved in this study. Observation periods were from 4 months to 14 years. Most of the patients were diagnosed in their first to second days after birth, while 8 patients were diagnosed at 3 to 12-month-old. 13 patients were transient, and 24 patients were diagnosed as persistent type CHI. 11 out of these 13 transient type were born preterm or LFD (Light for date). 14 patients were born HFD (Heavy for date), 10 of which had ATP-sensitive potassium channel abnormalities. Genetic evaluations were performed in 21 patients; particular gene mutations were found in 13 patients (ABCC8 gene mutation in 9, KCNJ11 gene mutation in 2, GLUD1 gene mutation in 2 ).The long-term prognosis of 24 persistent type CHI patients were; 1 case treated only with diet control, 11 cases with continued diazoxide, 2 cases with octreotide, 1 case with combination of diazoxide and octreotide. In 9 cases partial or subtotal pancreatectomy was performed, which was decided upon the result of <sup>18</sup>F-DOPA PET-CT. Among those who received pancreatectomy, 4 patients became insulin-dependent diabetes mellitus, and 2 patients needs to continue treatment for hyperinsulinemic hypoglycemia. Although at least 6 patients showed verbal delay in their infancy, considerable mental retardation was observed in only one grown-up case.

**Conclusions:** Genetic testing and imaging study using <sup>18</sup>F-DOPA PET-CT, in addition to clinical evaluation are helpful for the decision of treatment choice. Long-term neurological outcome with adequate medical and surgical treatment is better in recent cases when compared to old case, however, further evaluation is necessary.

P3-504

# AUXILIARY DIAGNOSIS WITH DOMESTIC 18F-DOPA PET/CT IN THE TREATMENT OF HYPERINSULINEMIA HYPOGLYCEMIA IN SHANGHAI

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**Objectives:** Hyperinsulinaemic hypoglycaemia (HH) is a rare cause of hypoglycaemia in infants and children with complex genetic etiologies. Patients with HH that fail to maintain euglycemia with proper medicine have to receive near-total

pancreatectomy without  $^{18}\text{F}$ -DOPA PET/CT lesion imaging. Heretofore,  $^{18}\text{F}$ -DOPA PET/CT auxiliary diagnosis in Chinese HH patients, related clinical features and the sequential prognosis have not been described yet.

**Methods:** 16 patients were diagnosed with HH between January and December in 2016 from the Department of Pediatric Endocrinology and Inherited Metabolic Diseases, Children's Hospital of Fudan University using integrated clinical diagnostic protocol of HH. After MR failed to localize the pancreas lesion, newly developed domestic novel  $^{18}\text{F}$ -DOPA PET/CT imaging technique were thereafter applied to localize the underline lesions. The relationship between clinical prognosis and histological, molecular data were analyzed.

**Results:** Ten of sixteen (62.5%) children developed hypoglycemia within the first 3 days after delivery. The result of  $^{18}\text{F}$ -DOPA-PET/CT scanning showed that 3 patients (18.75%) had focal form and the remaining 13 patients (81.25%) had diffuse form lesions. Mutations were identified in 4/16 patients (25%) and the commonest genetic variances were harbored in *ABCC8* gene. 15 patients were initially treated with medical therapy and only 2 patients were unresponsive to medicine. Based on the effects of medical therapy and parents' willing, 5 patients (3 cases with focal form, 2 cases with diffuse form) received operation and were euglycemia without any medical support after surgery, the resected pancreas tissue histological results were consistent with that of PET/CT imaging.

**Conclusions:** 62.5% of the HH patients developed hypoglycemia within the first 3 days after delivery; this highlights the importance of early blood glucose monitoring. In despite of the commonest identified mutations were harbored in the *ABCC8* gene, the genetic variances of the majority of HH patients are still unknown. Through surgical and pathological analysis confirmed that domestic  $^{18}\text{F}$ -DOPA PET / CT could successfully locate the lesion, greatly improve the prognosis in the treatment of HH children.

P3-505

#### MOLECULAR CHARACTERISTICS IN VIETNAMESE PATIENTS WITH NEONATAL DIABETIC

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**Objectives:** Neonatal diabetes mellitus (NDM) may be defined as hyperglycemia diagnosed within the first 6 months of life. The major causes of NDM are mutations of *KCNJ11*, *ABCC8*, *INS*, *EIF2AK3*, *FOXP3* genes or abnormal of chromosom 6q24.

Our aim is to identify mutations in *ABCC8*, *KCNJ11*, *INS*, *EIF2AK3* and *FOXP3* genes or chromosom 6q24

**Methods:** A prospective study was conducted on 40 cases with NDM. All exons of *KCNJ11*, *ABCC8*, *INS* and *EIF2AK3* genes were amplified from genomic DNA and directly sequenced. If the mutation has failed to detect, methylation-specific PCR will be performed to detect the loss of methylated region on chromosome 6q24. Whole exome sequencing will be performed if testing for all known NDM genes has failed to detect

**Results:** Mutations were identified in 33 cases (82,5%). Mutations of *ABCC8* were identified in 11 patients including c.3547C>T (3 cases), c.2239 G>T (1 case), compound heterozygote for missense c.2239 G>T and c.382G>A (1 case), c.3458C>G (1 case), compound heterozygous for splicing c.3403-1G>A and a novel missense c.4519G>C (1 case), c.1303T>C (1 case), c.3596C>T (1 case), c.4139G>A (1 case), and compound two missense c.1793G>A & c.2476C>T (1 case). Nine patients have heterozygous for missense mutation of *KCNJ11*: c.601C>T (2 cases), c.602G>A (2 cases), and c.149G>A, c.875A>G, c.685 G>A, c.553A>C, c.157G>A (1 case for each). Six patients have mutations in *INS* gene: c.265C>T (2 cases), c.127T>A, c.286T>C, heterozygous splicing mutation c.188-31G>A (2 cases). One patient has homozygous missense mutation in *EIF2AK3* (c.1894C>T). One patient with hemizygous for a novel *FOXP3* missense mutation (c.1133C>T). Five patients have abnormal of chromosom 6 including heterozygosity for 2 difference *ZFP57* mutations (7450delT and 7812C>T) (1 case), heterozygosity for three different *ZFP57* mutations 398delT (L133HfsX49), 499C>T (p.R167C) and 760C>T (p.L254F) (1 case), maternal hypomethylation at the *GRB10* and *PEG3* loci (1 case), maternal hypomethylation at the *TND* (6q24), *GF2R* (6q27), *SNRPN* (5q11), *GRB10* (7p12) (1 case) and loss of methylation of the *PLAGL1* DMR (1 case).

**Conclusions:** Determining gene mutations for NDM helps to understand the pathology, diagnosis and chose a suitable therapy.

P3-506

#### ROLE OF IONOTROPIN, A DIGOXIN-LIKE MATERIAL, IN ELECTROLYTE REGULATION DURING PREGNANCY

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**Objectives:** A new insight into electrolyte regulation in the peri-natal period

**Methods:** Potassium Sparing Diuretics (PSD), such as spironolactone, have two functions: first, they inhibit the NaK-ATPase pump and, second, they bind to the mineralocorticoid receptor (MR) and prevent aldosterone binding. We have assigned the name **Ionotropin** to a novel digoxin-like material (DLM) that we have isolated from human and animal plasma. LC-MS fragmentation of Ionotropin is consistent with a phosphocholine ester and the NMR is consistent with a steroid. Ionotropin shares structural features with PSD and may be an endogenous PSD.

**Results:** During the 3rd trimester of pregnancy, there are two unusual aspects of electrolyte regulation. **1st**, there is an unexplained absence of MR signaling in the fetus. We

observed that the serum concentration of Ionomotrin at parturition is more than 20  $\mu$ M, more than 10,000 times the concentration of aldosterone. While the Ionomotrin level was elevated, it would occupy the fetal MR and interfere with aldosterone signaling. During the first week of life, infants lose about 10% of birth weight, are salt wasting and fail to grow. The weight loss coincides with decreases in the extracellular fluids, but the intracellular fluids with high K<sup>+</sup> electrolytes are retained. This describes the biochemistry expected for a PSD. Ionomotrin is present in cord serum. Within two weeks, it disappears from the infant circulation. When the Ionomotrin disappears from the infant circulation, the MR would not be occupied by Ionomotrin, aldosterone responsiveness develops, salt-wasting terminates and growth resumes. **2nd**, during pregnancy, maternal blood pressure and serum Ionomotrin levels are both elevated. After child birth, both maternal blood pressure and Ionomotrin levels return to pre-pregnancy levels. An endogenous PSD that required components of the maternal and fetal compartments for its synthesis, similar to estradiol, would account for the changes in maternal and fetal blood pressure. **Conclusions:** We propose that Ionomotrin functions as [1] an endogenous PSD, [2] requires maternal and fetal components for its synthesis and [3] accounts for changes in electrolytes and blood pressure that occur during late pregnancy and immediately after birth.

P3-507

#### MANAGEMENT AND CLINICAL OUTCOME OF CONGENITAL HYPERINSULINISM DUE TO FOCAL TYPE

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**Objectives:** Focal form of Congenital Hyperinsulinism (FCHI) is characterized by a cluster of abnormal insulin over-secreting  $\beta$  cells within a restricted area of the pancreas. The distinction of FCHI based on genetic, radiologic, and intraoperative pathologic diagnoses is crucial for more effective management strategies. The objective of this study is to highlight the variable treatment response of FCHI patients.

**Methods:** Retrospective collection of FCHI patients from 1996 to 2014.

**Results:** 25 patients (17 males) with FCHI were collected. Paternally inherited heterozygous *ABCC8/KCNJ11* mutations were identified in 18 patients, with 7 cases having negative genetics. Two of the patients were diagnosed with syndromes (Kabuki, Beckwith-Wiedemann). 18F DOPA-PET CT scan confirmed a focal lesion in all 25 patients, with the pancreatic

head being the most frequent location of the lesion. Prior to surgery the majority (22/25) of the patients were unresponsive to Diazoxide treatment, with twelve responding to Octreotide, three to Sirolimus, one to Lanreotide and one to Diazoxide. Nineteen patients underwent surgery and six were treated with conservative treatment. 14 patients were cured post pancreatic surgery. The rest of them responded to one medication (8/25) or combination of two medications (3/25). Regarding post-surgery complications: two children resulted in pancreaticojejunostomy and two developed pancreatic insufficiency. None of our patients developed diabetes until now. Apart from one patient with developmental delay and epilepsy due severe hypoxic hypoglycaemic brain injury, the rest of didn't demonstrated any neurocognitive dysfunction.

**Conclusions:** Our cohort confirmed that the partial pancreatectomy remains the first line treatment for focal type CHI. Although, more conservative medical treatments might be an alternative option especially for patients with lesion in the pancreatic head. There is a need for further research in all of these areas, in order to establish the optimal therapy, that minimizes side effects and improves the outcome.

P3-508

#### NON-DIABETIC HYPOGLYCAEMIA IN CHILDREN ADMITTED TO A TERTIARY PAEDIATRIC ENDOCRINE CENTER IN 2015-2016

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**Objectives:** Hypoglycaemia is a common clinical problem related to many entities in non-diabetic patients. The aim of the study was to establish the frequency of hypoglycaemia observed in non-diabetic patients aged 0-18 years, who were admitted to a tertiary paediatric endocrine center outside the intensive care unit and to determine their possible clinical explanation.

**Methods:** We analysed data for 2015-2016 from the clinical database of a tertiary paediatric endocrine center to identify all non-diabetic hypoglycaemic patients. The clinical notes of the patients were reviewed for demographic data, presence of neurological symptoms/seizures during the hypoglycaemic episodes, developmental delay, relevant recorded morbidities or newly diagnosed conditions. Blood glucose levels (BGLs), treatment of detected hypoglycaemia (glucose solution or glucagon), mean hospital stay and outcome were evaluated. All patients with diabetes or prescribed diabetic medications were excluded from the analysis.

**Results:** We identified 64 hypoglycaemic episodes (3%) at a BG cut-off of 3.6 mmol/l during a total of 2130 hospital admissions. The mean age of included patients was 5.2 $\pm$ 3.8 years, 39.1% were boys. The mean BGLs during these episodes was 2.98 $\pm$ 0.55 mmol/l (1.0-3.6 mmol/l), 18.8% of

the patients had related neurological symptoms or generalized seizures. Previously recorded morbidities were determined in 39.1% (n=25), while 39 patients (60.9%) had newly diagnosed conditions that may explain the presence of hypoglycaemia. The most common morbidities associated with the development of hypoglycaemia were: acute infections with starvation (28.1%), hypopituitarism with combined pituitary hormone or isolated growth hormone deficiencies (26.6%) and congenital hyperinsulinism (14.1%). The mean hospital stay of hypoglycaemic patients was 4.42 days, which was 94% of the mean hospital stay of all admitted children. More than 1/3 of the patients needed glucose infusions to treat hypoglycaemia, 3.1% of children required a glucagon injection. More than 48% of children were continued on a specific therapy afterwards.

**Conclusions:** Non-diabetic hypoglycaemia in admitted patients is not frequent but has significant clinical importance.

P3-509

# 18F-FLUORO-L-DIHYDROXYPHENYLALANINE (18F-DOPA) PET SCANS USED IN THE INVESTIGATION OF CHILDREN WITH HYPERINSULINAEMIC HYPOGLYCAEMIA CAN BE SAFELY AND EFFECTIVELY PERFORMED USING ORAL CHLORAL HYDRATE SEDATION

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**Objectives:** To assess the safety and efficacy of oral sedation in children undergoing 18F-fluoro-L-dihydroxyphenylalanine (18F-DOPA) PET scans to differentiate between focal and diffuse disease in congenital hyperinsulinism (CHI).

**Methods:** 18F-DOPA PET scans have been performed in children with hyperinsulinaemic hypoglycaemia at our institution since 2010. A protocol to allow these to be performed under oral sedation with chloral hydrate was developed, in order to avoid general anaesthesia (GA). A retrospective case note review was performed to determine any adverse effects associated with the procedure, and the number of patients requiring progression to GA to obtain adequate images for diagnosis.

**Results:** 56 patients underwent a PET scan from 2010–2016. The indications were: molecular diagnosis of focal lesions (53.6%); CHI with negative genetics (41.1%); suspected insulinoma (5.3%).

An 18F-DOPA PET scan was performed with oral sedation in 50 (89%; age range 0.08 - 7.22 years, median 0.37 years; weight at time of scan 3.65 - 26.6 kg, median 6.76kg). All the

scans performed using oral sedation resulted in images that were of sufficient quality to allow interpretation (where reports were available). No patients required GA to complete the scan following oral sedation. One patient underwent elective GA due to concern about potential airway obstruction (Beckwith Wiedemann syndrome with large tongue). 5 (8.9%) patients were able to tolerate the procedure without any sedation (age >10.5 years). No post-procedure complications were documented in the patients.

**Conclusions:** Oral sedation for 18F-DOPA PET scans is a safe and effective technique. We present our locally developed sedation protocol for performance of the scan. This includes a period of sleep deprivation followed by a single dose of oral chloral hydrate 1 hour prior to the scan. Patients are accompanied to their off-site scan by a paediatrician or clinical nurse specialist, and are able to return to their base hospital immediately following the procedure. This protocol reduces the need for anaesthetic support, limits the transfer time and avoids the risks of GA.

P3-510

# EXENDIN-3 (9-39), A GLUCAGON-LIKE PEPTIDE 1 RECEPTOR ANTAGONIST AS POTENTIAL THERAPY FOR CONGENITAL HYPERINSULINISM (CHI)

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**Objectives:** Congenital Hyperinsulinism (CHI) is characterised by inappropriate insulin release, leading to hypoglycaemia. Glucagon-like peptide 1 (GLP-1) receptor antagonists have the potential to reduce insulin secretion in CHI. The GLP-1R antagonist exendin-3 (9-39) (Ex-3) has been trialled successfully in adults with CHI but not in young children. The efficacy of the GLP-1R antagonist Ex-3 in reducing insulin in CHI islets has not been reported and was examined in this study.

**Methods:** We monitored insulin release in response to either glucose (20mM) or leucine (10mM) using isolated CHI tissue following surgery (n=3 patients; diffuse CHI, ABCC8 mutation), and human (adult) control islets (n=4 donors). Both the acute and short-term (up to 24 hours preincubation) actions of Ex-3 (100nM) were investigated. Insulin content and release were quantified by ELISA.

**Results:** Untreated human islets responded to glucose by increasing insulin secretion by 195.1±57.3% (n=11). Acute exposure (1 hour) decreased basal secretion by 39.2±8.1%,

and prevented glucose-stimulated insulin secretion. Treating islets for 24 hours with Ex-3 decreased whole cell levels of insulin ( $21.5 \pm 2.5$   $\mu$ g insulin per mg protein, compared to  $34.5 \pm 1.8$  in control). In CHI pancreatic tissue glucose increased insulin secretion by  $239.6 \pm 22.9\%$ . When treated acutely with Ex-3 there was no significant action on basal insulin secretion, but insulin content and both glucose- and leucine-stimulated insulin secretion were severely attenuated. Under these conditions, 20mM glucose did not increase insulin secretion, and leucine-stimulated insulin secretion increased by  $195.3 \pm 11.6\%$  compared to  $580.9 \pm 69.4\%$  in untreated tissue.

**Conclusions:** Blocking receptor activity with Ex-3 inhibits insulin secretion, and also reduces total insulin content. Importantly, CHI tissue treated with Ex-3 is resistant to the stimulatory action of glucose and leucine, reinforcing the view that Ex-3 could have therapeutic benefit in the treatment of neonatal CHI.

P3-511

#### HETEROGENEOUS ISLET CELL ARCHITECTURE OF FOCAL CONGENITAL HYPERINSULINISM DUE TO ABCC8/KCNJ11 MUTATIONS

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**Objectives:** Focal Congenital Hyperinsulinism (F-CHI) is characterised by expansion of a  $\beta$ -cell mass harbouring defects in K-ATP channels within a localized domain of the pancreas. We aimed to examine the relationship between diversity in focal lesions in patients and their clinical phenotypes and outcomes.

**Methods:** Our study is based upon 19 subjects with CHI-F (confirmed mutations in ABCC8/KCNJ11) and originates from a single specialized treatment centre for CHI. Pancreatic surgery was performed for alleviation of sustained hypoglycaemia unresponsive to medical treatment. Post-operative tissue was used to support immunolabelling, gene array analysis and structural studies of focal lesion by serial-block face electron microscopy.

**Results:** Six CHI-F patients were found to have early-onset disease and presented within  $2.8 \pm 1$  day (range 1-7 days) following birth. Within this group of patients we found poorly organised focal lesions that were not readily detectable by  $^{18}\text{F}$ -DOPA PET-CT and surgery involved extended focal resections or sub-total pancreatectomy. We found post-

operative complications within this cohort, including sustained hypoglycaemia. By contrast, thirteen patients had later-onset symptoms of disease, on average  $50.3 \pm 15.3$  days (range 1 to 150 days) following birth and 12/13 cases were cured by lesionectomy. In these cases, focal lesions were detected by  $^{18}\text{F}$ -DOPA PET-CT and discrete, clearly demarcated lesions of endocrine cells were found encapsulated within a protein matrix when analysed post-operatively. The lesion capsule was found to support a dense network of capillaries with inferred protein:protein interactions based upon gene array expression studies implicating functional links to the vascular endothelial growth factor, VEGFA. Enhanced expression of VEGFA in focal lesions was confirmed by immunohistochemistry.

**Conclusions:** We found a degree of heterogeneity in tissue samples, which was strongly correlated with surgery and long-term clinical outcomes. We conclude that the  $\beta$ -cell pathology in CHI-F extends beyond the loss of function defects in K-ATP channels and includes hypervascularization of islets and heterogeneity in extracellular matrix organization.

P3-512

#### MRNA EXPRESSION OF INSULIN/IGF AXIS IN UMBILICAL CORD BLOOD OF SGA NEONATES AND NEONATES WITH HYPOGLYCEMIA

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**Objectives:** Hypoglycemia is the most common metabolic problem in neonatal period, especially in premature or small-for-gestational age (SGA) neonates. However, the pathological mechanisms still remain unknown, and the insulin/IGF signaling in neonate is also unknown. To determine insulin/IGF axis in neonates, we analyzed the mRNA expression of *INSR*, *IGF1R*, *IRS1*, *IRS2*, *SLC2A2* (*GLUT2*) and *SLC2A4* (*GLUT4*) in fetal umbilical cord blood.

**Methods:** We enrolled 52 neonates, mean gestational age was 38 weeks (range: 37-41 weeks), born in the Perinatal Medical Center of Tottori University Hospital, 42 appropriate-for-gestational age (AGA) neonates and 10 SGA neonates. We measured glucose level, serum levels of insulin and IGF-I from the umbilical cord. Umbilical cord blood was also collected immediately into PAX gene Blood RNA Tube, and total RNA from umbilical cord blood was purified using reagents provided in the PAX gene Blood RNA Kit within 4 days and RT-PCR was done. Quantitative real-time PCR analysis was applied for evaluating mRNA expression of *INSR*, *IGF1R*, *IRS1*, *IRS2*, *SLC2A2* and *SLC2A4*.  $\beta$ -actin was used as a control gene.

**Results:** Mean birth weight in AGA was  $2,931 \pm 473$  g (mean  $\pm$  SD) and in SGA;  $1,832 \pm 323$  g. Blood glucose level in SGA ( $41.2 \pm 5.1$  mg/dL) was significantly lower than that in AGA ( $82.7 \pm 33.2$  mg/dL). Serum IGF-1 level of AGA was significantly higher than those of SGA ( $p < 0.01$ ). The mRNA

expression of *IRS2* was significantly increased in SGA compared to AGA ( $p < 0.05$ ), while there was no difference in the expression of *IGF1R*, *INSR*, *IRS1*, *SLC2A2* and *SLC2A4* mRNA and serum insulin levels between SGA and AGA. In SGA neonates with hypoglycemia, *IRS2* mRNA expression was significantly higher than those with normoglycemia.

**Conclusions:** In SGA neonates, *IRS2* mRNA expression was significantly higher. Among SGA neonates, *IRS2* mRNA expression was significantly higher in hypoglycemia group. These findings suggest that intrauterine growth restriction induces the change of insulin/IGF axis and might provide clues as to the underlying cause of neonatal hypoglycemia on SGA.

P3-513

#### **CORD BLOOD ACYLCARNITINE LEVELS: ASSOCIATIONS WITH NEWBORN ADIPOSITY AND HYPERINSULINEMIA**

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**Objectives:** Acylcarnitines are metabolites that reflect mitochondrial metabolism of fatty and amino acids. High levels of various acylcarnitines are linked to obesity and insulin resistance in adults. The role of these metabolites in fetal metabolism is unknown. We examined the relationship between cord blood amino acid and acylcarnitine profiles and markers of adiposity and hyperinsulinemia in healthy infants. We hypothesize that cord blood acylcarnitines may emerge as a tool to identify at-risk children before obesity or insulin resistance develops.

**Methods:** 118 full-term infants born to mothers with normal glucose tolerance were studied. Cord blood acylcarnitine and amino acid levels were measured using a targeted mass spectrometry platform. Cord blood was assayed for leptin and C-peptide. Body composition was measured by air displacement plethysmography. Multivariate linear regression was used to analyze associations of cord blood acylcarnitine levels with measures of newborn adiposity and hyperinsulinemia. Nominal  $p \leq 0.0016$  was used to indicate statistical significance.

**Results:** In cord blood, acylcarnitines C2, C4-DC/Ci4-DC, and C8:1-OH/C6:1-DC were positively associated with leptin, a marker of fat tissue quantity ( $p \leq 0.0016$ ). Acylcarnitines C14, C14:1, C16, C18, and C18:2 were negatively associated with C-peptide ( $p \leq 0.0016$ ). After multiple comparisons adjustment, there were no associations between metabolites and %body fat or fat mass. Analyses were adjusted for newborn sex, race, gestational age, and maternal pre-pregnancy BMI, gestational weight gain, and fasting glucose.

**Conclusions:** C2 and C4-DC/Ci4-DC are products of fatty acid beta oxidation and branched chain amino acid catabolism, respectively, and have been linked to obesity and insulin resistance. The association of higher C2 and C4-DC/Ci4-DC levels in this cohort with leptin may reflect excess fat stores, higher fatty acid oxidation rate, and mitochondrial dysfunction leading to accumulation of acylcarnitine intermediates. While long chain acylcarnitines have been positively associated with insulin resistance in adults, we report a paradoxical negative relationship in newborns. Cord blood acylcarnitine profiles may provide insight into a newborn's metabolic state.

P3-514

#### **INFLUENCE OF FETAL DISTRESS ON THE ARTERIOVENOUS UMBILICAL CORD GLUCOSE CONCENTRATIONS OF TERM NEONATES EXPOSED TO LABOUR**

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**Objectives:** We aimed to establish the relationship between umbilical cord glucose concentrations and known markers of fetal distress among term neonates exposed to labour.

**Methods:** This is a retrospective study of non-diabetic primiparous women diagnosed in labour at term ( $>37$  weeks) from April 2011 to January 2012 in a tertiary maternity centre. Acid-base status and glucose concentrations of paired arterial and venous cord blood were tested using a point-of-care blood gas analyser. Delivery method, Apgar score, and presence of meconium were recorded. SPSS was used for statistical analyses.

**Results:** Data from 358 women and babies were studied. Mean arterial and venous cord glucose concentrations were  $5.3 \pm 1.2$  and  $5.6 \pm 1.2$  mmol/L respectively. 95.5% ( $n=342$ ) delivered vaginally (67% ( $n=240$ ) spontaneous; 28.5% ( $n=102$ ) instrumental) and 4.5% ( $n=16$ ) by emergency caesarean section (CS). Fetal distress precipitated either CS or instrumental delivery in 7.8% ( $n=28$ ) of labours. There was no significant difference in cord glucose concentrations between labours with and without fetal distress. Arterial glucose correlated negatively with venous pH ( $r=-0.16, p < 0.01$ ), venous base excess (BE) ( $r=-0.30, p < 0.01$ ), and arterial BE ( $r=-0.19, p < 0.01$ ). Arterial glucose correlated positively with venous ( $r=0.29, p < 0.01$ ) and arterial ( $r=0.20, p < 0.01$ ) lactate. Venous glucose correlated negatively with venous pH ( $r=-0.16, p < 0.01$ ), venous BE ( $r=-0.30, p < 0.01$ ), arterial pH ( $r=-0.13, p < 0.01$ ), and arterial BE ( $r=-0.19, p < 0.01$ ). Venous glucose correlated positively with venous ( $r=0.24, p < 0.01$ ) and arterial ( $r=0.18, p < 0.01$ ) lactate. Arterial glucose was significantly higher in infants with Apgar scores  $<9$  at five minutes compared with those scoring 9 or above ( $6.4 \pm 1.2$  vs  $5.2 \pm 1.1$  mmol/L,  $p=0.01$ ). Presence of meconium had no statistically significant impact on glucose concentrations.

**Conclusions:** Arteriovenous umbilical cord glucose concentrations rise as lactate rises and as pH and BE fall,

possibly due to stress-induced anaerobic metabolism and catecholamine-induced glucose release. However, several clinical markers of fetal distress had no significant impact on cord glucose. Thus, while a cord glucose concentration outside normative ranges may be part of the biochemical picture of perinatal distress, it is unlikely to be a reliable diagnostic marker.

P3-515

#### **INSULINOMA PATIENTS PRESENT WITH NEUROGLYCOPENIC SYMPTOMS IN THE ABSENCE OF NEUROGENIC SYMPTOMS OFTEN DELAYING THEIR DIAGNOSIS.**

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**Introduction:** Hypoglycemia secondary to insulinoma is rare occurring in 1-4:1,000,000 of the population with the majority >25 years old. Insulinomas can occur either in isolation or associated with multiple endocrine neoplasia type 1(MEN1). 90% of insulinomas are single, 90% are benign and 90% are <2cm. Clinical diagnosis of insulinoma is often delayed and typically presents with multiple episodes of neuroglycopenic symptoms such as disorientation, slurred speech, seizures, irrational and bizarre behavior, confusion and loss of memory.

#### **Aims**

1. To determine if Insulinoma patients present with classical neurogenic symptoms
2. To determine if the proinsulin: insulin ratio suggestive of insulinoma

**Methods:** A retrospective review was conducted on 6 patients that attended the Cook Children Hyperinsulinism Center.

**Results:** We studied 6 patients with insulinomas. The patients median age of diagnosis is 14 years of age (range 5-22 years). 5 patients were females and 1 male. Five of 6 patients had elevated proinsulin levels (mean 68, range 10-190, normal <20 pmol/L) at time of hypoglycemia) and all 6 had an elevated proinsulin: insulin ratios mean 58.3% range 17% to 129% (normal <10%). Neurogenic symptoms were absent in all 6 patients during time of hypoglycemia. All 6 presented with multiple neuroglycopenic symptoms consisting of disorientation, slurred speech, seizures, irrational and bizarre behavior, confusion and loss of memory. Various combination of abdominal MRI (n=3), endoscopic ultrasound (1) and arterial stimulation venous sampling (3) or intraoperative US (6) localized the insulinomas. After surgical resection of the tumors hypoglycemia resolved in all 6 patients. None of which have had a recurrence to date. 4 of the 6 patients were positive for MEN1 with 2 out of the 4 patients with a positive family history of MEN1.

**Conclusions:** Children and adolescents who present with hypoglycemia should be screened for insulinomas by obtaining a proinsulin to insulin ratio at the time of

hypoglycemia. Patients with neuroglycopenic symptoms and proinsulin: insulin ratio of >10% during hypoglycemia are more likely to have insulinoma.

P3-516

#### **OVARIAN FUNCTION AND METABOLIC PROFILE AT THE TIME OF BIRTH IN FEMALE OFFSPRING OF PREGNANCIES COMPLICATED WITH DIABETES**

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**Objectives:** To study the ovarian function and metabolic profile in daughters of pregnant diabetic women at delivery and evaluate the correlation of the offspring and maternal hormonal and metabolic profile.

**Methods:** Daughters exposed during pregnancy to type 2 diabetes (dT2D, n=24); gestational diabetes (dGD, n=26) and pregnancies without diabetes (dC, n=25); and their respective mothers (mT2D, mGD, and mC) were studied. A clinical assessment of the mother and her child was done. A maternal blood sample and venous blood cord were obtained at the time of delivery to measure: sex steroids, anti-Müllerian hormone (AMH) levels SHBG, insulin, glucose, adiponectin, IGF-1, and IGFBP.

**Results: (Table):** Similar gestational age and birth weight was observed in the three groups, but dT2D and dGD had a higher ponderal index and prevalence of large for gestational age. Higher AMH, insulin, IGF-1 levels were found in dT2D than dGD and dC. Lower adiponectin in dT2D compared with dGD and dC was observed.

mT2D had higher testosterone levels and HOMA-IR than mGD and mC. Maternal IGF-1 levels and HOMA-IR had a positive correlation with insulin levels in their female newborn ( $r=0.7$ ,  $P<0.05$ ;  $r=0.7$ ,  $P<0.001$ ; respectively). A positive association between IGF-1 and AMH levels in blood cord samples obtained from the female newborn ( $r=0.5$ ,  $P<0.05$ ) was observed.

**Conclusions:** Daughters of mT2D at the time of birth show similar alterations that have been reported in adult women with insulin resistance. Offspring of pregnancies complicated with gestational diabetes do not exhibit the abnormalities observed in T2D. Maternal insulin resistance is associated with elevated AMH and insulin levels in the newborn. These data suggest that pregestational diabetes may impair ovarian function and metabolic profile of their female offspring.

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### NOVEL ABCC8 MUTATION: PRESENTATION WITH CONGENITAL HYPERINSULINISM AND LATER DIABETES

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**Objectives:** Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in infants and children. Recessive inactivating mutations in the ABCC8 and KCNJ11 genes account for approximately 50% of all CHI cases. To describe a case of a child who was diagnosed with CHI at birth then developed diabetes mellitus at the age of 9 years due to a mutation in the ABCC8 gene.

**Methods:** The index case was a 9 year old boy who was consulted for coincidental hyperglycemia during acute appendicitis. Blood glucose 27.75 mmol/L measured before emergency surgery (perforated appendicitis). On physical examination, he was lethargic, with pale skin and gray in colour. His weight was 35 kg (0.8 SDS), height was 140 cm (0.7 SDS), BMI 17.8 (0.7 SDS). He was born at 29 weeks gestation with a birth weight of 3750 gram, and diagnosed with hyperinsulinism (serum glucose 1.33 mmol/L and simultaneously insulin 22.7 uIU/mL). His mother was diagnosed with gestational diabetes and started on insulin since third month of the pregnancy. Insulin regular and 0.9% sodium chloride intravenous infusion was started preoperatively and insulin was continued postoperatively because of high blood glucose levels. Genetic analysis of coding and flanking intronic regions of the KCNJ11, ABCC8, HNF4A and HADH genes was performed by Sanger sequencing.

**Results:** Blood glucose measured 238 mg/dl, simultaneously insulin: 8.82 uIU/mL (2.6-25), C-peptide: 1.28 ng/ml (0.9-7.1), HbA1c was 9.1%, islet cell, insulin and glutamic acid decarboxylase antibodies were negative. Insulin requirement decreased with improved diet and exercise and the patient was discharged without insulin. There was no requirement of insulin with slightly high HbA1c of 6.4% with diet and exercise. But, at 11.5 years, HbA1c was measured at 9.6% and elevated to 10.4% at follow-up. The patient was homozygous for a novel ABCC8 missense mutation, p.L171F, one of his siblings was homozygous (transient hypoglycemia in the first week of life) and the other heterozygous. Parents were heterozygous.

**Conclusions:** Homozygous ABCC8 gene mutations can present with CHI in the newborn period and diabetes later in life. Patients with homozygous ABCC8 gene mutations who are managed medically should be followed up with blood glucose monitoring.

### A RARE CASE OF NEONATAL THYROTOXICOSIS FOLLOWING TRANSIENT HYPOTHYROIDISM

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**Objectives:** Neonatal autoimmune hyperthyroidism is a rare disorder which occurs in 2% offspring of mothers with Graves' disease. Here we present a rare case of neonatal hyperthyroidism following transient hypothyroidism after birth.

**Methods:** A healthy female infant weighing 2634g was delivered by an uncomplicated lower segment caesarean section at 37 weeks of gestation. Her mother had been diagnosed with Graves' disease 6 years prior to pregnancy. The maternal disease was poorly controlled. The mother was prescribed 15mg methimazole per day. Thyroid function of cord blood was normal (TSH 3.13 µIU/ml, normal range 0.27-4.20 µIU/ml, fT4 1.19 ng/dl, normal range 1.00-1.80 ng/dl), but positive thyroid receptor antibody (TRAb 82.4 %, normal range less than 10 %). The baby was carefully observed, in case that she could have symptoms of thyrotoxicosis. However, her general condition had been fine and she did not present any clinical signs of hyperthyroidism or hypothyroidism. On day 4, thyroid function was tested. The data revealed elevated TSH level (10.86 mIU/l) and normal fT4 level (1.76 ng/dl), suggesting that she was in a state of subclinical hypothyroidism. She was discharged on day 6 with further follow-up appointment at clinic.

**Results:** When she visited our clinic on day 16, she presented tachycardia, poor weight gain and hyperexcitability. Blood test showed elevated fT4 level (3.22 ng/dl) with very low TSH level (0.03 mIU/l), indicating that she suffered from thyrotoxicosis. Ultrasound sonography showed no enlargement of thyroid gland. Thyroid-stimulating hormone receptor antibody was 1090 % (normal range, less than 120%). She was diagnosed with having neonatal Graves' disease switching from hypothyroidism. Methimazole, lugol's iodine and propranolol were started. Within a week, free thyroxine levels normalized and the tachycardia resolved. Levothyroxine was added to the treatment regimen.

**Conclusions:** Low dose of methimazole (lower than 30 mg per day) do not impair thyroid function in the newborn and are regarded as safe during breastfeeding. Simultaneous presence of maternally transmitted thyrotropin receptor-blocking antibodies (TBABs) could cause neonatal hyperthyroidism following transient hypothyroidism as seen in this case.

### CONGENITAL HYPERINSULINISM: BENEFIT ASSESSMENT OF GLYCOSE®<sup>®</sup>, A MODIFIED CORN STARCH.

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**Objectives:** In congenital hyperinsulinism, adequate supply of carbohydrates to avoid hypoglycaemia is an essential part of the treatment. Available starches were not always effective during the fasting periods. Dietary introduction of high amylopectin (Glycosade,Vitaflo), a modified maize starch has been reported to improve glycemia in patients with glycogen storage disease.

**Methods:** To evaluate metabolic impact and the repercussion on hypoglycemia (registration continuous glycemia) from Glycosade supplementation of our patients with congenital hyperinsulinism and continuous nocturnal feeding requeriments.

**Results:** Patient 1. Background: Birth weight 4075gr(+5,03DE). Diffuse nesidioblastosis. Subtotal pancreactetomy. Molecular study: no mutation detected. Examination: abundant adipose paniculus, normal psychomotor development, portal gastrostomy. Treatment: lanreotide, 60mg/m; Levothyroxine; continuous nocturnal feeding. Abdominal ultrasound: thin-walled gallbladder with lithiasis.

	Initial	Glycosade 6m	Glycosade 12m
IGF1(ng/mL)	90	95	107
Insulin(μU/mL)	5.35	2.9	2.32
HbA1c	6.2%	5.7%	6%
BMI	+2.64	+0.14	+0.18

Patient 2. Background: Linebreeding. Alpha-1-antitrypsin deficiency. Diffuse nesidioblastosis. Molecular study: c.3576delG in ABCC8. Diffuse hepatomegaly. Examination: abundant adipose paniculus, normal psychomotor development. BMI 22.83. Treatment: lanreotide, 60mg/m; continuous nocturnal feeding by gastrostomy. Abdominal ultrasound: hepatomegaly, fat infiltration. Both patients signed informed consent. Supplementation with Glycosade nocturnal was initiated, with BMI decreased in both patients. In patient 2 there was a decrease in hypertransaminasemia. In both patients the nocturnal enteral feeding has withdrawn. None of the patients reported gastrointestinal symptoms.

**Conclusions:** The use of modified starches of slow absorption has allowed to reduce the contribution of carbohydrates and calories and has withdrawn the nocturnal enteral feeding in both patients. Significant weight loss or improvement inBMI. None of the patients presented insulin resistance or worsening of hyperglycemia. It is important to develop new strategies for better glycemic control and improvement in the quality of life in this entity.

**VAGINAL BLEEDING IN A FORMER MICRO-PREEMIE AS PRESENTATION OF EXAGGERATED MINI-PUBERTY**

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**Objectives:** In both male and female neonates, there is transient activation of the hypothalamic-pituitary-gonadal (HPG) axis after birth. This phenomenon is referred to as mini-puberty and is well described in medical literature. However, the onset and duration of mini-puberty in former premature neonates is not well defined. Here we discuss a case of mini-puberty presenting with vaginal bleeding in a former extreme premature female infant.

**Methods:** This case describes a 5 month old former 24+2 week twin A of a di-di twin gestation who presented for evaluation for five days of vaginal bleeding. Initial laboratory and radiologic evaluation was consistent with activation of the HPG axis, including a pubertal configuration of the uterus and enlarged ovaries. Brain MRI had previously demonstrated a normal pituitary gland. Differential diagnosis for activation of the axis included multiple causes of central precocious puberty as well as an exaggerated mini-puberty. Bleeding spontaneously resolved and the patient had no further signs of pubertal change. She was closely observed with no recurrence of the bleeding. Her pelvic ultrasound normalized and there was no pubertal progression over her first year of life. Patient was ultimately diagnosed with an exaggerated mini-puberty secondary to her extreme prematurity.

**Results:** N/A

**Conclusions:** Physiologic mini-puberty should be included in the differential diganosis of extreme preterm infants presenting with vaginal bleeding in the first 4-6 months of age and possibly beyond this time period. Although the phenomenon of mini-puberty is well established in the term neonatal population, there is a paucity of literature discussing the effects of extreme prematurity. Literature review revealed three similar cases of extremely premature infants having exaggerated mini-puberty, all presenting between 4-6 months of age. In evaluation, serial monitoring will be paramount, and further work up should ensue if the patient has recurrent vaginal bleeding, develops additional signs of puberty or increased linear growth, or if the medical history or physical exam becomes concerning for an organic etiology. Cognizance of this phenomenon in the former premature infant may prevent unnecessary, invasive laboratory and radiographic evaluation and possibly medical treatment.

### INSULIN GONE ROGUE: A CASE OF HYPERINSULINISM IN A 4 YEAR OLD FEMALE

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**Objectives:** The human body is designed to protect itself from severe hypoglycemia with a plethora of hormones to normalize blood sugar. In the setting of hyperinsulinemia this counter regulatory balance fails to shield against hypoglycemia, leaving the patient vulnerable to the effects of low blood sugar. The cause of hyperinsulinemia varies widely and includes iatrogenic causes, genetic mutations, and insulin producing tumors. The etiology must be discovered quickly and treatment rendered to avoid further complications related to hypoglycemia.

**Methods:** A 4 yr 7 mo Caucasian female with no significant past medical history presented for evaluation of spells. Sporadically she would stare off, was slow to respond to questions, and have an unsteady gait. She was sent to neurology and an EEG showed findings characteristic of absence seizures. She was started on ethosuximide but the spells persisted. During one evaluation she had a blood glucose of 38 ng/dL. She had subsequent other blood glucose levels at various times of the day less than 50 mg/dL. Her work up with endocrinology began with an admission for a hypoglycemic fast. After 15 hours of fasting, the patient's blood glucose dropped to 38 mg/dL. Her labs during this episode of hypoglycemia showed elevated insulin and c-peptide levels without evidence of ketosis or acidosis. She had a robust response to glucagon with BG increasing to 128 mg/dL within 20 minutes of administration. She was started on diazoxide and responded well.

**Results:** These findings raised our suspicion of hyperinsulinism. Congenital hyperinsulinism testing was negative. The generous proinsulin levels were concerning for an insulinoma. We obtained an MRI of her abdomen which showed a 1.3 x 0.8 cm insulinoma. The insulinoma was removed and the patient has done well. Genetic testing was done given the young age of the patient and confirmed multiple endocrine neoplasia type 1.

**Conclusions:** Insulinomas are very rare; the estimated incidence is 4:1,000,000 with the average age of patients in their mid-40s. An exact incidence in children is unknown. This case illustrates highlights and unusual presentation of a very rare disorder. Symptoms of hypoglycemia can be vague and variable. Although rare, recognition of hyperinsulinism is life saving for patients.

P3-522

### NASO-JEJUNAL TUBE FEEDS AS AN ETIOLOGY OF HYPOGLYCEMIA IN A PREMATURE INFANT

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**Introduction:** Hypoglycemia is a serious problem in neonates leading to increased morbidity and mortality. Early recognition of the etiology and appropriate treatment is essential.

**Methods: Case Discussion:** Our patient, a 23 day old ex-35 week twin male was transferred from an outside hospital to the CHNOLA NICU for management of poor feeding and weight loss. The patient was intubated in NICU secondary to apneas and increased work of breathing from rhinovirus and enterovirus respiratory infections. While intubated, he received Enfamil® formula feeds via naso-gastric tube at 13ML/HR with normal BG (>60). On day 6 of hospitalization the NG tube was changed to naso-jejunal tube for feeding intolerance. The next day, the patient became persistently hypoglycemic with Blood Glucose as low as 47. D10W was started at 4ML/KG/HR to maintain BG levels > 50. At the BG of 57, C-Peptide was 0.4 with Insulin of 2. Urine Ketones were negative. With NJ tube in place but feeds held the patient remained normoglycemic on IV dextrose. However on resumption of formula feeding via NJ tube there was recurrence of hypoglycemia to 25 with a C-peptide of 1.2. On converting the tube to NG there was resolution of the hypoglycemia.

**Results: Discussion:** To our knowledge this is the first report of hypoglycemia in a neonate due to naso-jejunal location of a feeding tube and hypoglycemia associated with NJ feeds. This case illustrates the idea that transpyloric feeding may stimulate the pancreas' release of insulin leading to hypoglycemia. Recognition of this phenomenon is important to include in one's differential when faced with a patient who is persistently hypoglycemic and being fed by a naso-jejunal tube.

**Conclusions: Conflict of Interest and Disclosure**

**Statement:** None

P3-523

### HEREDITARY FRUCTOSE INTOLERANCE MASQUERADING AS HYPERINSULINISM

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**Objectives:** To describe an unusual case of hypoglycemia

**Methods:** Patient chart review

**Results:** A 5 week old girl was noted to have hypoglycemia and acholic stools while on standard term infant formula since shortly after birth. Labs were significant for cholestasis, hypoglycemia with a glucose of 46 mg/dL. Of note, patient's 4 year old sister had a liver transplant for unknown reason. Screening for hypopituitarism was normal. Liver biopsy showed giant cell hepatitis with cholestasis, steatosis, and bridging fibrosis. Patient developed worsening liver function and recurrent fasting hypoglycemia, requiring

initiation of continuous feeds and IV dextrose. Glucose infusion rates of over 12 mg/kg/m were needed to maintain euglycemia. A critical sample showed a glucose of 39 mg/dL, insulin of 3 uIU/mL, and absent ketones, suggestive of hyperinsulinism. However, patient didn't respond to IV glucagon and had persistent hypoglycemia on diazoxide. After transitioning to Progestimil, liver function and hypoglycemia both improved and eventually resolved. Formula history revealed association of sucrose-containing formulas with worsening hypoglycemia. Genetic studies were sent to evaluate for underlying genetic disorders. She was found to have a homozygous variant in the aldolase B gene, consistent with hereditary fructose intolerance. She has continued on fructose-free diet with resolution of liver disease and hypoglycemia.

**Conclusions:** Hereditary fructose intolerance (HFI) is a rare autosomal recessive condition due to a mutation in the aldolase B gene, resulting in accumulation of fructose 1-phosphate (F1P). F1P is thought to impair glycogenolysis in the liver, resulting in fasting hypoglycemia. There have been no reports of hyperinsulinism in HFI, though pancreatic islet cell hyperplasia has been seen on autopsy. The diagnosis of HFI should be considered in cases of non-ketotic hypoglycemia and thus may be easily confused with other conditions such as hyperinsulinism. A careful history of sucrose-containing formula use, timing of hypoglycemia, and other indicators may lead to diagnosis. Management with avoidance of dietary fructose results in patients living healthy lives and can spare profound consequences such as liver transplant or death.

P3-524

#### **CONFIRMED CONGENITAL HYPERINSULINISM IN A NIGERIA CHILD: A CASE PRESENTATION AND HIGHLIGHTS OF CHALLENGES OF MANAGEMENT AND OUTCOME**

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**Objectives:** Congenital hyperinsulinism is a cause of recurrent and persistent hypoglycaemia in neonates. It results from an unregulated secretion of insulin from the beta cell of the pancreas. In infants in developing countries, diagnosis is hardly made and most children die or survive with neurodevelopmental delays.

The objective of this presentation is to present the first genetically confirmed case of a Nigerian infant who developed recurrent hypoglycaemia due to inheritance of compound heterozygote mutations of the ABCCA gene from asymptomatic carrier parents and to highlight outcome and challenges in management.

**Methods:** Information about the case were obtained from case notes and follow up.

**Results:** Twenty day old female infant delivered at term to a multiparous mother at term. There was no history of gestational diabetes or preeclampsia. Baby was delivered by spontaneous vertex with good apgar score and a birth weight of 3.4Kg.

Developed recurrent hypoglycaemia from first day of life and was initially managed for meningitis. Hypoglycaemic episodes persisted and was referred to the Paediatric endocrine Unit of the University of Port Harcourt Teaching Hospital where a critical sample revealed hypoketotic hyperinsulinaemia. Attempts at purchasing diazoxide, octreotide and glucagon failed. She continued on frequent feeds and monitoring of blood glucose. She was then lost to follow up.

Samples from parents and infant sent out for genetic analysis revealed presence of compound heterozygote nonsense mutation of the ABCCA gene with both parents as asymptomatic carriers.

Infant had recurrent hypoglycaemia after loss to follow up and eventually developed absence seizures with cerebral palsy, tip toeing and microcephaly. Further evaluation could not be done due to non availability of PET Scan.

Hypoglycaemic episodes are less and child is presently 4 years old and undergoing physiotherapy with some improvement in motor and speech functions.

**Conclusions:** A confirmed case of Congenital hyperinsulinism due inheritance of the ABCCA mutation is reported in a Nigerian infant. Challenges of management which include delayed diagnosis, lack of availability of drugs and investigative scan and loss to follow up has led to a high rate of neurodevelopmental impairment in the infant.

P3-525

#### **GLYCOLATE OXIDASE DEFICIENCY AND HYPEROXALURIA IN A PATIENT WITH CONGENITAL HYPERINSULINISM DUE TO ABCC8 MUTATION**

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**Objectives:** Congenital Hyperinsulinism (CHI), a disorder of dysregulated insulin secretion, is generally caused by mutations in the genes encoding  $K_{ATP}$  channels (*ABCC8*, *KCNJ11*). Glycolate oxidase (GO), encoded by *HAO1*, catalyses the oxidation of glycolate to glyoxylate. Deficiency of GO is a very rare disorder with only 2 previously published cases. We report for the first time, the rare combination of CHI and GO deficiency due to homozygous mutations in *ABCC8* and *HAO1* respectively.

**Methods:** An Asian baby girl with a birth weight of 4.69kg (+2.7SDS), born at term to consanguineous parents, developed severe hypoglycaemia requiring intravenous glucose infusion upto 25mg/kg/min. The investigations showed an inappropriately raised plasma insulin concentration (460pmol/L) and suppressed beta hydroxy butyrate (<100µmol/L) and plasma free fatty acids (<100µmol/L) during hypoglycaemia (plasma glucose:

1.8mmol/L) confirming the diagnosis of CHI. The hypoglycaemia was unresponsive to maximum dose of diazoxide (20mg/kg/day) and she was subsequently managed with a combination of octreotide (40mcg/kg/day) and sirolimus therapy

**Results:** Genetic analysis revealed a homozygous nonsense mutation in *ABCC8* (c.1990C>T, p.Gln664Ter) inherited from both parents. The urinary analysis showed a persistently elevated glycolate (>1000µmol/L) and oxalate (>800 µmol/L) levels giving rise to the clinical suspicion of primary hyperoxaluria type 1 (PH1). However, further genetic analysis did not show mutation in *AGXT* but revealed a homozygous missense mutation in *HAO1* (c.493G>T, p.Gly165Cys). Enzyme activity analysis on liver biopsy revealed a normal AGT enzyme activity but absent GO enzyme activity, confirming GO deficiency.

**Conclusions:** This is the first reported combination of two rare autosomal recessive conditions namely CHI and GO deficiency in a patient with unexplained hyperoxaluria. GO deficiency is not predicted to have a pathological phenotype but the unusual association of hyperoxaluria can cause diagnostic difficulties and warrants a careful monitoring of renal function in the long-term.

## POSTER SESSION 3

**Saturday, September 16, 2017, 12:00-1:00pm**

### P3 - Gender dysphoria

#### P3-600 – P3-608

P3-600

#### GUIDELINE-DRIVEN LABORATORY TESTING IN THE CARE OF TRANSGENDER YOUTH: ARE ALL THE RECOMMENDED TESTS REALLY NEEDED?

*Lyne N. Chiniara, MD; Herbert J. Bonifacio, MD, MSc, MPH, MA; Mark R. Palmert, MD, PhD, Hospital for Sick Children/University of Toronto, Toronto, ON, Canada*

**Objectives:** Published guidelines addressing the care of transgender youth call for acquisition of many baseline and post-treatment laboratory tests. The aim of this project was to assess the utility of this routine testing.

**Methods:** Charts from 203 transgender adolescents were reviewed to obtain baseline demographic data and results of blood tests. Baseline blood tests were performed at the initial visit and included hormonal, renal, hepatic and hematologic tests; suppression labs (LH, FSH, testosterone, estradiol) were performed while on leuprolide acetate (Lupron depot); and safety labs (repeat of baseline testing) were performed while on cross-sex hormones to evaluate sex steroid levels and screen for potential complications. Data were analyzed with descriptive statistics, and paired t-tests were used for comparing baseline and follow-up tests.

**Results:** 156 and 47 male-bodied youth (MBY) were included. Mean age at presentation was 16.3 years SD 1.63 for FBY and 16.1 years SD 1.70 for MBY. Mean bone age was 15.9 years in both FBY (SD 1.3, range 12-18) and MBY (SD 2.2, range 11-

19). In 9 FBY (7.7%) and 2 MBY (6.5%), bone age was advanced more than 2 SD. Mean Tanner stage was 4.4 SD .8 for FBY (B4P4, median 5, mode 5) and 4.0 SD 1.1 for MBY (G4P4, median 4, mode 5). Baseline blood tests showed no abnormal hormonal results except in one youth with elevated FSH who was subsequently found to have Klinefelter syndrome. In 6 (4.5%) FBY, testosterone levels were slightly high (max value: 2.5 nmol/L) according to sex and Tanner stage norms. Suppression blood tests showed adequate suppression for LH and FSH in all youth. Safety tests did not reveal the development of any clinically significant abnormalities while on sex hormone therapy. However, statistically significant differences in hemoglobin levels (increased in FBY on testosterone  $p=.002$ , decreased in MBY on estradiol  $p=.019$ ) and in red blood cell count ( $p=0.000$ ; increased in FBY and decreased in MBY) were observed.

**Conclusions:** Our results need to be corroborated by additional studies. However, the results suggest that much of the routine testing recommended in care guidelines may not be warranted. Reducing unnecessary testing could improve both care for transgender youth and resource utilization.

P3-601

#### USE OF FERTILITY PRESERVATION BY TRANSGIRLS STARTING HORMONAL TREATMENT

*Sabine E Hannema, MD, PhD; Sebastian EE Schagen, MD; Martine C De Vries, MD, PhD, Leiden University Medical Centre, Leiden, Netherlands*

**Objectives:** Many transgender adolescents undergo treatment with GnRH analogues, followed by cross sex hormones and, in adulthood, gender affirming surgery which may include gonadectomy. Infertility as a consequence of such treatment may have a major impact on their lives. Current guidelines recommend fertility counselling. We aimed to investigate the use of fertility preservation in a Dutch cohort of transgirls.

**Methods:** Data on counselling about fertility preservation and its actual use were extracted from the medical files of transgirls who started treatment with a GnRH analogue between 2011 and 2016.

**Results:** The possibility of semen cryopreservation was discussed with 27/28 transgirls. Eleven adolescents were referred for semen cryopreservation, one of whom was unable to produce a semen sample. Three declined because they did not want to have children; two because they wanted to adopt; one because she abhorred the procedure and thought she would not use her semen; one because she disliked the idea of a woman being impregnated with her semen. In five no reason for declining fertility preservation was noted. Four individuals were in early puberty with testicular volume  $\leq 8$  ml; because semen cryopreservation was unlikely to be successful they were not referred. The one individual to whom semen cryopreservation was not offered had a testicular volume of 4-5 ml so was also unlikely to be able to produce a semen sample through masturbation.

**Conclusions:** Forty-one percent of transgirls who were offered fertility preservation attempted semen cryopreservation which is remarkably more than the 9% (2/23 transgirls) reported in a recent study from the United States. The reasons for this difference need to be clarified. We conclude that a substantial number of transgirls starting hormonal treatment wish to preserve fertility underscoring the importance of providing counselling on this subject.

P3-602

#### **"IS THE AGE OF FIRST MANIFESTATION OF GENDER DYSPHORIA IN TRANSGENDER YOUTH CHANGING?"**

*Rasha Alradadi, MBBS, Riley Hospital for Children, Indiana University School of Medicine, Indianapolis, IN, United States; Melinda Chen, MD; John S. Fuqua, MD, Riley Hospital for Children, Indiana University School of Medicine, Indianapolis, IN, United States; Erica A. Eugster, MD, Indiana University School of Medicine and Riley Hospital for Children, Indianapolis, IN, United States*

**Objectives:** Referrals to the pediatric endocrine clinic for gender dysphoria (GD) have risen steeply during the last several years. It is unknown whether the age at which children first manifest cross gender identification is different among those seen recently compared with earlier years. Our objective was to determine the timing of the onset of cross-gender behavior or overt GD among transgender youth referred to our clinic, and to investigate whether this has changed over time.

**Methods:** A retrospective chart review of patients with GD seen in the pediatric endocrine clinic at Riley Hospital for Children since 2002 was conducted. Variables examined included year of referral, age, natal sex, affirmed gender, and history of GD per patient and parent report during the initial consult visit. We considered cross-gender behavior or evidence of GD to be "early" if it occurred at  $\leq 5$  years of age and "later" if it commenced subsequently. We compared patients who were seen since January, 2014 to those presenting earlier.

**Results:** Of 78 patients aged  $14.6 \pm 2.6$  years with GD, 56 (72%) were referred in 2014 or later. Among those seen prior to 2014, 40% had a history of early GD compared with 26% of patients seen during the last few years. Examples of early onset cross-gender behavior or GD in male to female patients included an insistence on wearing girls' clothing, asking to have the penis "cut off," and a preference for girl-typical toys. Manifestations of early cross-gender behavior or GD in female to male patients included cutting hair, a refusal to wear dresses, the assertion that "I'm going to be a boy when I grow up," and a preference for rough and tumble play and boy-typical toys.

**Conclusions:** In our youth with GD, we observed a notable decrease in the number of patients reporting a history of early onset cross-gender identification among those presenting since 2014. Although strictly anecdotal, this suggests the evolution of a broader and more nuanced spectrum of GD amidst transgender youth over time. Further

studies are needed to investigate the factors that influence the emergence of GD in transgender children and adolescents at different ages.

P3-603

#### **THE TRANS YOUTH RESOURCE NETWORK OF WISCONSIN: AN INTEGRATED PATH FOR TRANSGENDER YOUTH**

*Jennifer Rehm, MD, University of Wisconsin - Madison, Madison, WI, United States; Sarah Bennis, BS/BA; Brittany Allen, MD, University of Wisconsin-Madison, Madison, WI, United States*

**Objectives:** The study aims to assess perceived community needs and barriers identified by transgender and gender nonconforming (TGNC) youth across Wisconsin. Transgender and gender nonconforming youth are at increased risk for mental health problems, including depression, anxiety, and suicidality. Barriers to care and support have not been well characterized in this population.

**Methods:** Data will be collected using a respondent-driven online survey with open access to TGNC-identified youth ages 12-22 across the state of Wisconsin. The study aims to collect 300 survey responses and implement small focus groups to further evaluate quantitative and qualitative experiences of TGNC access to support and resources.

**Results:** The study anticipates the documentation of specific barriers to accessing community resources and support for TGNC youth. Reported experiences may include several factors, such as supportive family and access to a knowledgeable healthcare provider.

**Conclusions:** Preliminary data for this study will be available by September 2017. We will implement six focus groups of 8-14 participants following the closure of the online survey. Data and dissemination will help available resources, community organizations, and healthcare providers tailor their services to reach a greater proportion of the TGNC population. Long-term outcomes will reduce mental and emotional stress experienced by TGNC youth in schools, home, and medical settings.

P3-604

#### **BODY MASS INDEX IN RELATION TO NATAL SEX AND AFFIRMED GENDER IN TRANSGENDER YOUTH**

*Victoria M Brocksmith, BS/BA, Indiana University School of Medicine, Indianapolis, IN, United States; Erica A. Eugster, MD, Indiana University School of Medicine and Riley Hospital for Children, Indianapolis, IN, United States*

**Objectives:** Referrals to the pediatric endocrine clinic for gender dysphoria (GD) are steadily increasing. These patients are known to be at risk for psychological problems including disordered eating. However, baseline weight status in children and adolescents with GD has not been described.

Our objective was to characterize body mass index (BMI) in transgender youth and to determine if there is a difference in

average BMI z-scores between male-to-female (M2F) and female-to-male (F2M) transgender patients.

**Methods:** A retrospective review of patients with GD followed in the pediatric endocrine clinic at Riley Hospital for Children was performed. Variables analyzed included age, natal sex, affirmed gender, weight and height at the first clinic visit. BMI percentiles and z-scores were calculated based on height and weight. An independent samples t-test was conducted to compare average BMI z-scores for M2F and F2M patients.

**Results:** Seventy-eight patients with GD were identified of whom 29 (37%) were M2F and 49 (63%) were F2M. Within the M2F cohort, aged  $14.2 \pm 3.15$  years, 86.2% were Caucasian and average BMI z-score was  $0.47 \pm 1.51$ . Based on BMI percentile, 7 (24.1%) patients were overweight and 7 (24.1%) were obese. In the F2M cohort, aged  $14.6 \pm 2.0$  years, 85.7% were Caucasian and average BMI z-score was  $0.87 \pm 1.15$ . Ten (20.4%) patients were overweight and 15 (30.6%) were obese. In the group as a whole, five patients (6.4%) were underweight and the remaining were of normal weight. No difference was seen in average BMI z-scores between M2F and F2M patients,  $p < 0.225$ .

**Conclusions:** In our cohort of children and adolescents with GD, ~50% were overweight or obese at their first clinic visit prior to hormonal intervention. Potential risk factors for abnormal weight gain in these patients include depression, anxiety, disordered eating and psychotropic medications. The high prevalence of overweight in transgender youth represents an important co-morbidity with the potential for adverse health consequences. How BMI is impacted by hormonal treatment in M2F and F2M pediatric patients remains to be determined.

P3-605

#### **BICALUTAMIDE AS AN ANDROGEN BLOCKER WITH SECONDARY EFFECT OF PROMOTING FEMINIZATION IN MALE TO FEMALE (MTF) TRANSGENDER ADOLESCENTS**

*Anna Neyman, MD, Indiana University School of Medicine and Riley Hospital for Children, Indianapolis, IN, United States; John S. Fuqua, MD, Riley Hospital for Children, Indiana University School of Medicine, Indianapolis, IN, United States; Erica A. Eugster, MD, Indiana University School of Medicine and Riley Hospital for Children, Indianapolis, IN, United States*

**Objectives:** GnRH analogs are first-line treatment for halting pubertal development in gender variant youth. However, this medication is often denied by third party payors. The pure androgen receptor blocker bicalutamide represents a potential alternative approach to blocking puberty in natal males. Here, we describe the use of bicalutamide in MTF transgender patients.

**Methods:** Medical records for patients with gender dysphoria (GD) followed in the pediatric endocrine clinic at Riley Hospital for Children were reviewed. All MTF transgender patients treated with bicalutamide were included. Variables evaluated comprised age, duration of follow up, timing of estrogen initiation, laboratory studies and physical exam

findings including change in breast Tanner stage during treatment.

**Results:** Of 77 patients with GD identified, 29 were MTF, of whom 14 (48%) aged  $15.8 \pm 1.9$  years (range 12-18.4yr) were treated with bicalutamide 50 mg daily between 2013 and 2017. Of these, 3 were started on estrogen concurrently whereas 11 received bicalutamide alone, 7 of whom have returned for follow up thus far. After an average of  $5.7 \pm 1.5$  months, 86% of the patients ( $n=6$ ) had breast development consisting of Tanner stage III in 4, Tanner stage II in 1, and Tanner stage III/II of the right and left breast in 1. The 7<sup>th</sup> patient was noted to have Tanner III breasts at her 2<sup>nd</sup> follow-up clinic visit 12.5 months after starting bicalutamide. LFTs were obtained on 4 patients, estradiol on 3 patients and testosterone on 2 patients while exclusively taking bicalutamide. LFTs were unremarkable and concentrations of estradiol and testosterone were 26-61 pg/mL and 524-619 ng/dL, respectively.

**Conclusions:** Bicalutamide is used in rare forms of precocious puberty in males and has a known side effect of gynecomastia. Here, we report the novel use of bicalutamide as a puberty blocker in MTF patients with GD in whom it also results in feminization by causing breast development. Additional studies are needed to further evaluate the potential role of bicalutamide in the therapeutic armamentarium for the treatment of transgender MTF adolescents.

P3-606

#### **CHILDREN AND ADOLESCENTS WITH GENDER DYSPHORIA - THE ISRAELI EXPERIENCE**

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**Objectives:** To describe patient characteristics at presentation, management and response to treatment of children and adolescents with gender dysphoria in Israel.

**Methods:** A retrospective chart review of 46 consecutive children and adolescents ( $< 18$  years) with gender dysphoria referred to and followed at the Israeli multidisciplinary Pediatric Gender Dysphoria Clinic from 2013- 2017.



**Results:** Of the 46 patients, 16 (35%) identified as female-to-male (FtM), 30 (65%) as male-to-female (MtF). The gender dysphoria population increased since the establishment of the clinic from 1-2 new referrals to 10 new referrals per 6 months. Median age at referral was 16.1 years (range 4.58-18 years). At time of referral, 80% had completed sexual maturation in their biological gender. Of 25 pubertal MtF patients, 8 (32%) underwent fertility preservation compared to none of FtM patients. Gonadotropin-releasing-hormone analog (GnRHa) treatment was prescribed in 33 (72%) patients at a mean age of 16±1.7 years. Cross-sex-hormones (CSH) were prescribed in 27 (59%) patients at a mean age of 16.7±1.3 years (range 14.2-18.5 years). No severe side effects were recorded. One MtF patient underwent genital sex reassignment surgery at age 18.2 years. Three FtM and one MtF patients underwent mastectomy and breast augmentation respectively.

**Conclusions:** After establishment of the Pediatric Gender Dysphoria Clinic, referral rate to the clinic increased fivefold. Treatment with GnRHa and CSH, in collaboration with mental health support, is an intervention that appears to be appropriate in carefully selected youth with gender dysphoria. Long-term follow-up studies are needed to determine the safety and efficiency of these treatments in this age group.

P3-607

#### CHALLENGE TO THE PARADIGM OF PRENATAL TESTOSTERONE EXPOSURE ON GENDER IDENTITY DEVELOPMENT

*Daniel T Klink, MD, ZNA Queen Paola Children's Hospital, Antwerp, Belgium; Anouk Balleur, MS/MA, Virenze Riagg, Gorinchem, Netherlands; Meredith Russell, MS/MA; Diane Ehrensaft, PhD, University of California San Francisco, San Francisco, CA, United States; Stanley Vance, MD, UCSF Benioff Children's Hospital, San Francisco, CA, United States; Laura Bachrach, MD; Chrysoula Dosiou, MD, Stanford University, San Francisco, CA, United States; Stephen Rosenthal, MD, University of California San Francisco, San Francisco, CA, United States*

**Objectives:** The origins of gender identity (GI) are not known but historically, prenatal testosterone levels are thought to be pivotal in the development of male GI. Indeed, an increased prevalence of male GI in 46 XX assigned females with virilizing congenital adrenal hyperplasia (CAH) was reported. Likewise, 46 XY individuals with complete androgen insensitivity almost invariably have a female GI. We report two cases that challenge the paradigm of prenatal testosterone exposure.

**Methods:** not applicable

**Results:** Case 1

The patient was diagnosed with salt-losing, virilizing 21-hydroxylase deficient CAH in the newborn period. No genital or gonadal abnormalities were described in this assigned male. Compliance with hormonal treatment was good. Male puberty began at 12-13 years, and proceeded in an expected

timeframe. At 9-10 years of age, the patient "always played with dolls and sister's make up" and expressed liking "girl things" and at 14-15 years began social transition to female which was completed at age 17. Formal gender evaluation was consistent with gender dysphoria (GD) and a female gender identity, with no evidence of psychopathology at age 20, and was followed by female gender affirming hormonal therapy.

Case 2

The patient presented with the absence of breast development at the age of 15 years and was diagnosed with 46 XY hypovirilization due to complete gonadal dysgenesis. Pubertal induction with 17-beta estradiol initiated breast development but the patient felt increasingly gender dysphoric and expressed the wish to become a boy. Although cross-gender behaviors had been present since early childhood, the stability of the patient's male GI was questioned because of two events: discovery of a male karyotype, and a negative sexual experience in the female role. Moreover, gender dysphoric feelings had never been verbally expressed, previously. After a thorough diagnostic phase the GI appeared stable. The patient started gender affirming treatment including testosterone therapy and surgery.

**Conclusions:** These cases, illustrating a female GI despite prenatal exposure to both testicular testosterone and excessive adrenal androgens, and a male GI despite a lack of prenatal testosterone exposure, highlight the complexity of factors contributing to GI development.

P3-608

#### GENDER VARIANCE AND THE CAPACITY TO CONSENT: AN INTERDISCIPLINARY APPROACH

*Naomi Libby, MD; Anisha Patel, DO; David Hersh, MD; Renae Koval, RN; Christy Olezeski, PhD, Yale School of Medicine, New Haven, CT, United States*

**Objectives:** At the conclusion of this panel presentation, participants will be able to:

1. Recognize the complex clinical needs of gender nonconforming youth and their families.
2. Address clinical challenges that arise in the course of caring for gender nonconforming youth through a collaborative, interdisciplinary framework.
3. Identify ethical and medicolegal concerns regarding informed consent in gender nonconforming children, including when and how to seek the support of a medical ethicist.

**Methods:** This panel, comprised of members of the Yale Gender Program (an interdisciplinary team consisting of pediatric endocrinologists, psychologists, psychiatrists, a gynecologist, and legal consultant), will present a case vignette to illustrate the complexities involved in the assessment and care of gender nonconforming youth. The panel will discuss challenges that arise around decision making and informed consent, and the experience of

managing these challenges through an interdisciplinary approach.

**Results:** A medical ethicist was recruited to assist in navigating differences of opinion. Utilizing the four fundamental ethical principles (autonomy, beneficence, non-maleficence, and autonomy) and Cottone's social constructivism model of ethical decision making, the team arrived at a consensus treatment decision. The collaborative, interdisciplinary clinical decision making process will be presented and discussed.

**Conclusions:** As a result of the case presented in this panel discussion, the Yale Gender Program expanded its interdisciplinary team to include a medical ethicist as a continuous member of the team. Collaborative decision making remains a fundamental principle guiding the practices of this clinic.

POSTER SESSION 3

Saturday, September 16, 2017, 12:00-1:00pm

P3 - Growth and GH/IGF Axis

P3-800 – P3-863

P3-800

FAMILIAL ISOLATED GROWTH HORMONE DEFICIENCY CAUSED BY THE R183H MUTATION IN THE GROWTH HORMONE GENE (GH1): A DETAILED CLINICAL ANALYSIS OF A FOUR-GENERATION FAMILY

Catalina Cabrera Salcedo, MD; Amy Shah, MD; Melissa Andrew, BS/BA; Leah Tyzinski, BS/BA; Vivian Hwa, PhD; Iris Gutmark-Little, MD; Philippe Backeljauw, MD; Andrew Dauber, MD, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States

**Objectives:** Via whole exome sequencing, we identified a four-generation family with six members affected by short stature secondary to the missense R183H mutation in GH1 (Figure 1), which leads to decreased, but not completely absent, growth hormone (GH) secretion. The long-term effects of this mutation into adult life are unknown. With the present study we aimed to describe in detail the phenotype of this family with six members affected by the R183H GH1 mutation

**Methods:** Three female adult patients and two female children affected by the R183H mutation participated in the study (Table 1). The adults underwent a comprehensive clinical evaluation including growth hormone stimulation test using glucagon, densitometry, a complete vascular assessment, and extensive biochemical profile to assess cardiovascular risk in addition to a quality of life (QoL) assessment. The affected children underwent growth hormone stimulation testing using arginine and clonidine.

**Results:** The subjects had variable degrees of short stature (-1.9 to -3.2 SD). All subjects exhibited delayed peak responses to growth hormone stimulation testing. The two children had normal peak values at 150 minutes but very low GH levels (<3

ng/dl) at all earlier time points. The two younger adults had abnormal peak GH of <3 ng/dL while the eldest subject had a peak of 16.4 ng/dl. The IGF-I concentrations were low-normal in the adults and <2.5% in both children. The adults had normal lipids, inflammatory markers and bone mineral density. Carotid intima-media thickness, pulse-wave velocity, flow-mediated dilation values and echocardiography were within normal limits for age and did not show abnormalities as observed in patients with adult GH deficiency. One adult with obesity had impaired fasting glucose with mild hyperinsulinemia.

**Conclusions:** Patients with partial GHD secondary to the R183H GH1 mutation exhibit delayed peak GH responses with variable IGF-I concentrations. Neither dyslipidemia, osteoporosis nor elevated inflammatory markers were present in the affected adults. There were no obvious findings suggestive of increased cardiovascular risk in these patients. It is possible that GH replacement is not necessary in adult carriers of this mutation.

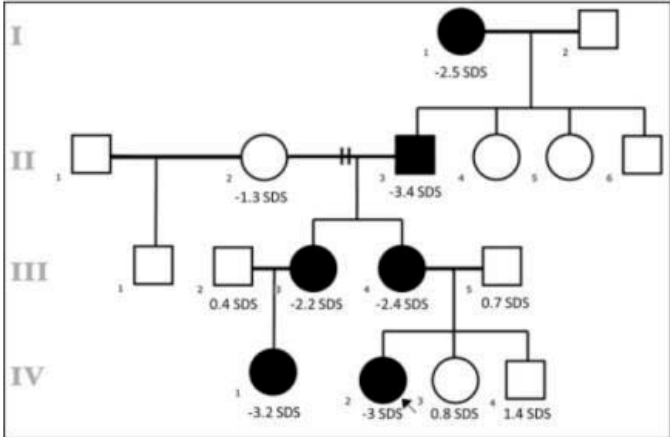


Figure 1. Family pedigree with affected individuals indicated by black squares and circles. When known, the height SD score is reported.

Table 1 Anthropometric characteristics.

	IV.1	IV.2	III.3	III.4	I.1
Gender	Female	Female	Female	Female	Female
Age (years)	6.6	5.9	30	33	73
Weight (kg)	19	12	72	96	43
Height (cm)	103	96	148	149	151
Height Z-score	-3.3	-3.8	-2.3	-2.2	-1.9
BMI (kg/m <sup>2</sup> )	18	14	33	43	18

P3-801

FINAL HEIGHT OF WOMEN WITH TURNER SYNDROME WITH AND WITHOUT RECOMBINANT HUMAN GROWTH HORMONE: A RETROSPECTIVE ANALYSIS OF 30 YEARS

Luiz Claudio Castro, PhD; Laís Oliveira, MD; Naiara Martins, MD; Delia Braz, MD; Renata Oliveira, MS/MA; Fernanda Lopes, MD; Mara Cordoba, PhD, University of Brasilia, Brasilia, Brazil

**Objectives:** To evaluate: (a) the proportion of women with Turner Syndrome (TS) who reached final height with and without recombinant human Growth Hormone (rhGH) treatment, throughout 30 years of follow-up; (b) to compare final height of TS women with and without rhGH treatment;

(c) analyse the reasons why some women were not treated with rhGH

**Methods:** Retrospective study of the records of patients with TS followed at the Pediatric Endocrinology and Adult Endocrinology Outpatient Clinics at a single University Hospital, who have reached final height from decade 1980 to decade 2010 . Patients with chronological age greater than or equal to 18 years and 6 months were included. Those who presented comorbidities that could affect final height were excluded. Patients were then gathered in treated and not treated with rhGH groups.

**Results:** Fifty one patients reached final height throughout the 30-year period and 49 met the inclusion criteria. Thirty six (73.4%) did not receive rhGH due to advanced age (mean 26.5 years) at diagnosis of TS and the mean final height of this group was 142.4 ± 6.7 cm (4.8 ft 8 in ± 2.6 in), mean height Z-score -3.1 ± 1.0 SDS. Mean age at diagnosis of TS in the group treated with rhGH was 11.4 years and they presented mean final height 150.1 ± 5.6 cm (4 ft 11 in ± 2.2 in), mean height Z-score -1.99 ± 0.85 SDS. Mean age at diagnosis and mean final height of both groups were statistically different (both p < 0.005).

**Conclusions:** These data endorsed the benefits of rhGH improving height potential in TS patients. At the same time, they have disclosed the fact that late diagnosis of TS has been still a reality throughout the last decades. Such finding also points out a concern about other systemic metabolic consequences of the late TS diagnosis, such as a delayed estrogen replacement therapy and a potentially compromised peak bone mass acquisition.

P3-802

**ENVIRONMENTAL AND BIRTH CHARACTERISTICS AS PREDICTORS OF SHORT STATURE**

*Ladan Davallow, MD; Mark Deboer, MD, University of Virginia, Charlottesville, VA, United States*

**Objectives:** Short stature is associated with increased risk of morbidity including worse economic and psychosocial outcomes. The aim of this study is to evaluate for environmental and birth characteristic predictors of short stature in a large nationally representative sample.

**Methods:** We evaluated data on 17422 children from the Early Childhood Longitudinal Study-Kindergarten cohort 2011. We used multivariable logistic regression to evaluate predictors of short stature (height <3<sup>rd</sup> percentile) in preterm and term children at spring of kindergarten until second grade. Predictors included birthweight, preterm status, sex, parental education, parental income and race/ethnicity.

**Results:** Preterm children (compared to term children) had higher odds of short stature [0.51 (CI 0.32-0.82) p=0.005]. Among preterm and term children in second grade, birthweight was a significant predictor of short stature, with each increasing kilogram of birthweight having an odds ratio (OR) for preterm children of 0.34 (CI 0.18-0.64) p=0.001, and for term children of 0.36 (CI 0.29-0.45) p < 0.0001. This relationship was similar at kindergarten. In terms of race,

compared to Caucasian children, African-American children had an OR for short stature of 0.42 (CI 0.19-0.91) p=0.04, with no difference for Hispanic or Asian children. Among preterm children, sex was also a significant predictor [OR 2.79 for female compared to male (CI 1.20-6.49) p=0.017]. For term children, income was a predictor of short stature [OR for each of 18 income categories compared to the lowest category, 0.94 (0.90-0.98) p=0.008] at second grade, but not at kindergarten. Parental education was not a significant predictor of short stature.

**Conclusions:** In a large nationally representative sample, birthweight is a significant predictor of short stature at kindergarten and second grade in term and preterm children. In preterm children, females had a 2.8 fold increase risk in short stature, which may represent survival bias in male preterm neonates. Although there were some racial and socio-economic influence in the risk of short stature, overall the relationship did not hold among all subjects. These data may assist pediatricians and parents in considering contributors to stature outcomes by early school age.

All subjects*				
Predictor	Odds Ratio	Confidence Limits		p-value
Birthweight (kg)	0.41	0.34	0.49	<.0001
Sex	1.47	1.06	2.04	0.021
Parent education	0.98	0.81	1.20	0.848
Income	0.98	0.95	1.02	0.408
Race: Other vs white	0.93	0.58	1.47	0.741
Race: Asian vs white	0.97	0.18	5.14	0.852
Race: Hispanic vs white	1.19	0.76	1.87	0.151
Race: African American vs white	0.42	0.19	0.91	0.041

\*For breakdown of term and preterm data, please see Results section

P3-803

**EFFICACY OF THE GROWTH HORMONE TREATMENT IN CHILDREN BORN SMALL FOR GESTATIONAL AGE. STARTING AGE AS A PROGNOSTIC FACTOR.**

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**Objectives:** The target of our study has been to analyze some characteristics of the population of children who were born SGA and were treated with GH in our environment, as well as evaluating its effectiveness in terms of improvement of height and growth rate during the first 5 Years of treatment.

**Methods:** Retrospective longitudinal multicenter study. Including all treated PEG patients at 5 Hospitals in our area, who strictly adhered to the established indications for their use, since their approval by the European Agency for the Evaluation of Medicines from June 2003 to August 2016.

**Results:** Total patients treated: 104 (35.6% of from the total of the indications). Sex: 48.08% boys, 51.92% girls. Mean gestational age: 37.34±3.42 SDS weeks; To term 72.12%, preterm 27.88%. PEG class: symmetrical 49.04%; asymmetrical with short length 43.27%, with low weight 7.69%. Gestation type: single 84.6%, multiple 15.4%. Boys

Target height (TH):  $-1.23 \pm 0.70$  SDS. Girls TH:  $-1.36 \pm 0.89$  SDS. Mean age when the treatment starts: 6.48 years  $\pm$  5.56 SDS (4-6 years: 55.34%, > 6 years, 44.66%). Height, weight, growth rate and bone age/chronological age ratio evolution during the 5 first years of treatment: Table 1. Excluded patients: cancelation for non-response after 1 year of treatment. Pearson's linear correlation coefficient between the starting age of the treatment and the improvement of height at the first year:  $-0.301$ ;  $P$  0.003. At 5 years:  $R$   $-0.414$ ;  $P$  0.008.

**Conclusions:** The child born SGA treatment is the second indication in frequency of treatment with GH in short height children in our environment. They have a normal TH, higher than in other SGA series published in our Country. In our series the normalization of height ( $<-2$ DE) was achieved from the second year of treatment, improving it over the first 5 years. The treatment achieves growth acceleration, more evident during the first two years, without BA pathological acceleration. There is a linear relationship between the starting age treatment and the height improvement at the first year of treatment. This relationship is consistent, and more strongly after 5 years of treatment.

	INITIAL	1 YEAR	2 YEARS	3 YEARS	4 YEARS	5 YEARS
Height (SDS)	N 94	N 84	N 76	N 61	N 47	N 38
Mean $\pm$ SDS	$-3.28 \pm 0.48$	$-2.4 \pm 0.52$	$-1.97 \pm 0.63$	$-1.60 \pm 0.94$	$-1.40 \pm 0.92$	$-1.17 \pm 1.00$
95% C.I.	$(-3.37, -3.18)$	$(-2.51, -2.29)$	$(-2.11, -1.83)$	$(-1.84, -1.36)$	$(-1.67, -1.13)$	$(-1.50, -0.84)$
Weight (SDS)	N 94	N 84	N 76	N 61	N 47	N 38
Mean $\pm$ SDS	$-1.81 \pm 0.48$	$-1.45 \pm 0.48$	$-1.16 \pm 0.83$	$-0.98 \pm 1.04$	$-1.03 \pm 0.95$	$-0.92 \pm 1.01$
95% C.I.	$(-2.01, -1.61)$	$(-1.65, -1.26)$	$(-1.51, -0.82)$	$(-1.41, -0.55)$	$(-1.42, -0.64)$	$(-1.34, -0.50)$
GR (cm/yr.)	N 94	N 84	N 76	N 61	N 47	N 38
Mean $\pm$ SDS	$4.96 \pm 1.47$	$9.39 \pm 1.71$	$7.44 \pm 1.10$	$6.73 \pm 1.4$	$6.81 \pm 1.77$	$6.09 \pm 1.77$
95% C.I.	$(4.66, 5.26)$	$(9.02, 9.75)$	$(7.19, 7.69)$	$(6.37, 7.09)$	$(6.29, 7.33)$	$(5.51, 6.67)$
VC (DE)	N 94	N 84	N 76	N 61	N 47	N 38
Mean $\pm$ SDS	$-1.68 \pm 1.32$	$3.64 \pm 1.88$	$1.58 \pm 1.22$	$0.99 \pm 1.25$	$1.02 \pm 1.48$	$0.65 \pm 1.40$
95% C.I.	$(-1.95, -1.41)$	$(3.24, 4.04)$	$(1.30, 1.86)$	$(0.67, 1.31)$	$(0.59, 1.46)$	$(0.19, 1.11)$
BA/CA Ratio (SDS)	N 94	N 84	N 76	N 61	N 47	N 38
Mean $\pm$ SDS	$0.75 \pm 0.18$	$0.79 \pm 0.17$	$0.85 \pm 0.14$	$0.90 \pm 0.12$	$0.93 \pm 0.12$	$0.98 \pm 0.11$
95% C.I.	$(0.71, 0.79)$	$(0.76, 0.83)$	$(0.82, 0.88)$	$(0.87, 0.93)$	$(0.89, 0.96)$	$(0.94, 1.01)$

Table 1. Annual evolution during the 5 first years of GH treatment. GR: Growth rate. BA: bone age. CA: chronological age.

P3-804

## TARGET GENE SEQUENCING TO IDENTIFY GENETIC CAUSE OF SHORT STATURE

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**Objectives:** Short stature is a common reason of medical consultation but many patients do not receive a final diagnosis. New technology in gene sequencing allow to screen many genes simultaneously. We aimed to discover genetic variants that contribute to short stature in a cohort of children with unknown genetic etiology.

**Methods:** We recruited 24 children with short stature of unknown etiology (height SDS  $-3.3 \pm 0.9$ ). We performed targeted sequencing using next-generation DNA sequencing technology of the exons of 254 genes, including genes known

to underlie syndromic growth disorders or skeletal dysplasias as well as genes involved in growth plate biology or GH signaling.

**Results:** We identified novel likely pathogenic variants in 7 out of 24 patients. In these subjects 6 rare non synonymous variants have been found in the ACAN, GLI2, SOS1, SHOC2, FGFR3 genes and one frameshift deletion in TRPV4 gene. All variants were confirmed by Sanger sequencing and studied in parents and siblings of the probands. Prediction software (Polyphen, SIFT and Mutation Tester) were used to predict pathogenicity of the new variants. In all cases phenotypes were concordant with the mutation found.

**Conclusions:** Target gene- sequencing could be useful to rapidly identify genetic etiologies of short stature. In clinical setting, this technology can provide clinically relevant diagnoses for these patients. However accurate selection and description of patients' phenotype is essential to facilitate genetic data interpretation.

P3-805

## MEASUREMENT OF IGF-I AND -II CONCENTRATIONS AT BIRTH BY MASS SPECTROMETRY IN A LARGE BIRTH COHORT: CORRELATION WITH ANTHROPOMETRY

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**Objectives:** Insulin-like growth factor (IGF)-I and -II measurement by immunoassays is complicated by interference from binding proteins (IGFBP), and this is particularly problematic in infancy where IGF concentrations are low and IGFBP levels may be high. Liquid chromatography mass spectrometry (LCMS) is now available to measure IGF-I and -II, and is not sensitive to this IGFBP interference. The aim of this study was to describe gestational age- and sex-specific IGF-I and -II concentrations in infants at birth using LCMS, and to correlate these measurements with neonatal anthropometry.

**Methods:** Term healthy infants enrolled in the Cork BASELINE Birth Cohort Study had IGF-I and -II concentrations measured at birth using LCMS. Weight, length and head circumference were measured at birth and 2-months. Linear regression analysis was used to describe associations between IGF-I and -II concentrations at birth and anthropometry.

**Results:** IGF-I and -II were measured in 1100 term infants (563 male) and gestational age- and sex-specific reference

curves were generated. Mean (SD) IGF-I and -II concentrations were 52.5 (23.9) ng/ml (males 48.5 (23.3) ng/ml, females 56.7 (23.9) ng/ml) and 424.3 (98.2) ng/ml (males 420.8 (95) ng/ml, females 428 (101.4) ng/ml) respectively. In these term infants, IGF-I concentrations decreased slightly as gestational age increased in both males and females. This association was not seen between gestational age and IGF-II. IGF-I and -II concentrations at birth are both associated with weight ( $R^2=0.19$ ,  $R^2=0.01$ ), length ( $R^2=0.07$ ,  $R^2=0.004$ ) and head circumference ( $R^2=0.03$ ,  $R^2=0.04$ ) at birth. At 2 months, only weight is associated with IGF-I concentration at birth ( $R^2=0.02$ ).

**Conclusions:** Using this new assay, we described IGF-I and -II concentrations in a large cohort of healthy male and female term infants. This study corroborates many of the previously known associations between IGF-I concentrations and anthropometry at birth and demonstrates a weaker but significant association between IGF-II and anthropometry at birth.

P3-806

#### ETIOLOGY AND CATEGORIZATION OF CHILDREN WITH SHORT STATURE: SINGLE CENTER EXPERIENCE.

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**Objectives:** Short stature is one of the most common reasons for referral to a pediatric endocrinologist. The study aimed at identifying the underlying etiology of short stature.

**Methods:** A retrospective study. Records of patients with short stature (height more than 2 SD below the mean for age and sex), who attended the Endocrinology Clinic of Alexandria University Children's Hospital between January 2009 and January 2014 were reviewed. Data included their clinical, laboratory, and radiological findings. They were categorized as per ESPE classification.

**Results:** A total of 203 patients were included in the study. They were 95 males (47%) and 108 females (53%). Their mean age at diagnosis was  $10.11 \pm 4.8$  year. Majority of cases (187=92%) were referred late because of single low height measurement and no documented growth charts. Endocrinal causes (growth hormone disorders & hypothyroidism) were the most common (54.6%). The second most common cause was clinical syndromes (16.8%) followed by skeletal dysplasias (9.4%) and idiopathic short stature (8.9%). Constitutional growth delay and familial causes represented 5.9% and 2.95% respectively.

**Conclusions:** Children with short stature was often referred late to our specialized center compromising their prognosis. Since treatable endocrinal conditions were the most common, increasing awareness of general pediatricians of the importance of documenting growth charts and early referral is crucial.

P3-807

#### COMPARISON OF THE HEIGHT VELOCITY IN THE FIRST YEAR OF TREATMENT IN CHILDREN WITH ORGANIC VS. IDIOPATHIC GROWTH HORMONE DEFICIENCY

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**Objectives:** Compare the height velocity at the first year of treatment in children with organic growth hormone deficiency versus idiopathic in our hospital.

**Methods:** Observational, longitudinal, retrospective and comparative study. Records of 36 pediatric patients with growth hormone deficiency were reviewed at Centro Medico Nacional del Noreste at Monterrey, Mexico.

Height velocity was compared in the initial year of the treatment. For the descriptive analysis we used central tendency measures, standard deviations, absolute frequencies and percentages. For the interference analysis was utilized a t Student test or U Mann-Withney and the ANOVA for mean comparison or Friedman.

#### Results:

A total of 36 patients diagnosed with growth hormone deficiency were included in the study, 25 (69.4%) were male. The mean age at diagnosis was  $6.9 \pm 3.1$  years.

The etiology of growth hormone deficiency, 22 patients (61%) were diagnosed with an organic deficiency.

The diagnosis was corroborated by clinical standard deviation of the height, obtaining a mean initial size of  $-4.27SD \pm 1.1$ , laboratory with measurements of somatomedin C with a mean of  $41.9 \pm 11.1$  ng / ml, and the maximum peak of growth hormone stimulation of  $2.35 \pm 0.3$  ng/ml. Radiographs were used to corroborate bone age with an average delay of  $3.1 \pm 2.2$  years. All patients received an average dose of 0.6UI/kg of growth hormone.

There was no significant difference between patients with organic and idiopathic deficits. The final bone age was  $2.2 \pm 0.9$  years, there was no significant difference ( $p = 0.06$ ), the levels of somatomedin C were  $191.1 \pm 74.2$  ng/ml, improving significantly ( $p < 0.05$ ). The growth rate after one year of growth hormone treatment was compared in patients with organic deficiency with an average percentile of  $78.5 \pm 13.5$  and idiopathic deficiency of  $73.9 \pm 17.4$ , obtaining that there was no statistically significant difference ( $p = 0.65$ )

**Conclusions:** There is no statistically significant difference between growth rate at the first year of growth hormone treatment in patients with idiopathic or organic deficiency, probably because patients using growth hormone at our hospital met similar criteria At the beginning of the treatment and by the same average dose used.

PLEASE SEE TABLE ON FOLLOWING PAGE



Tabla 1. Auxological characteristics of 36 pediatric patients with growth hormone deficiency.

	Growth Hormone deficiency			p
	Total (n=36)	Organic (n=22)	Idiopathic (n=14)	
Age (years)	6.9±3.1	7±2.1	8±3.1	0.562
Gender				
Male	25 (69.4%)	14 (38.8%)	11 (30.5%)	0.357
Female	11 (30.6%)	8 (22.2%)	3 (8.3%)	
Height SD				
Before	-4.27±1.1	-4.24±0.8	-4.31±0.8	0.901
After	-3.19±1.2	-3.16±0.72	-3.25±0.98	0.878
Growth hormone peak (ng/ml)	2.35±0.3	2.3±0.8	3.7±1.7	0.092
Somatomedin-C (ng/ml)				
Before	41.9±11.1	27.4±14.2	67.4±34	0.014
After	191.1±74.2	177.7±80.1	217.6±89.8	0.491
Bone age delay (years)				
Before	3.1±2.2	3.2±1	2.9±0.8	0.722
After	2.2±0.9	2.3±0.8	2.1±0.9	0.738
Other hormone deficiency	21 (58.3%)	18 (50%)	3 (8.3%)	0.816
Growth velocity percentile	76.7±34.5	78.5±13.5	73.9±17.4	0.657

P3-808

# **SAFETY OUTCOMES IN PEDIATRIC PATIENTS WITH TURNER SYNDROME TREATED WITH GROWTH HORMONE**

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**Objectives:** To report safety data, including incidence rates (IRs), of adverse drug reactions (ADRs), serious adverse events (SAEs) and serious ADRs (SADRs) in a pediatric population with Turner syndrome (TS) treated with growth hormone (GH) (somatropin [Norditropin®], Novo Nordisk A/S, Denmark) as prescribed according to real-life clinical practice and enrolled in NordiNet® International Outcome Study (2006–2016; NCT00960128).

**Methods:** Events were classified by MedDRA Preferred Term/System Organ Class (SOC). IRs (events/1,000 patient-years) during GH treatment were calculated. Data are reported descriptively as mean ± standard deviation (SD).

**Results:** We analyzed data for 1,353 patients with TS who started GH treatment at mean (SD) age of 8.6 (3.7) years, with height SD score (SDS) of -2.5 (0.9) and target height SDS of -0.3 (1.0) at baseline. During the follow-up for 4.6 (3.0) years, a total number of 45 adverse events (AEs) were reported in 39 patients (2.9%). Of these patients, 89.7% (n=35) had one AE, 7.7% (n=3) had two AEs and 2.6% (n=1) had ≥ three events. Among patients with AEs, mean (SD) treatment duration until the first AE was 3.2 (2.9) years and GH dose at onset of first AE was 42.5 (9.1) µg/kg/day. Following the AE, the GH dose was unchanged in 60% of patients, reduced in 8.9%, and GH therapy discontinued in 17.8% of patients. For 13.3%, the impact of AEs on GH dose was unknown. The IRs for ADRs, SADRs and SAEs were 3.7, 1.3 and 4.8 events/1,000 patient-years, respectively. Most

frequently reported (n≥5) events by SOC (n, %) were nervous system disorders (n=11, 24.4%), cardiac disorders (n=5, 11.1%), musculoskeletal and connective tissue disorders (n=5, 11.1%), and infections and infestations (n=5, 11.1%). During GH treatment, one case of type 2 diabetes was reported as an SAE, with BMI SDS of 2.1 (BMI: 24.4 kg/m²) at onset of the SAE. For one patient (karyotype 45,X/46,XX) diagnosed with type 1 diabetes, classified as a comorbidity, one event of diabetic ketoacidosis was reported as an SADR.

**Conclusions:** Data from NordiNet® IOS reveal no new safety signals. The low reported IRs for SAEs, SADRs and ADRs further support the favorable safety profile of GH treatment in children with TS.

P3-809

# **PROSPECTIVE EVALUATION OF SERUM IGF-I IN GHD AND SGA CHILDREN UNDER RHGH: TITRATION STRATEGY FOR OPTIMIZING RHGH THERAPY**

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**Objectives:** Elevated serum IGF-I are frequently found in children throughout rhGH therapy. Whether these sustained elevated serum levels expose them to develop greater long term adverse events (AE) remains controversial. Therefore, rhGH doses titration is nowadays recommended. Aim: To determine IGF-I in children on rhGH, evaluate the proportion of those who need to titrate (T) and their impact on efficacy. **Methods:** Prospective interventional study including prepubertal patients with growth hormone deficiency (GHD) and born small for gestational age (SGA) without catch up growth, naïve of rhGH therapy. Conventional weight based dosing of rhGH was indicated (GHD 0.21 ± 0.04 mg/kg/w; SGA 0.32 ± 0.04 mg/kg/w). IGF-I and IGFBP-3 were determined basally and every 3 months (IMMULITE 2000, Siemens). rhGH dose titration was conducted (10% diminished) when IGF-I was above +2 SDS in two consecutive controls. Efficacy was evaluated as Δ height gain.

**Results:** Forty eight patients were enrolled (35 boys) aged  $7.21 \pm 2.86$  years; 22 GHD and 26 SGA. Three patients were excluded (2 non-compliant, 1 serious AE probably not related to rhGH). Basal IGF-I, IGFBP-3 and IGF-I/IGFBP-3 molar ratio (mean  $\pm$  SDS) were in GHD  $-3.02 \pm 2.81$ ,  $-2.15 \pm 1.02$ ,  $-0.8 \pm 0.17$  respectively; in SGA  $-0.55 \pm 0.73$ ,  $-0.62 \pm 0.88$ ,  $-0.22 \pm 0.65$ , respectively. After 2 years the proportion of patients that required rhGH dose titration was 57% in GHD and 48% in SGA. The time of occurrence of the event (need to titrate) was similar for GHD (median 12 months) compared to SGA (median 9 months),  $p = 0.14$ .  $\Delta$  Height (mean  $\pm$  SDS) was in GHD  $T 1.37 \pm 0.71$  vs GHD non-T  $1.57 \pm 0.82$  ( $p = 0.61$ ) and in SGA  $T 0.95 \pm 0.57$  vs SGA non-T  $1.23 \pm 0.38$ , ( $p = 0.18$ ).

**Conclusions:** Significant proportion of children have elevated IGF-I concentrations throughout conventional rhGH weight based dose. In our study a titration strategy does not appear to affect efficacy based on 2 years of height gain, leading to a physiological circulating IGF-I under treatment aiming towards a more safety approach.

P3-810

#### LONG TERM LOW IGF1 SERUM LEVEL IN INTOXICATION-TYPE INBORN ERRORS OF METABOLISM REQUIRING HYPOPROTIDIC DIET IS NOT ALWAYS ASSOCIATED WITH GROWTH FAILURE

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**Objectives:** Intoxication-Type Inborn Errors of Metabolism (IEM) are diseases that affect proteins catabolism. Treatment requires strict protein restrictive diet. Since proteins are key regulators of IGF1 secretion, we **aimed** to investigate if a hypoprotidic diet impairs statural growth through diminution of IGF1 secretion.

**Methods:** Cross sectional study on 156 patients prospectively followed up in one reference center for Intoxication-Type IEM that required a hypoprotidic normocaloric diet since neonatal period or early infancy. Data are expressed as median [min-max].

**Results:** Patients had Urea Cycle disease (80, 51%), Organic Aciduria (66, 42.5%) or Maple Syrup Urine disease (10, 6.5%).

Final height in 49 adults was  $-0.9 [-5 - 1.8]$ SD. 13(26%) patients had a final height  $\leq -2$ SD.

At last follow up, age was  $11.2 [0.7-29.2]$ years, height was  $-1 [-5.1 - 4.2]$ SD and protein intake was  $0.77 [0.21-2.55]$ g/kg. Height was  $\leq -2$ SD in 29 patients and  $> -2$ SD in 125 patients. The 2 groups were not different for protein intake ( $0.86 [0.21-1.73]$ g/kg vs  $0.75 [0.35-2.55]$ g/kg,  $p = 0.5$ ), albumin value ( $40 [30-49]$ g/L vs  $42 [33-52]$ g/L,  $p = 0.1$ ), prealbumin value ( $0.23 [0.17-0.36]$ g/L vs  $0.22 [0.13-0.5]$ g/L,  $p = 0.4$ ) or proportion of low IGF1 (54% vs 35%,  $p = 0.15$ ).

Protein intake was  $\leq 0.7$ g/kg in 65 patients and  $> 0.7$ g/kg in 86 patients. The 2 groups were not different for proportion of patients with a height  $\leq -2$ SD (14% vs 23%,  $p = 0.14$ ), albumin value ( $41 [33.5-52]$ g/L vs  $42 [30-50]$ g/L,  $p = 0.2$ ), prealbumin value ( $0.22 [0.15-0.5]$ g/L vs  $0.22 [0.13-0.38]$ g/L,  $p = 0.1$ ) or proportion of low IGF1 (46% vs 33%,  $p = 0.1$ ).

IGF1 was low at least 3 consecutive years in 19 prepubertal patients, and normal in 30 prepubertal patients. The 2 groups were not different for proportion of patients with a height  $\leq -2$ SD (16% vs 7%,  $p = 0.3$ ), protein intake ( $0.9 [0.5-1.5]$ g/kg vs  $0.8 [0.38-2.16]$ g/kg,  $p = 0.5$ ), albumin value ( $42 [32.5-46]$ g/L vs  $41 [30-48]$ g/L,  $p = 0.4$ ) or prealbumin value ( $0.2 [0.15-0.33]$ g/L vs  $0.2 [0.15-0.32]$ g/L,  $p = 0.7$ ).

GH secretion was normal and IGF1 low in 17 patients who were tested.

**Conclusions:** In intoxication-type IEM with hypoprotidic diet, long term low IGF1 or low protein intake may be associated with normal growth. This suggests that 1/low IGF1 is not only secondary to hypoprotidic diet 2/other factors improve growth in these patients.

P3-811

#### LONGITUDINAL NEUROPSYCHOLOGICAL EVALUATION OF CHILDREN WITH GROWTH HORMONE DEFICIENCY (GHD) IN REPLACEMENT THERAPY COMPARED WITH HEALTHY SUBJECTS: A PILOT STUDY.

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**Objectives:** Few studies, and on adults have investigated the influence of GH on the development of human brain before now.

The main objectives of this study were to evaluate the relationship between GH and neurocognitive functions in short stature children, and to investigate the effects of GH and the therapy with recombinant GH (rGH) on some neuropsychological functions; in particular: attention, short- and long-term memory, visual and visuospatial memory, semantic memory and perception in children diagnosed with idiopathic GH deficit (GHD).

**Methods:** 19 short stature children (9 with GHD and 10 without GHD), aged between 6 and 12 years old, were administered with some specific tests (Continuous Performance Test, Raven progressive Matrices, Corsi block-



tapping test, Rey–Osterrieth complex *figure* test, BVN array for short-term memory, BVN and TEMA array for selective memory of words and visual-memory, BVN and MT array for shred reading, DDE-2 array for words and sentences dictation, AC-MT array for calculation abilities), and their parents completed the Child Behaviour Checklist, so we could examine, besides their auxological and biochemical characteristics, their neuropsychological abilities at diagnosis (T0) and after 6 months of rGH therapy (T1).

**Results:** At T0, the visual long-term memory came out to be significantly worse in GHD patients, in comparison to non-GHD ( $p=0.01$ ), and it improved in GHD patients 6 months after the beginning of the therapy. Visual long-term memory also resulted to be strongly correlated to the GH peak level after the stimulus test ( $p<0.001$ ;  $R=0.766$ ). Moreover, a correlation between some executive functions (visuospatial perception and verbal planning) and the basal GH level was found (respectively  $p<0.05$  and  $p<0.01$ ;  $R=0.586$ ). GHD patient's cognitive functions were not found significantly different when compared between T0 and T1, even though improvements in many neurocognitive functions were observed (verbal short-term memory, verbal and visual long-term memory, verbal planning, writing and calculation ability).

**Conclusions:** Our work showed for the first time an interesting association between GH level and memory in pediatric age. This result supports the hypothesis that GHD children with low levels of GH and IGF-1 could benefit of rGH therapy for cognition.

P3-812

#### SEXUAL DIMORPHISM IN THE ASSOCIATION OF SINGLE NUCLEOTIDE POLYMORPHISMS OF THE IGF1 GENE WITH SERUM IGF-1 LEVELS IN INBRED MOUSE STRAINS.

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**Objectives:** The objective of this study is to identify polymorphisms in the *Igf1* gene that are associated with serum IGF-1 levels in inbred mouse strains, and secondarily to address whether the associations exhibit sexual dimorphism.

**Methods:** We interrogated genomic sequence data of inbred mouse strains released by the Mouse Genomes Project, and identified 26 SNPs over a 150 kb region spanning the *Igf1* gene. rs29342496 maps to the 5' UTR of promoter 2, but none mapped to a coding region of the gene nor within 1 kb of 7 defined Stat5b-binding regulatory regions. We used standard student t-test to assess for significant associations of specific SNP (and haplotype) genotypes with serum IGF-1 levels measured in males and females across 24 inbred mouse strains by the Jackson Aging Center.

**Results:** We determined a significant association of a haplotype of 9 SNPs that includes rs29342496 with serum IGF-1 levels ( $270\pm47$  vs.  $343\pm62$  ng/ml,  $p=0.02$ ). Further analysis revealed the association is much stronger in female mice ( $252\pm55$  vs.  $349\pm74$ ,  $p<0.01$ ), and is not maintained in

the male mice ( $289\pm47$  vs.  $337\pm56$ ,  $p=0.07$ ). Similarly, a subset of other SNPs are significantly associated with IGF-1 levels in female but not male mice.

**Conclusions:** We have identified common SNPs of the *Igf1* gene associated with serum IGF-1 gene in inbred mouse strains, supporting the concept that less deleterious genetic defects may contribute to the growth phenotype. Importantly, we note sexual dimorphism in the association of specific SNPs with serum IGF-1 levels, and highlight that studies of the GH – IGF-1 pathway should include both sexes. Mechanisms whereby these specific SNPs could impact serum IGF-1 have yet to be elucidated, but we speculate that chromatin changes including DNA methylation could play a key role.

P3-813

#### LATEST RESULTS FROM PATRO CHILDREN, A MULTI-CENTRE, NON-INTERVENTIONAL STUDY OF THE LONG-TERM SAFETY AND EFFICACY OF OMNITROPE® IN CHILDREN REQUIRING GROWTH HORMONE TREATMENT

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**Objectives:** PATRO Children is an international, open, longitudinal study of the long-term safety of a recombinant human growth hormone (rhGH) (Omnitrope®, Sandoz). In particular, the study will assess the diabetogenic potential of Omnitrope®, the risk of malignancies and potential risks of Omnitrope® therapy in Prader-Willi syndrome. The long-term efficacy is a secondary objective of the study.

**Methods:** The study population includes infants, children and adolescents receiving Omnitrope® therapy according to local prescribing information. All adverse events (AEs) are monitored and recorded for evaluation of Omnitrope® safety. Laboratory values (including glucose metabolism and anti-hGH antibodies) are requested at least once a year. Height standard deviation score (SDS), height velocity and height velocity SDS are calculated using height measurements and country-specific reference tables to evaluate Omnitrope® efficacy.

**Results:** As of January 2017, 5330 patients were recruited from 295 sites in 14 countries. The mean (range) duration of treatment was 34.2 (0.0–121.1) months, with 1092 patients completing 5 years of treatment. To date, 7909 AEs have been reported in 2219 (41.6%) patients, with 440 AEs in 323 (6.1%) patients suspected to be related to treatment. Overall, 795 AEs in 437 (8.2%) patients were regarded as serious and of these 40 events in 29 (0.5%) patients were suspected to be related to treatment. Drug-related serious AEs included diabetes mellitus, craniopharyngioma and neoplasm progression in one patient each. No clinically relevant positive

anti-hGH antibody titres have been found in patients tested so far. Efficacy data indicate that Omnitrope® treatment has a positive impact on growth parameters in the majority of paediatric indications.

**Conclusions:** The latest results from the PATRO Children study show that Omnitrope® is safe and well tolerated across paediatric indications, and is effective in the majority of Omnitrope®-treated children. The results from this analysis show no evidence for an increased risk of developing diabetes mellitus or malignancies during Omnitrope® treatment.

P3-814

#### EFFECTS OF LONG-TERM GROWTH HORMONE TREATMENT ON COGNITION IN CHILDREN WITH PRADER-WILLI SYNDROME

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**Objectives:** Long-term growth hormone (GH) treatment in children with PWS improves body composition, linear growth, psychomotor development and cognitive function. GH receptors are expressed throughout the brain, and GH and insulin-like growth factor (IGF-I) are involved in brain growth, development and myelination. The positive effects of GH on cognitive abilities in PWS have been investigated in some RCTs. However, there is no information on the long-term effects of GH treatment in children with PWS. The objective of this study is to investigate the effects of 8 years of continuous GH treatment on cognitive functioning in a Dutch PWS Cohort. We hypothesized that the improved functioning after 4 years of GH treatment will persist on the long-term.

**Methods:** 27 children had cognitive tests during at least 6 years of GH treatment 1 mg/m<sup>2</sup>/day ( $\approx$ 0.035 mg/kg/day). Cognitive function was measured annually by a psychologist experienced in testing children with PWS. Cognitive functioning was assessed by the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) in children.

**Results:** Vocabulary SDS and Block Design SDS had significantly increased after 2 and 6 years of GH versus baseline ( $p=0.04$  and  $p=0.02$  resp.), but did not change after 6 years of GH treatment. Total IQ increased significantly during the first 4 years of GH treatment ( $p=0.04$ ) and remained similar thereafter. A younger age at start of GH treatment was associated with a better cognitive functioning after 8 years of GH treatment.

**Conclusions:** GH treatment improves cognitive functioning in the first 4 years of GH treatment. This improved cognitive functioning is maintained during the following 4 years of GH treatment. Starting GH treatment at a younger age results in better cognitive function on the long-term.

P3-815

#### ANALYSIS OF EFFECT OF GROWTH HORMONE TREATMENT ON IDIOPATHIC SHORT STATUS CHILDREN TO NEAR-ADULT HEIGHT

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**Objectives:** The principal aim of this study was to evaluate the effects of GH treatment in ISS children with baseline HtSDS  $\leq -2$  on near-adult height (NAH) outcomes.

**Methods:** ISS children were included in the current analyses if they had a baseline HtSDS  $\leq -2$  and were treated by GH, and had been discontinued and attained adult height or NAH. The main outcome measures included near-adult height (NAH) standard deviation scores - target HtSDS in response to GH treatment ( $?HtSDS = NAH HtSDS - T HtSDS$ ), and analysis of correlation with  $?HtSDS$ .

**Results:** A total of 176 cases of ISS into the group, 106 males and 70 females. Mean chronological age at baseline of male and female were  $12.9 \pm 2.12$  years and  $12.1 \pm 1.72$  years, bone age were  $9.5 \pm 2.53$  years and  $10.1 \pm 2.16$  years, respectively. The current average age were 16.74 years and 16.56 years. The follow-up period was 0.27-8.8 years. Mean HtSDS baseline to NAH; male: -3.31 to -1.98 and female: -2.86 to -1.39. There were significant difference between baseline to NAH of HtSDS, both male and female were  $P = 0.0000$ . Percentages of patients reaching near-adult HtSDS  $> -2SD$  were male 55.7% (59/106), female 71.4% (50/70). Analysis of non-inferiority test showed that male NAH HtSDS were shorter than target HtSDS, while female were not shorter than target HtSDS. Baseline HtSDS, sex and duration of treatment were significantly correlated with  $?HtSDS$ ,  $P$  values were 0.0046,  $<0.0001$ , 0.0265, when analyzed by multiple linear regression.

**Conclusions:** Despite a relatively advanced children age, the majority of GH-treated patients attained mean near-adult HtSDS within the normal range (HtSDS  $> -2SD$ ). Female, higher baseline HtSDS, longer duration of GH treatment would likely have resulted in greater adult height achieved in ISS children.

P3-816

#### LONG-TERM EFFECTS OF GH REPLACEMENT THERAPY ON GLUCOSE METABOLISM IN CHILDREN WITH GH DEFICIENCY

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**Objectives:** The aim of our study was to evaluate the effects of GH deficiency (GHD) and GH replacement therapy (GHRT) on glucose metabolism in a large cohort of children with GHD before and during GHRT.

**Methods:** We evaluated glucose, insulin, HOMA, QUICKI and HbA1c levels in 100 GHD children aged  $9.4 \pm 3.7$  years at diagnosis and 1 and 5 years after the start of GHRT. One

hundred healthy children age-, sex- and BMI-comparable to patients were evaluated at baseline and after 1 and 5 years of follow-up as controls.

**Results:** At baseline glucose metabolism parameters were comparable between patients and controls. In GHD children one year of GHRT was associated with a significant increase in insulin ( $7.2 \pm 4.8$  vs  $4.5 \pm 3.3$  mcU/ml,  $p < 0.001$ ) and HOMA ( $1.32 \pm 0.98$  vs  $0.93 \pm 0.72$ ,  $p < 0.001$ ) levels and a decrease of QUICKI ( $0.39 \pm 0.06$  vs  $0.42 \pm 0.06$ ,  $p < 0.001$ ) in absence of significant modifications of glucose and HbA1c. Glucose metabolism parameters remained stable during treatment until the end of the study in GHD patients (insulin  $7.5 \pm 4.0$  mcU/ml, HOMA  $1.34 \pm 0.79$ , QUICKI  $0.38 \pm 0.06$ ). In contrast, healthy controls showed no significant changes in insulin ( $4.6 \pm 3.0$  vs  $4.7 \pm 3.0$  mcU/ml), HOMA ( $0.91 \pm 0.65$  vs  $0.89 \pm 0.63$ ) and QUICKI ( $0.41 \pm 0.04$  vs  $0.41 \pm 0.04$ ) after the first year of follow-up. At the fifth year of the study a significant increase in insulin ( $6.4 \pm 3.6$  vs  $4.6 \pm 3.0$  mcU/ml,  $p < 0.001$ ) and HOMA ( $1.36 \pm 0.73$  vs  $0.91 \pm 0.65$ ,  $p < 0.001$ ) and a decrease in QUICKI ( $0.39 \pm 0.04$  vs  $0.41 \pm 0.04$ ,  $p < 0.001$ ) levels were documented in these children. Consequently, glucose metabolism parameters resulted comparable between the two groups at the end of the study.

**Conclusions:** Untreated GHD is not associated to insulin-resistance in childhood; GHRT determines a reduction in insulin-sensitivity during the first year of therapy while glucose parameters return to be similar to healthy children in the subsequent years.

P3-817

#### **A NATIONAL, MULTICENTRE, OBSERVATIONAL STUDY TO ASSESS ADHERENCE AND LONG TERM OUTCOMES OF GH THERAPY IN PAEDIATRIC SUBJECTS WITH SMALL GESTATIONAL AGE USING EASYPD™ DEVICE IN SPAIN: ECOS STUDY.**

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**Objectives:** To assess the adherence and impact on clinical outcomes of GH treatment in patients with small gestational age (SGA).

**Methods:** Patients aged  $>2$  to TM, were enrolled in this national, multicentre, observational study (NCT01376921). Of the patients identified the ones with SGA were stratified in a prepubertal and pubertal group. The primary endpoint was to assess the adherence of GH therapy (Saizen®) via easypod™ in paediatric subjects with SGA. Secondary objectives were to evaluate the impact of adherence on clinical outcomes and on the levels of IGF-1, to identify

adherence subject profiling in order to assess the impact and the proportion of subjects with an adherence rate  $\geq 85\%$ . Adherence was measured by the mean percent of daily recorded adherence over time. Data were primarily derived from the easypod™ device combined with physician data entry of outcome measures and were collected in follow-up visits (at 6 months, 1, 2, 3 and 4 years after starting the treatment).

**Results:** A total of 238 subjects were enrolled, and data of 86 children with SGA were analyzed over a period of 4 years after starting the treatment. The mean treatment adherence rate was high (93.0%, 95%CI: 89.1-96.9) and similar to the total population analyzed (94.5%, CI95%: 92.2-96.3). During the study visits, this rate remained high (98.1% [97.5-98.7] at 6 months, 97.4% [96.1-98.7] at 1 year, 93.1% [88.7-97.5] at 2 years, 92.3% [84.5-100.1] at 3 years and 94.4% [87.0-101.9] at 4 years). The adherence was similar between the prepubertal and pubertal groups. Good compliance (adherence  $\geq 85\%$ ) was high (97.7%) at 6 months and was maintained during the follow-up visits while poor compliance ( $<85\%$  adherence) was low (1.16-14.3%) throughout the study. Patients with good compliance showed a significantly higher weight change (at 2 years). No impact of adherence on IGF-1 status was observed.

**Conclusions:** Data indicate that subjects with SGA treated with Saizen® via easypod™ showed a high adherence in long period treatments with the consequent impact in the clinical outcome which supports its use in the clinical practice.

P3-818

#### **SCREENING OF MONOGENIC MUTATIONS IN PATIENTS WITH IDIOPATHIC SHORT STATURE**

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**Background:** Mutations in skeletal dysplasia genes such as *SHOX*, *ACAN* and *FGFR3*, and those in genes in the growth hormone (GH)-insulin-like growth factor 1 (IGF-1) axis have been identified in multiple patients with idiopathic short stature (ISS). However, the clinical significance of these mutations as genetic causes of ISS remains uncertain.

**Objective:** To clarify the contribution of monogenic mutations to the etiology of ISS.

**Methods:** We studied children whose stature was less than -2.0 standard deviation. We excluded patients who were born small for gestational age and those who had syndromic features or chronic disorders. First, we examined the frequency of *SHOX* haploinsufficiency in 340 patients using array-based comparative genomic hybridization and PCR-based mutation analysis. Then, we performed next generation sequencing of three skeletal dysplasia genes (*NPR2*, *ACAN*, and *FGFR3*) and seven GH-IGF-1 axis genes (*GHRHR*, *GH1*, *GHR*, *STAT5B*, *IGF1*, *IGFALS* and *IGF1R*) for 86 patients. We searched for nonsynonymous variants and sequence variations at exon-intron boundaries. To assess the pathogenicity of the identified variants, we examined allele frequencies in the general population and performed *in silico* functional prediction.

**Results:** We identified *SHOX* abnormalities in 13 of 340 patients. Sequence analysis of 10 genes detected 19 nonsynonymous variants in 21 of 86 patients. Of the 19 variants, eight affected *ACAN* and included a frameshift mutation (p.Pro846Phefs\*9) and three putative pathogenic variants. Variants in the GH-IGF-1 axis genes were identified in nine patients, although pathogenicity of these variants remained unknown.

**Conclusions:** The results indicate that mutations in skeletal dysplasia genes, particularly those in *SHOX* and *ACAN*, play a significant role in the etiology of ISS. In contrast, genetic defects in the GH-IGF1 axis appear to be rare in patients with ISS.

P3-819

#### GENOMIC APPROACHES TO INVESTIGATE CHILDREN BORN SMALL FOR GESTATIONAL AGE (SGA) WITHOUT CATCH UP-GROWTH

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**Objectives:** To assess the usefulness of a genomic approach to establish the etiology of growth disorder in children born SGA without catch-up.

**Methods:** A total of 197 SGA children were evaluated clinically, laboratory and radiologically by professionals with expertise in dysmorphology. Clinical diagnosis was unable to be obtained in 152 patients. According to the presence/absence of dysmorphic features, developmental

delay and/or intellectual disability they were classified as syndromic (S=65) or non-syndromic (NS=87) short stature. We conducted SNP/CGH microarray analyses in 71 patients (S=48/NS=23) and whole exome (n=39)/targeted panel (n=59) sequencing in 96 patients (S=48/NS=48).

**Results:** Among NS patients, we did not find any pathogenic/probably pathogenic CNVs, however we identified 9 (19%) pathogenic SNVs using whole exome sequencing/genic panel in *IGF1R* (2x), *IHH* (2x), *ACAN*, *NF1*, *NPR2*, *PTPN11*, *LTBP3* genes. Among group S, we found 13 (27%) CNVs and 8 (16.5%) SNVs classified as pathogenic or probably pathogenic, including variants in *COL2A1* (2x), *SRCAP* (2x), *ANKRD11*, *NPR2*, *POC1A*. All identified SNVs are extremely rare or absent in public database, were predicted to be deleterious and segregated with the phenotype. The genes involved are associated with rare diseases (i.e. KBG or Floating-Harbor syndrome), genetic syndromes with high phenotypic variability (i.e. Noonan or Cornelia de Lange syndrome), which prevented their clinical recognition. Additionally, we identified three novel candidate genes for short stature of prenatal onset: *BRCA1*, *DGCR8* and *RAB3IP*. The variants identified in these genes are loss-of-function (LoF: 2 frameshift and 1 stopgain). Two of them were identified in homozygous state (*BRCA1* and *RAB3IP*) and another is a heterozygous de novo mutation (*DGCR8*). All novel candidate genes are involved in critical cellular function and, based on ExAC database, they are intolerant of LoF variation.

**Conclusions:** The great heterogeneity of short stature phenotype difficult the clinical diagnosis of children born SGA. The new genomic approaches are effective to establish the etiology of growth impairment diagnosis of a larger number of previously undiagnosed patients and also identified novel genes involved in this phenotype.

P3-820

#### ANALYSIS OF RESULTS FROM THE GLOBAL, 5-YEAR EASYPD™ CONNECT OBSERVATIONAL STUDY (ECOS) STUDY IN CHILDREN WITH GROWTH DISORDERS

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**Objectives:** The easypod™ connect observational study (ECOS), a 5-year, Phase IV open-label study, was started in 2010 in 24 countries to assess 'real-world' adherence and growth outcomes with GH via the easypod™ electronic drug delivery device in patients with growth hormone deficiency (GHD), small for gestational age (SGA), Turner syndrome (TS) and chronic renal failure (CRF). This is the first analysis of data from the full population. Individual country analyses will follow.

**Methods:** Demographic, auxological and diagnostic data were obtained from medical notes, with adherence data obtained directly from the patients' easypod™. Adherence was

expressed as the % of days with injections received, divided by days with injections planned.

Data were analysed for adherence rates, growth response (changes in height SDS) and the correlation between adherence and outcomes.

**Results:** The complete analysis set included 1,203 patients (GHD n=897, SGA n=207, TS n=82, other/missing n=17), of whom 610 were naïve to GH treatment. The easypod™ adherence data analysis set included 1,190 patients (GHD n=886, SGA n=206, TS n=82, other/missing n=16) for whom adherence data were available for ≥ 3 months after starting easypod™, of whom 606 were GH-naïve.

Adherence was maintained at ~80% for up to 3 years of treatment for the easypod™ adherence data set and also for GH naïve patients. GH naïve patients with congenital GHD achieved the highest median growth response at 1 yr (ΔHtSDS 0.72), followed by patients with idiopathic isolated GHD (ΔHtSDS 0.55), and non GHD patients (ΔHtSDS 0.47). Median adherence levels at 1 yr were 91.1%, 92.3% and 94.2% in these groups. Spearman's correlation between adherence and 1<sup>st</sup> yr outcome was strongest in GHD patients (p<0.001) and in all patients naïve to GH.

IGF-1 levels at 1 yr were generally maintained within the normal range for the easypod™adherence dataset (80.3% patients within normal range, 11.7% above and 8% below).

**Conclusions:** This is the first report of large scale digital assessment of adherence over 5 years using easypod™ to deliver Saizen® GH in children with growth disorders. High levels of adherence were generally maintained over time and were associated with a positive growth outcome.

P3-821

**PUBERTAL GROWTH DYNAMICS IN CHILDREN WITH SEVERE PRIMARY IGF-1 DEFICIENCY (SPIGFD): RESULTS FROM THE EUROPEAN INCRELEX® GROWTH FORUM DATABASE (EU-IGFD)**

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**Objectives:** To describe pubertal growth dynamics in short children with SPIGFD treated with rhIGF1 (Increlex®) therapy, which remain largely unknown 10 years after rhIGF1 was approved for this use.

**Methods:** The EU-IGFD is a multicentre, observational, post-authorisation registry. This analysis included children who were prepubertal (Tanner stage [T] 1) at first Increlex® intake w/o receiving GnRH analogs and who were entered in the EU-IGFD as of 10th-OCT-2016. First registrations of pubertal stages T2–T5 were noted. Pubertal duration was measured between first registrations of T2 and T5. Maximum height velocity during each Tanner stage was calculated. Pubertal peak height velocity (PPHV) was defined as the maximum

annualized height velocity between two visits ≥ 6 months apart during T2 to T5, and the stage at which it occurred was noted. Results are given in median [range] for continuous variables.

**Results:** Of 234 children in the EU-IGFD, 177 were prepubertal. The duration of follow-up from rhIGF1 start was 4.3 [0.3 to 8.2] years. For the majority of patients, final heights were not available at the time of analysis. Pubertal duration was 3.0 [0.9 to 5.8] years in boys (n=13) and 3.1 [2.5 to 4.5] years in girls (n=6). PPHV was 8.0 [3.9 to 13.0] cm/year in boys (n=52) and 6.7 [1.3 to 9.6] cm/year in girls (n=35) and was predominantly observed at T3 in both genders (Table). Pubertal growth recorded between T2 and T4 was 11.8 [4.5 to 29.3] cm in boys (n=24) and 13.0 [5.5 to 15.9] cm in girls (n=15). Between T2 and T5 it was 18.4 [10.7 to 33.3] cm in boys (n=13) and 15.6 [6.0 to 18.4] cm girls (n=6). Height at T5 was -2.0 [-6.9 to -0.7] SD in boys (n=16) and -1.6 [-6.5 to -1.0] SD in girls (n=7).

**Conclusions:** Compared to population references, rhIGF-1 treated girls and boys with SPIGFD started puberty almost 1.5 year late, had height gain from T2 to T5 less than expected to ensure a normal total pubertal height gain, while the PPHV was similar. To establish the overall impact of these pubertal growth dynamics on adult height, patients are being followed in the EU-IGFD registry.

*This study was supported by Ipsen.*

Table: Pubertal growth dynamics by Tanner stage in children with SPIGFD prepubertal at first Increlex® intake

Tanner Stage	Gender	Mean reference age of entry, years (-2 to +2 SD) <sup>1</sup>	n	Mean age at first registration, years (SD)	Occurrence of PPHV, n (%) <sup>*</sup>	Maximum height velocity at each stage, cm/year median [range]
T1	M	---	112	---	---	---
	F	---	65	---	---	---
T2	M	11.8 (9.9–13.8)	46	13.4 (2.0)	7 (13.7)	6.6 [3.9–11.4]
	F	10.9 (8.7–13.1)	29	12.2 (1.6)	7 (22.6)	6.7 [2.2–9.6]
T3	M	13.3 (11.2–15.4)	38	14.5 (1.5)	21 (41.2)	8.2 [2.1–13.0]
	F	12.4 (10.3–14.5)	28	13.1 (1.6)	18 (58.1)	6.0 [1.3–9.1]
T4	M	14.3 (12.3–16.3)	32	15.5 (1.6)	17 (33.3)	7.4 [2.5–13.0]
	F	13.5 (11.4–15.6)	19	13.9 (1.3)	6 (19.4)	3.9 [0.5–7.3]
T5	M	15.4 (13.2–17.6)	17	16.2 (1.8)	6 (11.1)	4.9 [0.5–12.0]
	F	14.7 (12.4–17.0)	7	15.2 (1.3)	0	3.3 [1.6–5.1]

Some children were not recorded at every Tanner Stage they reached, depending on the time between visits.  
\*% of patients who started puberty with available data on PPHV, and stage at which PPHV occurred (51 boys, 31 girls). PPHV, peak pubertal height velocity; SPIGFD, severe primary IGF-1 deficiency.  
1) A. Juul et al. *Int J Androl*, 2005.

P3-822

**ASSOCIATION BETWEEN SERUM VITAMIN A CONCENTRATIONS AND HEIGHT OF ADOLESCENTS IN NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEYS (NHANES)**

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**Objectives:** Vitamin A deficiency is associated with linear growth impairment in developing countries. However, the relationship between vitamin A status and height are less well studied in developed populations.

**Methods:** We used the National Health and Nutrition Examination Survey (NHANES) cycles 1999-2006

to investigate the association between serum vitamin A concentrations and height in a nationally representative sample of children and adolescents. Analyses were stratified for gender, and participants were categorized by age [in females: 6-9 years (n=1053), 10-13 years (n=1575), and 14-15 years (n=921); in males: 6-10 years (n=1357) and 11-17 years (n=3168)]. Multiple linear regression analyses were controlled for age, race/Hispanic origin, family poverty income ratio, and BMI z-score.

**Results:** Mean serum vitamin A concentration was  $40.1 \pm 0.3$  and  $42.8 \pm 0.3$   $\mu\text{g/dL}$  (mean  $\pm$  SE) in females and males, respectively. The covariates age, race/Hispanic origin, family poverty income ratio, and BMI Z-score showed significant associations with height. After controlling for these covariates, a statistically significant association between vitamin A and height was seen among females aged 10 to 13 years ( $P = 0.0003$ ) and males aged 11 to 17 years ( $P = 0.0003$ ). An increase of 10  $\mu\text{g/dL}$  in serum vitamin A was associated with an increase of  $0.9 \pm 0.2$  cm in height among females aged 10 to 13 years and an increase of  $0.7 \pm 0.1$  cm among males aged 11 to 17 years. A sensitivity analysis using percent body fat by DXA instead of BMI z-score confirmed the association.

**Conclusions:** Our findings suggest a positive association between serum vitamin A concentration and height in adolescents in the U.S. general population.

P3-823

#### GROWTH HORMONE (GH) THERAPY IMPROVES ADULT HEIGHT IN CHILDREN WITH NOONAN SYNDROME AND IDENTIFIED MUTATIONS IN PTPN11 GENE.

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**Objectives:** To evaluate the response to recombinant human GH (rhGH) treatment in short children with Noonan syndrome (NS) and mutations in PTPN11 gene.

**Methods:** Twenty-five patients with NS (20 males; 19 prepubertal) were daily treated with rhGH (mean rhGH dose of  $47 \mu\text{g/kg/d}$ ). The main outcome measures were changes in height SDS (Noonan syndrome standards), growth velocity and IGF-1 levels at 1st year and end of treatment and adult height SDS.

**Results:** At the start of rhGH treatment, the mean age was  $10.0 \pm 3.9$  yr, and bone age was  $8.0 \pm 3.6$  yr. The mean height was  $-3.4 \pm 0.8$  and  $-0.8 \pm 0.7$  for reference population and Noonan syndrome standards (HNS-SDS), respectively. The growth velocity (GV) increased from baseline values of  $4.1 \pm 1.0$  cm/yr to  $7.3 \pm 1.8$  cm/yr at the 1st year of therapy, an

increment of  $3.3 \pm 3.3$  cm ( $p < 0.001$ ). Height SDS significantly improved after the 1st year (mean change in HNS-SDS of  $0.5 \pm 0.3$ ,  $p = 0.02$ ). IGF-1 levels also increased during the first year of treatment ( $104 \pm 51$   $\mu\text{g/L}$  to  $263 \pm 108$   $\mu\text{g/L}$ ,  $p < 0.001$ ). After a mean duration of rhGH treatment of  $5.2 \pm 1.5$  years, 13 patients achieved the end of therapy. The average HNS-SDS was  $0.4 \pm 1.2$ , with an increment of  $1.3 \pm 0.6$  concerning start of treatment ( $p = 0.002$ ). Two patients were lost to follow-up. Ten patients achieved adult height and the total height SDS gain concerning NS standards was  $1.7 \pm 0.5$  (from 0.9 to 2.5).

**Conclusions:** The use of rhGH to promote linear growth in short children with NS is still controversial regarding the magnitude of rhGH effect on adult height. However, our current findings support a benefit of the use of rhGH therapy to improve the adult height in patients with PTPN11 mutations.

P3-824

#### ESTIMATION OF SERUM IRISIN LEVELS IN PREPUBERTAL CHILDREN WITH GROWTH HORMONE DEFICIENCY BEFORE AND AFTER 6 MONTHS OF GROWTH HORMONE THERAPY

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**Objectives:** Background: Irisin (Ir) is an adipomyokine involved in metabolic homeostasis, including adipocyte browning stimulation.

Ir is suggested to have an antiobesity and antidiabetic influence. GH deficiency (GHD) is associated with altered body composition and increased metabolic risk, which improves during GH treatment.

**Objective an hypotheses:** To estimate the effect of 6-month GH therapy on serum irisin concentration in prepubertal children with isolated GHD.

**Methods:** The study group consists of 30 non-obese prepubertal children (20 boys, 10 girls) with GHD (mean height  $111.3$  cm,  $-2.59$  SD, mean BMI  $-0.48$  SD), mean age  $7.38$  years. Control group (CG): 25 (12 boys, 13 girls) age matched healthy children (mean height  $122.69$  cm,  $-0.31$  SD, mean BMI  $-0.3$  SD). Fasting serum irisin level was measured in CD group and in GHD children before and after 6 months of GH therapy. In GHD group the following exams were done: body composition (anthropometry, bioimpedance), OGTT and insulin sensitivity (IS) was estimated (HOMA, QUICKI, Matsuda index). In statistical analysis t-Student and U Mann-Whitney tests were used.

**Results:** The mean serum Ir level did not differ significantly between CG, GHD before and after 6-month therapy (respectively  $9.23$ ;  $9.50$ ;  $9.34$  ng/ml). There were no significant correlations between Ir and IS before and after GH therapy.  $\Delta \text{Ir}$  (Ir level GHD after 6 months – Ir level GHD untreated) correlates negatively with  $\Delta$  fasting glucose ( $r =$

0,38,  $p < 0,01$ ).  $\Delta$ Ir correlates positively with  $\Delta$  fat body mass ( $r = 0,41$ ,  $p < 0,01$ ).

**Conclusions:** GH therapy does not influence serum irisin concentration in non-obese prepubertal children with GHD. It seems that  $\Delta$  irisin levels may influence glucose metabolism during GH therapy in GHD children.

**Funding:** This work was supported by Department of Medicine and Health Sciences, Jan Kochanowski University, Kielce, Poland (internal grant).

P3-825

#### FOOD RESTRICTION FOLLOWED BY REFEEDING WITH A CASEIN- OR WHEY-BASED DIET DIFFERENTIALLY AFFECTS THE GUT MICROBIOME OF PRE-PUBERTAL MALE RATS

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**Objectives:** Researchers are gaining an increasing understanding of host-gut microbiome interactions, but studies of the role of gut microbiome in linear growth are scarce. The aim of this study was to investigate the effect of food restriction and refeeding with different diets on gut microbiota composition in fast-growing rats.

**Methods:** Young male Sprague-Dawley rats were fed regular rat chow ad libitum (control group) or subjected to 40% food restriction for 36 days followed by continued restriction or ad libitum refeeding for 24 days. Three different diets were used for refeeding: regular vegetarian protein chow or chow in which the sole source of protein was casein or whey.

**Results:** In the control group, the composition of the microbiota remained stable. Food restriction for 60 days led to a significant change in the gut microbiota at the phylum level, with a reduction in the abundance of Firmicutes and an increase in Bacteroidetes and Proteobacteria. Rats refed with the vegetarian protein diet had a different microbiome composition than rats refed the casein- or whey-based diet. Similarities in the bacterial population were found between rats refed vegetarian protein or a whey-based diet and control rats, and between rats refed a casein-based diet and rats on continued restriction. There was a significant strong correlation between the gut microbiota and growth parameters: humerus length, epiphyseal growth plate height, and levels of insulin-like growth factor 1 and leptin.

**Conclusions:** In conclusion, the type of protein in the diet consumed can significantly affect the gut microbiome and, thereby, health and metabolism.

P3-826

#### LONG-TERM ADHERENCE TO GROWTH HORMONE THERAPY IN A LARGE HEALTH MAINTENANCE ORGANIZATION COHORT

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**Objectives:** The therapeutic outcome of Growth Hormone (GH) therapy is depended on patient's adherence to treatment regimen. Our aim was to assess the long-term adherence to GH therapy in a large cohort.

**Methods:** From the 1.2 million children aged 0-18 insured by Clalit Health Services, all patients aged 1-16 who were treated with GH during the period 2006-15 for more than 2 years were included

Adherence was measured using the number of months per year in which GH prescriptions were dispensed. Adherence data was categorized using the cut offs: good- 11 and 12 months, moderate 7-10 months and poor <7 months per year.

**Results:** There were 2263 patients (59% males) with more than 2 years of treatment. Mean age at the beginning of treatment was  $8.3 \pm 3.6$  years, 74% were secular Jews, 6.8% were ultra-orthodox Jews and 18.9% were of Arab origin. We stratified the patients using the socioeconomic status (SES) of their clinic, 20% were in the upper third, 38% in the middle third and 42% in the lower third. 76 (3.4%) patients were treated due to chronic renal failure. Only 30% of the patients had good adherence to GH therapy. Patients who started the treatment before age 8 had the poorest adherence rate.

We did not find an association between adherence and gender, SES of clinic, or the indication for treatment idiopathic short stature vs. GH deficiency.

In a multivariate analysis which included gender, age groups (0-8 years, 9-10, 11-12 and 13+ years) origin and SES we found that being an ultra-orthodox Jew was a risk factor for non-adherence (OR 2.16, CI 95% 1.46-3.19). The poorest adherence was in the youngest age group.

In patients who were treated for more than 5 years ( $n = 668$ ), adherence rate declined slightly over the years (table 1).

**Conclusions:** Long term adherence to GH therapy is suboptimal. Measures for improving adherence especially among younger and extremely religious patients are needed.

PLEASE SEE TABLE ON FOLLOWING PAGE



Table: Level of adherence to treatment over years  
(for 668 patients with more than 5 years of treatment)

Months per year	Second year N (%)	Third year N (%)	Fourth year N (%)	Fifth year N (%)
1-6	115(17)	126(19)	165(24.5)	170(25)
7-10	346(51)	346(51)	318(47.5)	315(47)
11-12	222(32)	202(30)	187(28)	183(27)
Mean $\pm$ SD	8.9 $\pm$ 2.6	8.7 $\pm$ 2.8	8.3 $\pm$ 3.0	8.2 $\pm$ 3.1

P3-827

### C-TYPE NATRIURETIC PEPTIDE LEVELS ARE ALTERED IN CHILDREN WITH DIFFERENT FORMS OF OSTEOCHONDRODYSPLASIA.

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**Objectives:** C-type natriuretic peptide (CNP), acting through natriuretic peptide receptor-B, promotes chondrocyte differentiation and plays a key role in the regulation of growth. We have shown that CNP and its amino-terminal propeptide (NTproCNP, a marker of CNP biosynthesis) are elevated in children with acromesomelic dysplasia, Maroteaux type, or with achondroplasia. The objective of this study was to survey children with other forms of osteochondrodysplasia, to identify those with altered CNP production or signaling.

**Methods:** Children with any osteochondrodysplasia where studied. Plasma levels of CNP and NTproCNP were determined using RIAs. Standard deviation scores (SDS) were determined using published age- and sex-specific reference ranges.

**Results:** 87 children were studied, ages 4 m to 17-1/2 y. Children with osteogenesis imperfecta (OI)(2 type II, 5 type III, and 8 type IV) had reduced levels of CNP (SDS  $-1.8 \pm 1.3$ , mean  $\pm$ SD,  $p < 0.0001$ ) and NTproCNP ( $-0.9 \pm 0.7$ ,  $p < 0.001$ ) compared to the general population. Children with type II collagenopathies (6 spondyloepiphyseal dysplasia congenita, 3 Kniest syndrome) had elevated levels of NTproCNP ( $0.7 \pm 0.8$ ,  $p < 0.05$ ), as did children with metatropic dysplasia ( $0.8 \pm 1.0$ ,  $n=8$ ,  $p < 0.05$ ) and microcephalic

osteodysplastic primordial dwarfism type II ( $1.2 \pm 1.0$ ,  $n=7$ ,  $p < 0.05$ ).

The NTproCNP-to-CNP ratio is a marker of CNP clearance. In children with diastrophic dysplasia ( $0.7 \pm 0.5$ ,  $n=8$ ,  $p < 0.005$ ) and multiple epiphyseal dysplasia ( $1.0 \pm 0.6$ ,  $n=5$ ,  $p < 0.05$ ), this ratio was elevated.

Children with mucopolysaccharidosis or with other forms of spondyloepiphyseal dysplasia had CNP and NTproCNP levels within the expected range.

**Conclusions:** Children with OI have significantly reduced production of CNP. We suggest that abnormal type I collagen is impacting the regulation of CNP. In contrast, syndromes of abnormal type II collagen show increased CNP production, suggesting resistance to CNP, as seen in achondroplasia. Other syndromes show altered NTproCNP-to-CNP ratio, suggesting alteration of CNP clearance.

Although we know the genetic causes of many forms of osteochondrodysplasia, for most we do not yet understand the mechanisms that alter the regulation of growth and the growth plate. We suggest that alterations in the regulation of CNP is one such mechanism.

P3-828

### CLINICAL PHENOTYPES AND METABOLIC PROFILES OF SIX ADULTS WITH SILVER-RUSSELL SYNDROME

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**Objectives:** There is little information on long-term natural history of Silver Russell syndrome (SRS). The aim of the study is to describe the clinical and metabolic outcomes of 6 adult Caucasian patients (aged 18 to 46 years, mean age 26,7 years) with a molecular diagnosis of SRS.

**Methods:** Two patients had 11p15 loss of methylation (LOM), 2 had chromosome 7 maternal disomy (mUDP7) and 2 had 11p15 duplication. Clinical and metabolic evaluations including a standard 2-hours oral glucose tolerance test (OGTT) and HbA1c were performed. Bone densitometry (lumbar spine L1–L4, total body, femoral neck and total hip), Lean Body Mass (LBM), absolute (kg) and percentage fat mass(FM%) were measured by Dual-energy X-ray Absorptiometry (DXA).

**Results:** Netchine Harbison (NH) score, anthropometric characteristics, OGTT and DXA results are shown in table 1. All but one patient were born small for gestational age (mean birth weight  $-2,37$  SD, mean birth height  $-2,8$  SD). Body asymmetry was found in patients with 11p15 LOM (case 3 and case 5). At the time of diagnosis all patients showed typical facial features of the syndrome: frontal bosses, relative macrocephaly, triangular facies, micrognathia. The NH

clinical score declined in all but two of the six patients. Mean adult height was  $-3,16$  SD and only one received GH replacement therapy. Two patients (case 1 and case 2) were underweight, three had a normal BMI and one was obese; case 4 had a cognitive delay. Metabolic assessment showed a glucose intolerance and hyperinsulinemia in two cases (2 and 4). Bone densitometry was within the normal range (mean L1-L4 Z-score  $-0,05\pm1,236$ ; mean total body Z-score  $0,267\pm0,95$ ) and a high percentage of fat mass was found (mean  $39,4\%\pm10,65$ , range 26-55,7%).

**Conclusions:** The diagnosis of SRS based on the NH scoring system seems to be reliable in adults with SRS although some clinical signs may become less pronounced with age. Glucose intolerance and insulin resistance should be monitored during adulthood. Long-term follow-up in more SRS patients is warranted in order to understand the natural history of the disease and improve the management of these patients.

Table1. Characteristics of the 6 patients with Silver-Russell Syndrome

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age	21	26	25	18	46	23
Sex	female	male	female	male	female	female
Genetics	mUDP7	mUDP7	11p15 LOM	11 duplication	11p15 LOM	11 duplication
NH score in childhood	4	5	6	5	6	5
NH score in adulthood	4	5	5	4	5	4
Height SD	-1,4	-3,6	-4,1	-5	-2,1	-2,8
BMI SD	-2,8	-2	2,5	0	0,3	-0,6
Head circumf. SD	-0,5	2,3	-1,2	1,4	-0,5	-1,9
Glucose mg/dl T 0	80	78	96	95	86	97
Glucose T 120 min	101	150	138	168	68	134
Insulin T 120 min	63,7	125,8	52,2	296,3	16	74,4
HbA1c %	5,12	5,02	4,86	5,32	4,93	4,97
Fat mass %	26	31	55,07	36,6	45,7	41,5
L1-L4 Z-score	1,2	0,7	0,7	-2,1	-0,9	0,1
Total Body Z-score	1	-0,1	1	-1,5	0,5	0,7

P3-829

**INSULIN LIKE GROWTH FACTOR (IGF) SYSTEM COMPONENTS IN PEDIATRIC TUMORS OF CENTRAL NERVOUS SYSTEM (CNS): ASSOCIATION WITH CLINICAL OUTCOME. A KEY ROLE FOR IGF-2?**

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**Objectives:** CNS tumors are the most frequent solid tumors in pediatric population. The IGF system of ligands and receptors are known to play an important role in both normal and neoplastic growth. Quantitation of components of this system have been reported in adult CNS tumors, but information from pediatric patients is scarce. Our aim was to characterize the expression of IGF-1, IGF-1R, IGF-2 and IR in

pediatric CNS tumors and its association with clinical outcome.

**Methods:** We performed a prospective study (6/2012-12/2016) of pediatric patients with CNS tumors without previous medical treatment that underwent surgery in our Hospital. Tissues were collected at the time of surgery. Gene expression was measured by qPCR. Specimens were classified based on WHO2007 classification. Patients were categorized by clinical outcome as dead, alive with or without tumor (follow up  $2.24\pm1.36$ yr). Mann-Whitney, Kruskal-Wallis followed by Dunn’s Test were used for comparisons.

**Results:** We included 104 patients (57 M/47 F), median age 8.5yr, (range 0.8-18.6). The most common subgroups of CNS tumors were gliomas (n:43); ependymomas (n:21); medulloblastomas (n:13). We detected mRNA levels of the genes studied in all samples being IGF-2 the most variable. In gliomas, IGF-2 mRNA was lower while IGF-1 expression was higher in high compared to low grade tumors. When analyzed by follow up, IGF-2 and IR were increased in living patients with tumors respect to tumor free group. In ependymomas, IGF-2 and IR were lower in grade II & III compared to grade I tumors. IGF-1R expression differed between living patients carrying or not tumor. No differences were found in IGF-1, IGF-1R, IGF-2 and IR between classic and anaplastic medulloblastomas. However, an increase in the expression of all genes was found in living patients bearing tumors, with a mean follow up of 1.8yr.

**Conclusions:** IGF-2 was the most variable gene of the IGF system. In gliomas and ependymomas IGF-2 was higher in lower grade tumors and IGF-2/IR circuit prevailed in living patients carrying tumors suggesting a role in their biological behavior. Initial elevated IGF-2 expression levels may be usefull as prognosis marker for clinical outcome in low grade gliomas.

P3-830

**THE GENETICS AND NEUROENDOCRINOLOGY OF SHORT-STATURE INTERNATIONAL STUDY (GENESIS): DATA FROM 15 YEARS OF SURVEILLANCE OF GROWTH HORMONE THERAPY IN GERMANY, FRANCE AND THE USA**

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**Objectives:** To describe characteristics and outcomes of children with growth disorders treated with GH in daily

## TWO YEARS USE OF ANASTROZOLE IMPROVES THE PREDICTED ADULT HEIGHT OF MALE ADOLESCENTS WITH AND WITHOUT ASSOCIATED GH THERAPY.

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### Objectives:

Estrogen is an essential regulator of bone maturation, growth plate fusion and cessation of longitudinal growth. Aromatase inhibitors (AI) block the conversion of androgens to estrogens, and can be used to delay bone maturation in males.

We sought to determine whether the blockage of estrogen biosynthesis due to the use of Anastrozole increases the Predicted Adult Height (PAH) in boys with short PAH, with and without associated Growth Hormone (GH) therapy.

### Methods:

43 boys with short PAH used oral Anastrozole 1 mg/day for one year. 21 completed 2 years of treatment. 29 received GH therapy for GH deficiency or Intrauterine Growth Retardation ("GH group"). 14 were diagnosed with familiar short stature, precocious puberty or congenital adrenal hyperplasia and did not receive GH ("OGH").

PAH was calculated based on Bayley/Pinneau formula. Clinical parameters were assessed every 3 months. Hormonal data were collected twice a year. Statistical Analyses: CI 95% at a significance level ( $p < 0,05$ ).

### Results:

The medium basal PAH was 6,47 cm below the Target Height (TH) ( $p < 0,001$ ). After one year of treatment with Anastrozole, the PAH was 3,35 above the TH ( $p < 0,001$ ) and 9,82 cm above the Basal PAH ( $p < 0,001$ ).

For those who completed 2 years of treatment, the basal PAH was 7,32 below the TH ( $p < 0,001$ ). After 2 years the PAH was 5,86 cm above the TH and 13,18 cm above the basal PAH ( $p < 0,001$ ).

The enhancement in PAH after treatment with Anastrozole was observed in the "GH" and "OGH" groups. Tables 01 and 02 summarize the results.

### Conclusions:

The use of Anastrozole in boys with short PAH can improve the PAH after one and 2 years of treatment. The complete follow up until adulthood will determine if this increase in PAH will reflect in better final height.

Table 01 - Comparison of TH, basal PAH and 1 year PAH.

Group (N)	TH (cm)	PAH basal (cm)	PAH 1 year (cm)	$p^*$
"OGH" (14)	173,32 ± 3,88	170,92 ± 3,55	176,65 ± 4,23	<0,001
"GH" (29)	171,09 ± 5,52	162,66 ± 28,35	174,46 ± 4,84	<0,001
Total (43)	171,82 ± 5,11	165,35 ± 23,56	175,17 ± 4,72	<0,001

\*Friedman test

Table 02 - Comparison of TH, basal PAH, 1 year PAH and 2 years PAH.

Group (N)	TH (cm)	PAH basal (cm)	PAH 1 year (cm)	PAH 2 years (cm)	$p^*$
"OGH" (5)	172,10 ± 3,01	171,22 ± 3,93	177,44 ± 4,84	178,28 ± 4,55	0,004
"GH" (16)	171,09 ± 5,52	162,66 ± 2,83	174,46 ± 4,84	176,73 ± 5,06	<0,001
Total (21)	171,24 ± 5,20	163,92 ± 2,63	174,90 ± 4,89	177,10 ± 4,88	<0,001

\*Friedman test

clinical practice in 2 European countries, Germany and France, and the USA.

**Methods:** The open-label, multinational, observational study, GeNeSIS, collected data on clinical management, safety and treatment outcomes in children with growth disorders treated with GH according to standard of care. Etiology and auxology data, as reported by the investigators, were analyzed at baseline, follow-up and near-adult height [defined by at least one of: closed epiphyses, height velocity <2cm/year, bone age >14 years (girls) or 16 years (boys)]. Data are presented as mean±SD (95% CI) or number of patients (% of total).

**Results:** A majority of patients in each country had a diagnosis of GH deficiency (GHD; Germany 1736/2682 [65%], France 940/1667 [56%], USA 5187/9810 [53%]), predominantly idiopathic, followed in Germany by Turner syndrome [10%], in France by short for gestational age [16%] and in the USA by idiopathic short stature [26%]. Overall mean(±SD) GH therapy duration was 5.7±3.5, 4.8±2.8, 4.6±3.5 years in Germany, France and the USA, respectively, and respective mean starting doses were 0.21±0.07, 0.27±0.08, 0.33±0.10 mg/kg/week. The Table shows data for patients with GHD and available near-adult height information (males: Germany 58%, France 54%, USA 69%). At baseline, German patients had lowest mean age and height SDS, and greatest deficit from parental target height. GH dose was lower in Germany and France than in the USA; therapy duration was longest in Germany. Near-adult height SDS was similar for each country and height SDS gain from baseline was at least as good for the European countries as the USA. For patients with GHD, near-adult height SDS was above -2 SDS for 91% in Germany, 91% in France and 87% in the USA. No new safety concerns were identified.

**Conclusions:** For children treated with GH for short stature, a majority in each country had a diagnosis of GHD. For patients with GHD at near-adult height, more than 85% in each country reached height SDS within the normal range. Patients with GHD in Germany and France had similar outcomes after GH therapy to those in the USA, despite lower mean GH dose in the European countries.

Variable	Germany (N=622)	France (N=342)	USA (N=881)
Baseline age (y)	10.0±3.6 (9.7;10.3)	11.6±2.6 (11.3;11.9)	11.5±3.7 (11.2;11.7)
Baseline bone age (y)	8.2±3.9 (7.8;8.6)	10.1±2.7 (9.7;10.4)	10.7±3.8 (10.4;11.0)
Baseline height SDS	-2.39±0.99 (-2.47;-2.31)	-2.24±0.73 (-2.32;-2.16)	-2.16±1.03 (-2.23;-2.09)
Target height SDS	-0.21±0.82 (-0.27;-0.14)	-0.64±0.75 (-0.72;-0.55)	-0.25±0.87 (-0.31;-0.19)
Height SDS - target height SDS	-2.19±1.09 (-2.28;-2.10)	-1.63±0.87 (-1.73;-1.53)	-1.92±1.19 (-2.00;-1.83)
Initial GH dose (mg/kg/wk)	0.19±0.05 (0.19;0.20)	0.25±0.07 (0.24;0.25)	0.32±0.11 (0.31;0.33)
Last GH dose (mg/kg/wk)	0.21±0.09 (0.20;0.21)	0.26±0.08 (0.26;0.27)	0.35±0.14 (0.34;0.36)
Duration of GH therapy (y)	7.0±3.9 (6.7;7.3)	4.9±2.6 (4.7;5.2)	5.7±3.9 (5.4;5.9)
Near adult height SDS	-0.77±0.98 (-0.85;-0.70)	-0.92±0.80 (-1.01;-0.84)	-0.81±1.22 (-0.89;-0.73)
Near adult height SDS gain	1.62±1.13 (1.53;1.71)	1.32±0.84 (1.23;1.41)	1.36±1.20 (1.28;1.43)
Near adult height SDS - target height SDS	-0.57±0.93 (-0.64;-0.49)	-0.28±0.81 (-0.37;-0.19)	-0.52±1.20 (-0.61;-0.43)

Data are mean±SD (95% CI). SDS = standard deviation score

### THE ASSESSMENT OF GROWTH HORMONE TREATMENT AND ADULT HEIGHT IN PATIENTS WITH GROWTH HORMONE DEFICIENCY

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**Objectives:** Growth hormone(GH) increases height prognosis in children with GH deficiency(GHD). Several factors affect the growth response and adult height(AH) following GH therapy. Optimizing long-term response to GH treatment requires description of these factors. Aim of study was evaluate response to GH treatment and AH of patients with GHD.

**Methods:** The records of patients with GHD between 1988 and 2014 were reviewed retrospectively. Only patients with organic and idiopathic GHD included.

**Results:** 194 had idiopathic GHD, 83 had organic GHD. The median age at the onset was 10.9(0.7-16.5) years. 147 patients were prepubertal. In idiopathic GHD, 172(88.7%) had isolated GHD and 22(11.3%) had multiple pituitary hormone deficiency and in organic GHD, it was respectively, 52% and 48%. The most common organic pathology was pituitary hypoplasia. In idiopathic GHD group, GH therapy was started at a median age of 9.1 years in prepubertal patients and 12.8 years in pubertal patients and in organic GHD, it was 8.5 and 13.5 respectively. In prepubertal patients, heightSDS at onset was significantly lower in organic GHD( $-3.8 \pm 1.5$ ) than idiopathic GHD( $-3.0 \pm 1.1$ )( $p=0.0001$ ). In both group, maximal growth velocity was at sixth months and at first year. In idiopathic GHD group, 72% of patient reached a normal AH and 45% reached their target height(TH). In organic GHD, 69% of patients reached a normal AH, but none of them reached their TH. AH was negatively correlated with age and bone age delay at the onset and positively correlated with heightSDS at the onset, height velocity on first year, THSDS, prepubertal duration and height gain. Multivariate analysis showed that more delayed bone age, first-year responsiveness and higher GH dosage were the most important predictors of AH.

**Conclusions:** Early diagnosis and first-year responsiveness are important to achieve AH within genetic height potential. Patients with idiopathic GHD had a better long-term height outcome.

P3-833

### RESPONSE TO GROWTH HORMONE TREATMENT (GHT) AFTER RADIATION THERAPY (RT)

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**Objectives:** Cancer survivors have elevated risk for developing GH deficiency and those who do receive GHT after a year or longer observation to ensure stable status/resolution of tumor. We hypothesized that RT to brain, spine, or extremities alters growth response to GH. The goal was to identify differences in growth response according to type and location of RT.

**Methods:** The Pfizer International Growth Database (KIGS) was searched for cancer survivors on GHT for at least 5 years. Patients were grouped by tumor type, and data were analyzed for therapy [surgery, chemotherapy, RT--focal CNS, whole brain, craniospinal, total body RT (TBI) as part of bone marrow transplantation, other focal RT], gender, peak stimulated GH, age at GH start, and duration from RT to GH start. Growth was compared to KIGS prediction models of expected growth response in idiopathic GHD (no tumor history). For statistical analysis Wilcoxon rank sum test was performed.

**Results:** Of 1149 (male 733; median age 8.4; GH peak 2.8 ng/ml) cancer survivors with GHD treated with GH, 431 had craniopharyngioma (251 with cranial RT), 224 had medulloblastoma (all with craniospinal RT), and 134 leukemia (72 with TBI). 361 had other tumors. 1y and 5y median ( $10^{\text{th}}$ - $90^{\text{th}}$  %ile) delta height SDS ( $\Delta\text{HtSDS}$ ) were greatest for craniopharyngioma, 0.8 (0.1-1.5) and 1.6 (0.3-3.0) resp., with or without cranial RT. For medulloblastoma, 1 and 5y  $\Delta\text{HtSDS}$  was 0.51 (0.1-0.9) and 0.9 (0.0-1.9), resp.. For leukemia, 1y  $\Delta\text{HtSDS}$  after TBI (including cranial RT) was 0.3 (0.0-0.7) compared to 0.5 (0.0-0.9) for leukemia with no RT, difference in deviation from expected prediction model (studentized residuals)  $P<0.05$ ; 5y  $\Delta\text{HtSDS}$  after TBI 0.4 (-0.6-1.3) compared to 1.0 (0.2-1.9) for leukemia with no RT ( $P<0.05$ ). In total there were 1189 AE's reported and 325 considered as serious but none unexpected AEs.

**Conclusions:** At 1 and 5y of GHT, leukemia survivors who had received TBI had the most significant impairment of growth response. Survivors of medulloblastoma with craniospinal RT had intermediate growth response, while craniopharyngioma with cranial RT did not alter growth response. Both spinal and epiphyseal irradiation negatively affected growth response compared to only cranial RT or no RT.

P3-834

### CORRELATION OF ADIPONECTIN CONCENTRATION, BODY MASS AND SELECTED PARAMETERS OF CARBOHYDRATE METABOLISM IN PREPUBERTAL NON-OBESE CHILDREN WITH GROWTH HORMONE DEFICIENCY

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**Objectives:** Adiponectin is an adipokine which decreases in insulin resistance and correlates negatively with body mass. Growth hormone therapy influences carbohydrate metabolism and is associated with increased risk of developing insulin resistance. To estimate the correlation of adiponectin concentration and body mass and carbohydrate metabolism in non-obese prepubertal children with isolated GHD before (GHD untreated group) and 6 months of GH therapy (GHD after 6 m group).

**Methods:** The 32 (22 boys, 10 girls) non-obese, short children with GHD (mean height 117.9 cm, -2.77 SD, mean BMI -0.75 SD), mean age 8.87 years. Control group (CG) consisted of 18 (11 boys, 9 girls) age matched healthy children (mean height 125.8 cm, -0.93 SD, mean BMI -0.28 SD). Serum fasting adiponectin was measured in all children. In GHD untreated and GHD after 6 m body composition was assessed and glucose oral test done. HOMA, Quicki and Matsuda indexes were calculated.

**Results:** The mean concentration of adiponectin did not differ significantly between CG and GHD untreated and GHD after 6 m ( $p>0.05$ ). Fasting insulin was significantly higher in GHD after 6 m comparing to GHD untreated ( $7.6 \pm 6.6 \mu\text{IU/mL}$ ,  $p<0.05$ ), whereas HOMA, Quicki and Matsuda indexes were similar. After 6 m of GH there was significant decrease of fat body mass and increase of lean body mass ( $p<0.00001$ ). There was significant negative correlation of adiponectin and chronological age, growth age, weight and height in the GHD untreated group (respectively:  $r=-0.43$ ;  $-0.43$ ;  $-0.35$ ;  $-0.47$ ;  $p<0.05$ ). In GHD untreated group there was negative correlation of adiponectin and HOMA ( $r=-0.41$ ,  $p<0.05$ ) and positive correlation of QUICKI ( $r=0.55$ ,  $p<0.005$ ) and MATSUDA ( $r=0.51$ ,  $p<0.01$ ) indexes. These correlations after 6 m of GH were not significant.

**Conclusions:** Negative correlation between adiponectin concentration and HOMA and positive with QUICKI and MATSUDA indexes in the GHD group before GH therapy confirms the beneficial impact of adiponectin on glucose metabolism in prepubertal non-obese children with growth hormone deficiency before start of GH therapy but this effect is not clear after 6 m of GH.

P3-835

#### IMPACT OF USING DIFFERENT GROWTH REFERENCES ON INTERPRETATION OF THE ANTHROPOMETRIC INDICES OF CHILDREN 8-15 YEARS.

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**Objectives:** To compare the effect of the application of three different growth reference (KN Aggarwal (KNA), Indian Academy of Paediatrics (IAP)–2015 and World Health

Organisation (WHO)–2006) charts on estimation of childhood thinness, overweight/ obesity and short stature in school children of 8-15 years.

**Methods:** This cross-sectional study was conducted on school children aged 8-15 years studying in 3<sup>rd</sup>-10<sup>th</sup> grades at 2 schools (1 government and 1 private) of North Delhi in July 2016. The age and gender specific z-scores of height-for-age and BMI-for-age were estimated for each student enrolled, using the 3 growth references (KNA, IAP-2015 and WHO-2006) independently. The proportion of childhood thinness, overweight/ obesity and short stature determined on the basis of each growth reference were compared.

**Results:** A total of 1237 students (661 from government and 576 from private school) participated in the study with a male to female ratio of 1.6:1. No significant differences in the mean z-scores of BMI-for-age and sex were observed between KNA, IAP and WHO growth charts. However, significant differences in the mean z-scores of height-for-age were found in boys. The WHO charts reported 8.7% children with short stature as compared to 3.6% and 2.9% with IAP and KNA charts respectively. The childhood thinness estimated by WHO charts (10.5%) was 7 times higher as compared to IAP (1.5%) charts. A good degree of agreement existed between the IAP and WHO charts for diagnosing overweight (Kappa (k) - 0.72, p value - 0.01) and obesity (k - 0.70, p value - 0.01), while for short stature good concordance was observed between KNA and IAP charts (k - 0.72, p value - 0.01).

**Conclusions:** There exists wide variation in the interpretation of anthropometric indices in older children and adolescents using different growth charts. Hence, use of national population derived reference data is suggested to correctly define growth trajectories in children, ensure coherence among pediatricians and plan strategies to improve child health.

P3-836

#### ENDOCRINE MANIFESTATIONS OF DI GEORGE SYNDROME – TERTIARY CENTRE EXPERIENCE

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**Objectives:** Di George syndrome encompasses a spectrum of endocrine abnormalities including hypocalcaemia secondary to transient or permanent hypoparathyroidism, thyroid abnormalities and short stature. The aim of this study was to describe the clinical and biochemical characteristics of Di George syndrome patients referred to tertiary endocrine clinic.

**Methods:** We performed a retrospective chart review of 55 patients with Di George syndrome who presented to The Children's Hospital at Westmead between 1995 and 2015. Data collected included age, gender, reason for referral, anthropometry, pubertal status, bone age, calcium, PTH, TFT, growth velocity, GH treatment details.

**Objectives:** Objectifying an association between adherence to growth hormone (GH) treatment versus the growth response is hampered by suboptimal methods of measuring adherence, multiple confounders associated with the growth response and restriction of the outcome parameters to yearly growth velocities. We aimed to investigate the effect of suboptimal adherence using automated continuous assessment of adherence through Easypod™, novel techniques to model the growth response, and adjustment for confounders in children naïve to GH treatment participating in the ECOS study.

**Methods:** Inclusion criteria were idiopathic isolated GH deficiency naïve to GH treatment, complete data on growth and adherence for the first 2 years, availability of target height (TH), ≥3 height data before pubertal onset and height SDS (HSDS) and degree polynomial and monomolecular growth models with HSDS-THSDS as outcome, and the Index of Responsiveness (IoR) according to KIGS prediction model. We adjusted height gain and growth parameters for age at start, GH peak after provocation (GHmax), birth weight SDS, and GH dose, using linear regression models.

**Results:** In 89 children, mean (SD) HSDS at year 0, 1, and 2 was -2.8 (0.7), -2.1 (0.7) and -1.7 (0.7), respectively. THSDS was -0.7 (0.6). Median (P25-P75) adherence was 95.0% (84.9%-98.5%) and 90.7% (70.0%-97.7%) in the 1<sup>st</sup> and 2<sup>nd</sup> year. HSDS gain (0-2 yr) in children with high and medium/low adherence (0-2 yr) (≥ or <86%) was 1.14 (0.58) and 0.92 (0.49). GHmax was available for 53 children. After adjustment for confounders, HSDS gain (0-2 yr) correlated with mean adherence in 0-2 yrs, either expressed as % or categorical (p= 0.003 and 0.02). Adherence % and categories also significantly correlated with growth velocity parameters of the polynomial and monomolecular models (p=0.004 and 0.02 for %, p=0.04 and 0.03 for high vs medium/low). Age at start was the strongest confounder. The IoR in the 1<sup>st</sup> and 2<sup>nd</sup> years did not significantly correlate with adherence.

**Conclusions:** In conclusion, the growth response to Saizen in the first 2 years is positively affected by adherence as assessed by Easypod™, after adjustment for confounders.

P3-838

# A HYBRID FC-FUSED HUMAN GROWTH HORMONE, GX-H9, SHOWS A POTENTIAL FOR WEEKLY AND TWICE-MONTHLY ADMINISTRATION IN CHILDREN WITH GROWTH HORMONE DEFICIENCY.

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**Results:** 47% of the patients had transient neonatal hypocalcemia due to transient hypoparathyroidism (median age 14 days, IQR (6-51)) and 20% of them had longer-standing hypoparathyroidism (median age 30 days (11-105)). In patients with hypoparathyroidism mean (SD) calcium level at presentation was 1.7 (0.23) mmol/L and median PTH level was 1.9 (0.7-2.8) pmol/L. Reference range for calcium is 2.1-2.65 mmol/L and PTH is 1-7 pmol/L. 13% of the patients presented at a later age (10 years, IQR (3.3-13.2)) with hypocalcemia detected on routine bloods or during viral illness. 11 patients were referred for short stature with a median age of 5.4 years (4.3-7.1). 8 patients received GH treatment, starting at a median age of 11.8 years (8.4-12.6). Median change in height SDS after GH treatment was 1.2 SDS (0.5-2.1) after median duration of GH treatment of 3.6 years (2-7). Pretreatment expected mature height (EMH) was 157.5 cm (6.3) and latest EMH 168.1 cm (13.8). We have demonstrated that patients on GH had an improvement in height SDS, growth velocity and EMH (table 1).

**Conclusions:** Transient hypoparathyroidism was the common reason for referral during infancy to our tertiary service. Short stature requiring growth hormone therapy is not uncommon and patients receiving GH responded well to the GH treatment, although final height data are not yet available. Longitudinal analysis of larger group of patients warranted to confirm this.

Table 1 – Characteristics of patients on GH

	Mean (SD)
MPH	168.5(9.6)
Baseline IGF 1	15.85(11.8)
GH peak	29(18.3)
Height SDS first visit	-2.9(0.99)
Height SDS after GH	-1.7(0.7)
Weight SDS first visit	-3.2(1.2)
Weight SDS after GH	-2.5(1.4)
Bone age at the start	8.6(3.5)
BA at end	12.3(2.9)
Expected Mature height at the start	157.5(6.3)
Latest Expected Mature height	168.1(13.8)

P3-837

# EFFECT OF ADHERENCE ON THE 2 YEAR GROWTH RESPONSE TO GROWTH HORMONE TREATMENT IN PREPUBERTAL CHILDREN WITH IDIOPATHIC ISOLATED GROWTH HORMONE DEFICIENCY PARTICIPATING IN THE EASYPOTM CONNECT OBSERVATIONAL STUDY (ECOS)

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# STAT5B MUTATION: DIORDER OF GROWTH HORMONE INSENSITIVITY AND IMMUNE DYSREGULATION

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**Objectives:** GH insensitivity is a genetic disorder characterized by severe postnatal growth failure, craniofacial disproportion, elevated serum GH, low IGF1 and the inability to respond to endogenous or exogenous GH. Majority of GHI cases are caused by GHR defects.

Mutations in the signal transducer and activator of transcription 5B gene (STAT5B) have been described recently causing GHR signaling defect at post-receptor level. Besides the clinical and hormonal phenotype of GHI, majority of these patients develop immune dysregulation resulting in autoimmune disease and progressive lung disease. To date, STAT5B deficiency has been described in a total of 10 patients worldwide.

We report a case series of three siblings with STAT5B deficiency, highlighting their clinical presentation, biochemical findings and associated disorders.

**Methods:** Three siblings (5-yo girl, 3-yo boy and 17-month old girl) were evaluated for severe failure to thrive. Their weight and height Z-scores were extremely low (< -3 SDS). Review of systems was unremarkable except for documented variable degree of multiple food allergies, eczema and asthma in all of them. Clinically, all had typical GHI phenotype with prominent forehead and depressed nasal bridge.

**Results:** Hormonal workups were compatible with GHI including normal GH levels with both IGF1 and IGF1BP3 levels being low. A Homozygous STAT5B mutation was confirmed. Immunology testing of the three were unremarkable except for mild-moderate CD8 lymphopenia. At this point, all patients had no evidence of pulmonary involvements. All of them were started on rhIGF-1 and they are regularly following up with our endocrinology, pulmonology and immunology teams.

**Conclusions:** GHI due to STAT5B deficiency is a rare, potentially lethal genetic disorder that manifests as severe growth failure associated with immune dysfunction. Early recognition of the disorder will prompt earlier screening for associated disorders and earlier intervention to improve associated morbidities and mortality. Overall long-term prognosis remains poor. Treatment with rhIGF-1 can be considered although very little data is available, at present, regarding its efficacy.

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**Objectives:** GX-H9 is a hybrid Fc-based long-acting recombinant human growth hormone (hGH). A Phase 2 study is being conducted to investigate the PK/PD, safety, efficacy and tolerability of multiple doses of GX-H9 compared to daily hGH in pediatric growth hormone deficiency (PGHD).

**Methods:** A Phase 2, randomized, open-label, active-controlled, dose finding study of GX-H9 is being conducted in pre-pubertal treatment-naïve children with GHD (n=52). Subjects are receiving one of the three doses of GX-H9 (0.8mg/kg/weekly, 1.2mg/kg/weekly or 2.4mg/kg/twice-monthly) or 0.03mg/kg/daily of Genotropin. Pharmacokinetics, Pharmacodynamics (IGF-1 levels), 3-month and 6-month annualized height velocity (HV) and safety are being measured.

**Results:** All subjects (n=52) completed 3 months of the total two year treatment. The full 3-month annualized HV results and the 6-month annualized HV data of approximately 50% of the total enrolment in the study are analyzed.

Pharmacokinetics shows dose-dependent increases in magnitude and duration of IGF-1 responses, demonstrating both weekly and twice-monthly dosing potentials. Annualized mean HV for the two weekly GX-H9 doses shows increase in a dose-dependent manner. The twice-monthly treatment of GX-H9 demonstrates increase in annualized HV not statistically different from that of daily GH. The profile of AEs in GX-H9 treated subjects is similar to that of Genotropin and no formation of injection site nodules or lipatrophy was observed. Immunogenicity responses are comparable to that of daily GH treatment.

**Conclusions:** GX-H9 is safe and well tolerated in pre-pubertal children with GHD. The 3 month annualized height velocity results show a potential of GX-H9 for both weekly and twice-monthly administration. The safety and efficacy data from on-going Phase 2 studies will be presented.



# A NOVEL HETEROZYGOUS MUTATION OF THE AGGREGAN GENE IN A JAPANESE FAMILY WITH IDIOPATHIC SHORT STATURE AND MULTIPLE INTERVERTEBRAL DISC HERNIATION

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**Objectives:** Aggrecan, encoded by the *ACAN* gene, is a major proteoglycan component of the extracellular matrix of the growth plates and the articular cartilage. *ACAN* mutations have been identified in patients with highly variable phenotype of syndromic or non-syndromic short stature. We herein aimed to report a Japanese family with a novel heterozygous *ACAN* mutation.

**Methods: Patients:** A Japanese male patient was referred to us because of short stature at 10 years of age. His height was 121.2 cm (-2.5 SD), and arm span 125 cm. He had no dysmorphic features. At 11.0 years of age, his bone age was assessed as 12 years and 4 months. Because he had a partial GH deficiency and entered puberty at short stature, he was started on the combination treatment of GH and GnRH analog. The combinational treatment seems to have been effective in slowing the bone age acceleration and accelerating his height growth. The younger brother also had short stature. At 8.0 years of age, his height was 110.4 cm (-2.7 SD), arm span 115 cm, bone age 8.5 years. He had dysmorphic features with mild mid-facial hypoplasia, and brachydactyly. At 9.0 years of age, GnRH analog therapy was started; however, the therapy failed to show drastic effects in height growth. At 12 years and 7 months of age, his height was 126.8 cm (-2.5 SD), and his bone age was still advanced at 13.0 years. Their mother's height was 141.5 cm (-3.0 SD), and the maternal aunt's height was 140 cm (-3.1 SD). Both had mildly dysmorphic features with mid-face hypoplasia. The mother had been diagnosed with multiple lumbar disc herniation since 10 years of age.

**Results:** We performed whole-exome sequencing in the family, and identified a novel heterozygous frameshift mutation in the *ACAN* gene (c.1744delT; p.Phe582fs\*69) in all of the affected family members.

**Conclusions:** Our study has provided further evidence that *ACAN* haploinsufficiency causes short stature with accelerated bone maturation and has also expanded the clinical spectrum of aggrecan-related bone disorder. Further studies are needed to clarify the effectiveness of GH and GnRH analog treatment for patients with *ACAN* mutations.

# EARLY INTERVENTION FOR THREE SIBLINGS CARRYING A NOVEL HOMOZYGOUS NONSENSE STAT5B MUTATION

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**Objectives:** Three siblings were found to carry a novel homozygous nonsense mutation in signal transducer and activator of transcription 5B (*STAT5B*). The young ages of the patients prompted close clinical monitoring and therapeutic considerations for improving growth.

**Methods:** Whole exome and Sanger sequencing identified and confirmed the mutation in *STAT5B*. Site-directed mutagenesis was used to regenerate the mutation for HEK293 reconstitution studies. Serum samples of these patients were obtained to evaluate endocrine and immune parameters. Twice daily subcutaneous injections of recombinant human IGF-1 (rhIGF-1), 120 mcg/kg/dose, were initiated for P1 and P2.

**Results:** Three siblings presented with severe short stature with height standard deviations (SDS) -6.57 (P1, 5.1y), -5.88 (P2, 2.9y), and -6.12 (P3, 14.3 months). Endocrine evaluations revealed normal GH levels and persistently low serum IGF-1 levels, indicating GH insensitivity. Prolactin levels in these patients were elevated, and a history of eczema and autoimmune thyroiditis was noted in P1 and P2. Whole exome sequencing of DNA from P1 and parents identified a homozygous c.1892G>A variant in exon 15 of *STAT5B*, changing tryptophan to a stop codon, p.W631\*. P2 and P3 carry the same homozygous mutation. In reconstitution studies, p.W631\* generated a truncated protein with decreased expression that could not be activated by GH. The patients are currently in stable condition and have not yet developed the severe immune complications normally associated with *STAT5B* deficiency. A course of rhIGF-1 therapy was initiated for P1 and P2 to improve growth. The long term efficacy of rhIGF-1 therapy for *STAT5B* deficiency is currently unknown. After 3 months, P1 has gained 0.2 SDS and P2, 0.3 SDS.

**Conclusions:** We have identified a novel nonsense mutation immediately adjacent to the first reported *STAT5B* mutation, p.A630P. The early identification of *STAT5B* p.W631\* and the young age of each of the patients, permit close monitoring for *STAT5B* deficient symptoms. The efficacy of early intervention with rhIGF-1 treatment will be evaluated.

# A NOVEL HETEROZYGOUS MUTATION IN POU1F1 IS ASSOCIATED WITH COMBINED PITUITARY HORMONE DEFICIENCY.

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**Objectives:** Mutations in POU1F1 is a rare case of multiple pituitary hormone deficiency (MPHD), which commonly includes GH, TSH and prolactin deficiencies and is characterized by hypoplastic anterior pituitary. We described a sibling case of CPHD carrying a heterozygous mutation in *POU1F1* gene.

**Methods:** Hypopituitarism panel' genes were sequenced using a custom Ion Ampliseq gene panel and PGM semiconductor sequencer (Ion Torrent).

**Results:** A 19 months old boy was admitted to our hospital because of short stature. He was born at term from consanguineous and phenotypically normal parents. The father is 176 cm (SDS:+0.2) tall and the mother is 170 cm (SDS:+1.33) tall. This boy was one of dichorionic dizygotic twins (the second child was a healthy girl). His birth length and weight were 48 cm (SDS:-1.47) and 2760 g (SDS:-1.95) respectively. The karyotype is 46 XY. In this family there are other dichorionic dizygotic twins who are healthy, 18-year-old boys with normal height (184 cm (SDS:+1.40) and 186 cm (SDS:+1.70) respectively).

During the first week of life laboratory testing revealed recurrent asymptomatic ketotic hypoglycemia (2.0-2.7 mmol/l). Psycho-motor delay was noted since the first months of life. He was diagnosed central hypothyroidism at 12 months and started on Levothyroxine. But two months later his mother on her own initiative canceled Levothyroxine. Since then his fT4 levels were always low. On examination at 19 months his height was 56,5 cm (SDS:-8.69) and his weight was 5.3 kg (SDS:-7.88), he had severe developmental delay and some mild dysmorphic features (prominent forehead, saddle nose and blue sclera). Laboratory testing revealed undetectable IGF-1 level, low fT4 but normal random cortisol level.

Genetic analysis revealed heterozygous ?500?>G: p.Q167R mutation in *POU1F1* gene. The boy started GH therapy and Levothyroxine. After the first year of this treatment his height was 76.6 cm, (SDS: height-3.88), he grew 20,1 cm and showed some improvement in psychomotor development. His IGF-1 and fT4 levels were normal.

**Conclusions:** We described a sibling case with two pairs of dichorionic dizygotic twins. Only one child in the family was diagnosed MPHD carrying a new heterozygous mutation in *POU1F1* gene. These mutations have never been described before.

# FAMILIAL GROWTH HORMONE DEFICIENCY IN ATYPICAL RUBINSTEIN-TAYBI SYNDROME

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**Objectives:** To present patients with familial growth hormone deficiency in a possible atypical Rubinstein-Taybi syndrome.

**Methods:** Targeted resequencing with probe sets for enrichment and analysis of the coding regions of >4,800 clinically relevant genes and molecular karyotyping with genome wide microarray.

**Results:** We report two patients in whom only mild skeletal abnormalities were observed. The mother had hypoplasia of the both metatarsal bones, while the proband had mild dysmorphic features. The mothers height is 131 cm (-5.9 SD), the fathers 168 cm, while the sons height is 89.9 cm (-3.7 SDS) at the age of 4.1 years. Tests of pituitary growth hormone (GH) reserve showed low GH levels in both the mother and the son.

In both mother and son targeted resequencing was performed with probe sets for enrichment and analysis of the coding regions of >4,800 clinically relevant genes revealed the *EP300*c.4798C>G mutation. *In silico* missense prediction tools classified this variant as pathogenic grade 2. However, there is an entry for this *EP300* variant in the dbSNP database (dbSNP rs140154690). According to this entry the *EP300* variant c.4798C>G was already found in the heterozygous state in 188 healthy individuals and in the homozygous state in 1 (also healthy). In addition, molecular karyotyping with genome wide microarray showed that both mother and son had a heterozygote mikroduplication 8q22.3 with the pathogenic grade 3.

**Conclusions:** Rubinstein-Taybi syndrome (RSTS) is an autosomal dominant disorder characterized by broad thumbs and halluces, growth retardation, facial dysmorphisms, skeletal abnormalities and mental retardation. Mutations in the CREB-binding protein gene (*CREBBP*) is found in 40-50% of the patients, while *EP300* mutations are found in ~8% of the patients.

This is the first report of family occurrence (mother and son) of hypopituitarism, *EP300* c.4798C>G mutation. mikroduplication 8q22.3 and features of possible atypical RSTS syndrome. Further analysis with whole genome sequencing is to further clarify the molecular basis of this disorder.

# GROWTH FAILURE DUE TO MULTIPLE PITUITARY HORMONE DEFICIENCY IN A CHILD WITH GLYCOGEN STORAGE DISEASE TYPE 9

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**Objectives:** Glycogen storage disease type 9 (GSD 9) results from glycogenolytic enzyme phosphorylase kinase (PhK) deficiency. Symptoms and biochemical abnormalities of liver PhK deficiency improve with age. Children with GSD 9 initially exhibit poor growth but later catch-up to normal final height due to diminishing glucose requirement with age. Intervention for growth retardation is not usually warranted. We describe a boy with GSD 9 with growth failure due to multiple pituitary hormone deficiency (MPHD).

**Methods:** Case Report

**Results:** A 10 year old boy was diagnosed with GSD 9 at 2 years of age when he presented with failure to thrive, transaminitis and hepatomegaly. Other abnormal physical features were absent. Liver biopsy revealed absent PhK activity and high glycogen content. At 4 years of age, his evaluation for poor growth (height SDS -4.1) revealed IGF-1 <14 ng/mL (ref 25-157), free thyroxine (FT4) 0.81 ng/dL and TSH 6.0 mIU/L. He was treated with rhIGF-1 and levothyroxine by his previous endocrinologist for 2 years with improved growth (6.7 cm/year). At 8.5 years of age, after being lost to follow-up, his hepatomegaly was mild but he had poor growth velocity 3.5 cm/year (height SDS -3.9), delayed bone age of 6 years, low IGF-1 (33 ng/mL, ref 52-231) and IGFBP3 (1.57 mg/L, ref 2-4.8) and normal thyroid function. Stimulated peak growth hormone (GH) of 0.4 ng/mL confirmed GH deficiency. He had a normal pituitary gland with 4 mm enhancing hypothalamic structure that remained stable on repeat MRI every 6 months. He responded well to rhGH 0.3 mg/kg/wk at 9 years of age with improved height SDS -2.3. Central hypothyroidism (FT4 0.63 ng/dL, TSH 3.0 mIU/L) was suspected; prior to treatment, further testing revealed central adrenal insufficiency after failed 1 mcg ACTH stimulation (cortisol level 7.5 mcg/dL at baseline, 14 at 30 min, 9 at 60 min) but sufficient cortisol response after 250 mcg ACTH (22 mcg/dL). The rest of his pituitary function was normal.

**Conclusions:** Our patient had significant growth failure which was out of proportion to his diet controlled GSD 9. After treatment was started for MPHD, his growth improved. To the best of our knowledge, panhypopituitarism in a case of GSD 9 has not been previously reported.

# TWO SGA SHORT BOYS WITH EXCESSIVE BONE MATURATION

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**Objectives:** Growth hormone (GH) treatments for short children born small for gestational age (SGA) have started since 2008 in Japan, and its safety and effectiveness were reported. In the report, no clinically significant changes were observed for bone age. We experienced two SGA short boys whose bone age matured excessively during GH treatment.

**Methods:** two cases report

**Results:** The first case is 18-year-old man who received GH therapy since he was 10 years old. He was born small (birth weight 1,092 g) at 35 week of GA with hypospadias. He underwent orchiopexy, caught height well, but final height was short due to excessive bone maturation. Roentgenograms of his hands showed cone-shaped epiphysis in the middle phalanx of the 5th finger. Although testosterone level was normal, FSH was relatively high, which suggested Sertoli cell dysfunction. The 2<sup>nd</sup> case is 13-year-old, born small (558 g) at 27 week of GA. Inguinal hernia was present, and cone-shaped epiphysis in the middle phalanx of the 5th finger was also seen. Growth response of GH treatment has been good, but bone age matured excessively with testosterone level reaching in adult normal range early.

**Conclusions:** Orchiopexy for hypospadias or inguinal hernia might be risk factor for excessive bone maturation. Although being born SGA does not impair Sertoli cell function, orchiopexy might sometimes influence Sertoli cell function, increasing the level of gonadotropin, and resulting in early bone maturation. Girls with low birth weight tend to progress relatively rapidly to an early menarche and to a reduced final height. As for boys, low birth weight boys with the history of orchiopexy require periodic monitoring. Another further study is needed whether cone-shaped epiphysis is a sign for being short finally in SGA short children, even though GH treatment has been done.

# NOVEL ASSOCIATION OF HEMOPHILIA B AND GROWTH HORMONE DEFICIENCY POSSIBLY DUE TO CONTIGUOUS GENE DELETION SYNDROME

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**Objectives:** We report a novel association of growth hormone deficiency (GHD) and hemophilia B in two brothers without intellectual disability that may be due to a contiguous gene deletion syndrome spanning Xq27.1 - Xq27.2.

**Methods:** An 11-year old male with known hemophilia B and normal intellect was referred for growth failure. His height was -2.8 SD with findings of increased abdominal adiposity, multiple skin moles, but normal penile size. Bone age was delayed by 2 years and growth factors were low (<-2 SD) for age. GHD was confirmed on provocative testing (peak GH 3.6 ng/mL) with normal thyroid and cortisol levels. MRI showed normal pituitary but absent corpus callosum, cavum septum pellucidum, and cavum vergae with an incidental small pineal cyst. He responded well to growth hormone therapy, and had delayed but spontaneous pubertal progression and has attained Tanner 4 sexual maturity (now 17.5 years) with a near adult height of 65.8". His younger brother (12.5y) who also had hemophilia B and normal intellect had a similar clinical phenotype. He was also confirmed to have GHD (peak GH 5ng/mL) and is responding to GH therapy.

**Results:** Chromosomal microarray (Affymetrix cytoscanner) of the proband showed a 2293 kb deletion of Xq27.1 - Xq27.2 with complete loss of the F9 gene (associated with Factor IX deficiency) and SOX3 gene (associated with isolated growth hormone deficiency, combined pituitary hormone deficiency, abnormalities of the corpus callosum, and intellectual disability). While SOX3 deficiency may explain the GHD in these individuals, other genes in the Xq region have also been implicated in short stature and GHD. Genetic studies on the brother and parents are underway.

**Conclusions:** This is the first report of a contiguous gene deletion syndrome associated with hemophilia B and GHD without associated intellectual disability (ID). Two previous patients were reported with severe ID, hemophilia, and short stature, one of whom also had hypogonadotropic hypogonadism. Our case may further expand the previously described clinical syndrome of a contiguous gene deletion spanning F9 and SOX3 genes, but the clinical and genetic phenotype needs further definition.

P3-847

#### PITUITARY GIGANTISM, REGARDING A CASE

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**Objectives:** Describe clinical presentation and management in a sixteen years old man with pituitary gigantism

**Methods:** Presenting a case report with pituitary gigantism

**Results:** A sixteen years old man with one year of disease characterized by blurred vision, headache, photophobia, polyuria, polydipsia and rapid growth. In the physical exam these were the findings: weight: 112 kilograms (>95 percentile), height: 184 centimetres (>95 percentile) and blood pressure: 140/95. Tanner stage was 5. Magnetical resonance imaging showed a pituitary macroadenoma (dimensions: 3.3 cm x 2.8 cm x 2 cm) with elevated somatomedin (IGF1= 1230 ng/mL) and oral glucose tolerance test (OGTT) with growth hormone dosage showing no suppression (Growth hormone > 50 ng/mL). Craniotomy and resection of macroadenoma were performed. Biopsy and pathology were done. Immunohistochemistry showed positive

cells to growth hormone. After surgery levels of somatostatin didn't decrease much (IGF1= 1147 ng/mL) and OGTT continued showing no suppression (GH = 32 ng/mL). This could have been due to the presence of the tumor in cavernous sinus. For this reason he started radiotherapy and after that Cabergoline in order to suppress the growth hormone levels. Also he presented hypopituitarism (hypocortisolism, hypothyroidism, hypogonadism) and because of that he started treatment with Prednisone, Levothyroxin and Human chorionic gonadotropin (hCG)

**Conclusions:** Pituitary gigantism is a rare condition that should be suspected in children with rapidly growth velocity or tall stature as in the presented patient. Surgery is the first line of treatment, and in cases of failure or inoperable tumors, these can respond effectively to the somatostatin analogs or like in the presented case to the dopaminergic agonists.

P3-848

#### SHORT STATURE WITHOUT ACCELERATED SKELETAL MATURATION ASSOCIATED WITH A HETEROZYGOUS AGGRECAN MUTATION

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**Objectives:** Aggrecan is a proteoglycan found in the extracellular matrix of the growth plate and articular cartilage. Mutations in ACAN, the gene that encodes aggrecan, have been identified in patients with isolated short stature and advanced skeletal maturation, often with a family history of early-onset osteoarthritis. In all previously reported cases of isolated short stature associated with ACAN mutations, the bone age has been equal to or greater than the chronologic age, serving as an important diagnostic clue.

**Methods:** A 12-year-old boy was evaluated for familial short stature (height SDS, -3.9). Multiple family members (father, paternal grandmother, paternal great aunt, paternal aunts) also had short stature (height SDS between -2.8 and -3.6), suggesting an autosomal dominant inheritance, with early-onset osteoarthritis in some affected members. Routine clinical and biochemical evaluation, including growth hormone stimulation testing, did not reveal the cause of his short stature. At last evaluation, his chronological age was 12 years and 7 months, while his bone age was 11 years, 6 months by the Greulich and Pyle method and 11 years, 9 months by the TW3 method.

**Results:** Exome sequencing, confirmed by Sanger sequencing, of the proband and 4 affected family members in this 3 generation pedigree identified a novel nonsense mutation in ACAN(c.4852C>T: p.Q1618X). The mutation is predicted to result in a truncated protein lacking 912 amino acids. The

mutation co-segregated with short stature and was not found in any unaffected family member.

**Conclusions:** To our knowledge, this is the first reported case of an *ACAN* mutation presenting as isolated short stature with a bone age less than chronological age. These findings expand the phenotypic spectrum of heterozygous *ACAN* mutations and indicate that this diagnosis should be considered in short children without accelerated skeletal maturation. The relative frequency of this atypical presentation remains to be determined.

P3-849

#### PSEUDO TUMOR CEREBRI COMPLICATING SUCCESSFUL GROWTH HORMONE THERAPY IN A CHILD WITH PYCNODYSTOSIS

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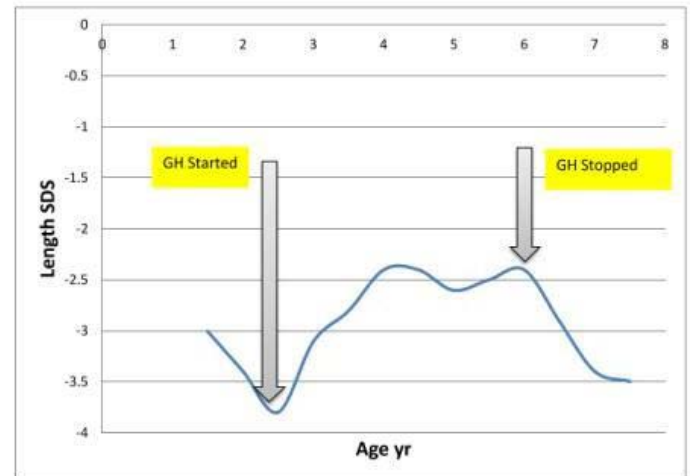
**Objectives:** We report the occurrence of pseudo tumor cerebri as a complication of growth hormone therapy in a child with pycnodysostosis and the effect of rhGH therapy on linear growth.

**Methods:** A 7 years -old girl with the classic clinical features of pycnodysostosis was diagnosed at the age of 1.5 years. She had small face, prominent forehead, pointed nose, prominent eyes, small jaw brachydactyle, small flat nails and short stature. CTSK gene sequencing confirmed pycnodysostosis (mutation c.338delGg, p.G113VfsX48, in exon 4 of CTSK gene (homozygous state) and she did not have growth hormone receptor (GHR) mutation. We followed up her clinical course and linear growth for 6 years.

**Results:** Her skeletal survey showed large calvaria with widened sutures and increased bone density of the long bones and short middle and distal phalanges. Her hemogram, renal and hepatic functions and karyotype (46 XX), were normal. At the age of 20 months, growth hormone stimulation test using clonidine showed deficiency (peak GH = 3.90 ug/L ) and her serum insulin-like growth factor 1 (IGF-1) concentration was low ( 37 ng/mL). At the age of 2 years the patient was started on recombinant human growth hormone therapy (rhGH) , 0.03 mg/kg per day, subcutaneous injection every day. Her growth rate improved markedly with partial catch-up as her LSDS increased from -3.4 to -2.4 in two years. After the first two years her growth rate was maintained in the normal range for her age (on rhGH dose = 0.05 mg/kg /day) and LSDS was maintained at -2.7 till the age of 6 years. At 6 years she presented with severe attacks of headache and visual changes. Fundus exam revealed papilledema. Lumbar puncture opening pressure revealed high ICP. The diagnosis of pseudo tumor cerebri was entertained. She was started on acetazolamide and GH therapy stopped. Her headaches and visual complaints disappeared with mild improvement of papilledema. However, her linear growth slowed down markedly.

**Conclusions:** We report a rare case of pseudotumor cerebri (PTC) in a child with pycnodysostosis after 4 years of successful GH therapy. This emphasizes the need of close collaboration between ophthalmologists, neurologists and endocrinologists in monitoring children receiving rhGH.

**Length SDS in a patient with pycnodysostosis before and after rhGH therapy**



P3-850

#### SHOX DUPLICATION AND GROWTH FAILURE: A CLINICAL CASE

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**Objectives:** Few cases of selective SHOX duplication have been reported associated with variable effect on height. We report a clinical case of SHOX duplication and whole Y long arm deletion associated to severe short stature and future azoospermia.

**Methods:** Born at 40 GA, weight 3180 g, length 52 cm (AGA). Target height 179.1 (+0.42 SDS). Currently: age 13.3, weight 34.5 kg (-2.07 SDS), height 137 cm (-2.86 SDS, delta to target height -3.28 SDS), BMI 18.4 kg/m<sup>2</sup> (-0.73 SDS), SPAN/HIGH 97%, TRUNK/HIGH 52%, growth velocity 2.59 cm/yr on 5 months (-4.8 SDS). Harmonic, no Madelung deformity, no muscle hypertrophy, cubitus valgus, shield chest, increased intermamillar distance. Bone age: 1.5 year retard, no pathologic radiological signs. Exams performed: negative short stature screening, normal thyroid function, no GH deficiency (ITT 2.1 ng/ml, clonidine 12.9 ng/ml, glucagone 11.7 ng/ml, IGF1 261 ng/ml); LH 0.6 mU/ml, FSH 0.8 mU/ml, testosterone 0.79 ng/ml. Brain MRI, cardiological evaluation and intellectual development: normal. Karyotype: Y short arm duplication (where PAR1 is located) and whole Y long arm deletion, known to be causative of azoospermia. SHOX duplication through MLPA (Yp11.32p11.2 and Yp11.2 duplication) was found.

**Results:** People with triple SHOX due to sex chromosome trisomy usually show high stature (Triple X syndrome or Klinefelter), this finding is not always true in individuals with

microduplications of PAR1 involving SHOX or its regulatory sequences: the breakpoints of the microduplications can alter or disrupt its complex transcriptional regulation, resulting in functional SHOX haploinsufficiency. Therefore in these patients, GH treatment can be considered to improve final high (as already used in regular SHOX deficiencies children). At our knowledge only one patient affected by SHOX duplication has been treated with GH, with satisfying results.

**Conclusions:** In our patient SHOX duplication can explain the severe short stature; GH treatment has just been started and the response is not available yet. Additional reports are needed to better define this condition and give conclusions on long term efficacy of GH treatment.

P3-851

#### **HOMOZYGOUS DELETION OF THE 5'UTR EXON 1-2 OF THE BLM GENE - A NEW CAUSE FOR BLOOM SYNDROME**

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**Objectives:** Bloom syndrome (BS) is an autosomal recessive disorder characterized by proportionate pre- and postnatal growth deficiency; sun-sensitive, telangiectatic, hypo- and hyperpigmented skin and predisposition to Type 2 Diabetes and malignancies with shortened life span. Hallmark is chromosomal instability, leading mostly to interchanges between homologous chromosomes, i.e., sister chromatid exchanges (SCE). BS is due to homozygous mutations in *BLM*, which is a DNA helicase and functions in DNA double-strand-break repair; mutations affect the conjugational recombination and ultraviolet resistance of DNA. Premature stop codons in *BLM* make up the vast majority of BS mutations, with only 13 single amino acid changes identified in the syndrome. It is important to identify BS because GH treatment is contra-indicated. We aimed to identify a new genetic cause for Bloom syndrome.

**Methods:** Targeted Sanger Sequencing and Whole Exome Sequencing (WES) in a child with a clinical diagnosis of Bloom Syndrome

**Results:** The index case was born at 35 weeks gestation weighing 1.09kg (IUGR) from consanguineous parents. She had severe growth failure, microcephaly, café au lait patches, learning difficulties, recurrent parotitis and immune deficiency but absence of photosensitivity of the skin. At 6.8 years of age, her height was -4.8SD and her BMI -5.9SD. Endocrine investigations were normal. Chromosomal breakage studies showed a 10 times increased SCE, consistent with Bloom Syndrome. Targeted sequencing of *BLM* coding region was normal. Diagnostic WES did not look for copy number alterations, but

a homozygous large deletion in the 5'UTR, exon1 and exon 2 of the *BLM* gene was detected by assessing the coverage data and was confirmed using a fluorescent dosage assay (QF-PCR).

**Conclusions:** We have, for the first time, identified a homozygous deletion in the 5'UTR of *BLM* as a cause for Bloom Syndrome in a child with typical features apart from photosensitivity. Identification of *BLM* syndrome is important because of a contra-indication for GH treatment. Both coding and non-coding regions of the *BLM* need to sequencing to detect responsible gene variants although diagnosis on clinical criteria remains important.

P3-852

#### **NON-FAMILIAL SHORT STATURE DUE TO A DE NOVO MUTATION IN AGGRECAN**

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**Objectives:** Heterozygous mutations in the aggrecan gene (*ACAN*) cause autosomal dominant short stature with bone age (BA) acceleration, and premature growth cessation.

**Methods:** The patient is a 6-year-old Caucasian male with non-familial idiopathic short stature and advanced skeletal maturation. Exome and Sanger sequencing was used to identify the genetic cause of the growth failure.

**Results:** The patient was born AGA (birth length; 48cm; -1.5 SDS; birth weight; 2.8 kg; -0.4 SDS) at 40 weeks of gestation to healthy parents of normal height (father -1.3 SDS; mother 0.0 SDS). There was no short stature in the extended family. From 1 to 4 years of age, his height was just above -2 SDS for age. Evaluation for short stature detected a 3-year BA advancement, but no evidence of a skeletal dysplasia and also no explanation for the short stature or the advanced bone age. At 4 years of age, he was started on daily growth hormone treatment. During treatment, height improved from -1.8 to -1.0 and -0.4 SDS after 1 and 2 years of treatment, respectively.

Simultaneously, BA advancement (BA-CA) increased from +3 to +4y but the predicted adult height increased from 143 (-5.4 SDS) to 151 cm (-4.3 SDS). He remained prepubertal. Using exome sequencing followed by Sanger sequencing, a novel heterozygous frameshift mutation in exon 12 (c.6404delC), which is predicted to cause truncation of the aggrecan protein at amino acid 2,135, was detected and confirmed to be present in the proband, but not in the unaffected parents. Paternity was confirmed by SNP array.

**Conclusions:** We present a boy with non-familial short stature and advanced bone age caused by a *de novo* mutation in *ACAN*.

To our knowledge, this is the first report of a *de novo* mutation in *ACAN*. Previously, all patients with this disorder have shown an autosomal dominant inheritance. The current report indicates that mutations in *ACAN* should also be suspected in non-familial short stature.

P3-853

#### HETEROZYGOUS MUTATION IN *FBN1* IN A PATIENT WITH SHORT STATURE, JOINT HYPERMOBILITY, AND SKIN LAXITY

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**Objectives:** Some mutations in *FBN1* cause Marfan syndrome with tall stature but other mutations in *FBN1* have been identified in patients with gelophysic dysplasia (GD), acromicric dysplasia (AD), and Weill-Marchesani syndrome (WMS), which include short stature likely altering TGF- $\beta$  signaling. Patients with AD display severe short stature similar to GD and WMS, with features of short hands and feet, facial dysmorphism, joint stiffening, thickened skin and skeletal abnormalities.

**Methods:** The patient is an 8-year-old Caucasian boy evaluated for short stature. He was born to unrelated parents of normal height (paternal height 0.5 SDS, maternal height 1.1 SDS). He had normal birth weight and length, with subnormal growth velocity during the first year of life. He had no significant medical history with the exception of frequent radial subluxation in early childhood. The family history was unremarkable. On physical examination, he had severe short stature (height SDS -3.8), normal head circumference, mild facial dysmorphism with a round face and a broad flat nasal bridge, hypermobility of the joints, skin laxity and slight shortening of the fingers without other evidence of a skeletal dysplasia. The bone age was delayed. Laboratory evaluation was normal including IGF-1, IGFBP-3, thyroid function, karyotype, *SHOX* gene analysis and microarray for copy number variation. The patient was placed on growth hormone therapy from 4 to 6.6 years of age with minimal response.

**Results:** Exome sequencing was performed on the patient, his parents, and 2 unaffected siblings. A *de novo* heterozygous missense mutation in *FBN1* (c.5183 C>T: p.A1728V) was identified, which has previously been reported to be a cause of AD and GD. This mutation is not found in Exome Aggregation Consortium (ExAC) and is predicted to be pathogenic by multiple in silico analyses. The patient's subsequent echocardiogram and ophthalmological exam were normal.

**Conclusions:** We report a patient with AD due to a *FBN1* mutation. This patient's phenotype included joint hypermobility and skin laxity, whereas AD is typically associated with joint stiffening and thickened skin. Our case report helps expand the known phenotypic spectrum associated with *FBN1* mutations in patients with AD.

P3-854

#### FIFTY SHADES OF *SHOX* DEFICIENCY: A CASE OF INTRAFAMILIAL PHENOTYPIC VARIABILITY

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**Objectives:** Describe the variability of clinical expression of *SHOX* deficiency among members of the same family sharing the same chromosomal deletion

**Methods:** Five members of an Italian family affected by short stature were analyzed (two children, their mother, aunt and grandfather). We collect their auxological data. The children also underwent X-Rays of arm, wrist and hand. We used Rappold scoring system for the diagnosis of *SHOX* deficiency. Multiplex ligation probe-dependent amplification (MLPA) analysis has been performed.

**Results:** We present a three generation family with a *SHOX*-related haploinsufficiency phenotype caused by a deletion residing in the PAR1 region containing *SHOX* gene in X chromosome. The proband, a 11-years-old boy, presented with overweight, lightly disproportionate short stature (height -1.76 SDS, span/height ratio of 0.96 and trunk/height of 0.56). No Madelung deformity. Rappold score 8/24. He was affected by mitral valve prolapse. The remainder of his examination was otherwise unremarkable. His Xrays showed triangular form of the distal radial epiphysis, pyramidalization of the carpal row, increased radiolucency of the distal radius on the ulnar side. His 10-years-old brother had a height of 136.2 cm (25th–50th centile), with mesomelic limb shortening (trunk/height 0.56). He had clinical and radiological evidence of Madelung deformity. Their mother at the age of 40 had marked mesomelic shortening with a height of 139.6 cm and an arm span of 122 cm (reduced span/height ratio of 0.88). She had a Madelung deformity bilaterally. Her sister had a similar disproportionate short stature; her son was not evaluated clinically; however, he was not reported as having short stature. Grandfather had a degree of short stature and bilateral tibia vara. MLPA revealed a deletion within the PAR1 region at chromosomal band Xp22.33 in the boys and her mother (genetic analysis not available for other members). The deletion was mapped within the coding region of the *SHOX* gene.

**Conclusions:** Genomic alterations involving *SHOX* may result in a broader phenotypic traits even among family members, exhibiting a significant interfamilial and intrafamilial variabilities with a high severity in females, a finding which may be explained by the presence of higher estrogen levels in females.



### GIRL WITH COSTELLO SYNDROME: A 4-YEAR OBSERVATION OF RECOMBINANT GROWTH HORMONE THERAPY

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**Objectives:** Costello syndrome is a rare syndrome of multiple congenital anomalies. The typical clinical traits include dysmorphic craniofacial features, skin hyperpigmentation and excess, feeding difficulties leading to severe postnatal growth retardation, joint hypermobility, and delayed psychomotor development. Syndrome may present with an increased incidence of congenital heart disease and increased risk of both benign and malignant tumors. Furthermore, cases of patients with endocrine disorders such as adrenal insufficiency and endogenous growth hormone deficiency have also been documented.

**Methods:** We report a six-year-old patient with Costello syndrome, who has been successfully treated with rhGH for 42 months

**Results:** AM, was born at 40 weeks gestation by caesarean section (due to large fetal mass) as the first baby of healthy and nonconsanguineous parents with a birth weight of 4270 g (> 97 c), length of 55 cm (50 c) and head circumference of 38 cm (> 97c). Her Apgar score was 7/7/8 points. At the age of 2 years and 9 months Costello syndrome was suspected on the basis of phenotypic traits (large mouth, wide lips, short nasal bridge, loose skin deeply fissured on the palms and soles of the feet, joint laxity, and abnormal feet position). The diagnosis was confirmed by molecular tests, which identified c.35G>C (p.G12A) substitution in the HRAS gene. Growth hormone was administered by subcutaneous injection once daily, in the evening, at a dose of 0.031 mg/kg/day. Throughout the first year of treatment, her growth rate was 9.49 cm/year, and in the next two years it was 12.36 cm/year and 7.71 cm/year, respectively, while during the pretreatment period her average growth rate was 4.28 cm/year. Currently, after 42 months of rhGH treatment, the girl has grown 30.3 cm, reaching a body height above the 3<sup>rd</sup> percentile (115 cm; SD: -1.61), her weight gain has been 10.4 kg. Her current weight is 20.3 kg (10–25 percentile; SD: -1.28). So far, no serious adverse events have been observed.

**Conclusions:** The possibility of growth hormone (GH) treatment can be considered in cases of documented GH deficiency in patients with Costello syndrome, but only under close oncologic and cardiologic supervision.

P3-856

### IS GROWTH HORMONE INSENSITIVITY A CAUSE OF IMPAIRED GROWTH IN CONGENITAL TUFTING ENTEROPATHY?

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**Objectives:** To assess growth hormone (GH) secretion in children with congenital tufting enteropathy (CTE) and short stature.

**Methods:** Retrospective review of clinical records of patients with CTE referred for paediatric endocrinology assessment.

**Results:** 3 patients were included (females, 1 set of twins). They were born at term following uneventful pregnancies with a mean ( $\pm$ SD) birth weight of 3243.3 gr ( $\pm$ 489.7 gr). Profuse diarrhoea and weight loss were recorded soon after birth. The diagnosis of CTE was confirmed at the age of 12.66 months ( $\pm$ 1.154 months). Patients were referred for endocrine assessment of short stature at the mean age of 6.08 years (5.7 to 6.86 years). They were prepubertal with severe growth failure: mean height 95.5 cm (-4.14 SDS), weight 14.26 kg (-2.91 SDS) and growth velocity 1.63 cm/year (-4.97 SDS). The bone age was delayed, and the IGF-1 was low (27 ng/ml  $\pm$  3.46. Ref value: 45-302) with normal growth hormone response to glucagon stimulation (GH peak: 11.4 ug/L  $\pm$  3.6). An IGF-1 generation test was suggestive of a variable degree of GH insensitivity: Patient 1 (twin 1) responded to recombinant human GH (rhGH) at a standard dose of 0.7mg/m<sup>2</sup>/day while patient 3 had a flat response to same initial dose but IGF-1 concentrations improved when a higher dose (1.4 mg/m<sup>2</sup>/day) was given. Patient 2 (twin 2) failed the test, with no response to rhGH at a maximal dose of 2.8mg/m<sup>2</sup>/day. Trial with rhGH treatment (21  $\mu$ gr/kg/day) has been successful in patient 1 (growth velocity increased from 1.8 to 9.4 cm/year), but no effect was seen in patient 2, who was subsequently started on recombinant IGF-1. She developed secondary hypoglycaemia and treatment was paused for nutritional optimisation. Patient number 3 has just been commenced on rhGH (26  $\mu$ gr/kg/day).

**Conclusions:** Patients with CTE may experience a degree of growth hormone insensitivity that could explain the severity of their growth retardation in spite of adequate nutritional support.

P3-857

### RELATIVE CHANGES IN BONE AGE AND LINEAR GROWTH IN CHILDREN WITH GROWTH HORMONE DEFICIENCY (GHD) TREATED WITH TWICE-MONTHLY SOMAVARATAN (VRS-317)

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**Objectives:** Human adult height is a product of growth rate and duration of growth. Linear growth is generally complete

when epiphyseal fusion of long bones occurs at a bone age (BA) of ~16 years (y) in girls and ~18y in boys. Rapid advances in BA, sometimes seen in precocious puberty, can be associated with rapid linear growth in children, but may result in short adult stature. Optimal treatment of GHD therefore requires similar pacing of relative change in height age (HA) and BA. Here we report relative change in HA and BA in children with GHD treated with somavaratan in the Phase 1a/2b VERTICAL study (NCT01718041) and long-term safety study, VISTA (NCT02068521).

**Methods:** Chronological age (CA), BA, and HA (age at which height is 50<sup>th</sup> percentile) were evaluated at baseline, and after 1 and 2y of somavaratan (N=49). BA was determined by a central reader using the Fels method. HA was calculated using NCHS database. Deficits in HA and BA are expressed as a fraction of CA (eg, at time t, deficit  $BA_t = (CA_t - BA_t)/CA_t$ ).

**Results:** At baseline, mean BA ( $6.30 \pm 2.5y$ ) and mean HA ( $5.42 \pm 2.0y$ ) were delayed compared to mean CA ( $7.76 \pm 2.5y$ ;  $P < 0.0001$ ), with greater delay in HA than BA ( $P < 0.0001$ ). This pattern persisted through 2y of treatment (BA:  $8.71 \pm 2.9y$ ; HA:  $8.10 \pm 2.3y$ ; CA:  $9.76 \pm 2.5y$ ) with BA < CA ( $P < 0.0001$ ), HA < CA ( $P < 0.0001$ ), and HA < BA ( $P < 0.002$ ). Over 2y, there were significant increases in the BA/CA ratio ( $0.79 \pm 0.1$  at baseline vs  $0.88 \pm 0.1$  at 2y) and HA/CA ratio ( $0.69 \pm 0.07$  vs  $0.83 \pm 0.08$ ; both  $P < 0.0001$ ). The HA/BA ratio also increased ( $0.90 \pm 0.2$  vs  $0.97 \pm 0.2$ ;  $P < 0.006$ ), indicating greater change in HA than BA. At 2y, the BA deficit decreased from  $0.21 \pm 0.1$  at baseline to  $0.12 \pm 0.1$ , and HA deficit from  $0.31 \pm 0.07$  to  $0.17 \pm 0.08$  (both  $P < 0.0001$ ). Regression analysis showed the largest changes in BA and HA deficits in those with greatest initial deficits.

**Conclusions:** In this GHD population, the pattern of CA > BA > HA persisted from baseline through 2y of somavaratan treatment, with increasing BA/CA and HA/CA ratios suggestive of catch-up growth. Change in HA/CA exceeded change in BA/CA ratios, indicating relatively greater improvement in linear growth than skeletal maturation. Greatest catch-up growth in BA/HA was observed in those with greatest initial deficits.

P3-858

#### GROWTH HORMONE THERAPY IN TURNER SYNDROME: AN INDIAN EXPERIENCE

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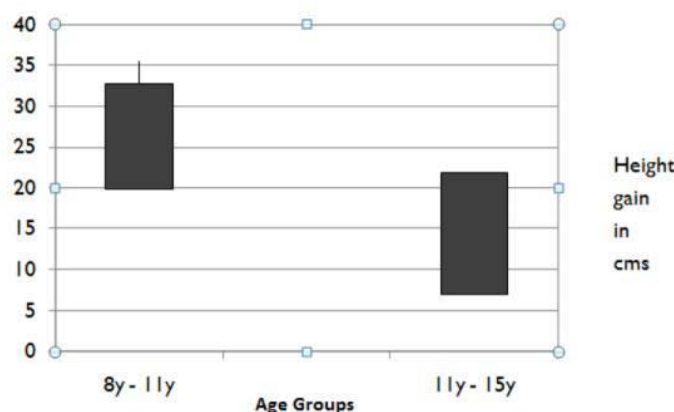
**Objectives:** To evaluate the factors for optimal growth in response to recombinant Growth Hormone Therapy in girls with Turner Syndrome. Growth hormone deficiency is not implicated in Turner short stature. However Recombinant human Growth Hormone (rhGH) has been shown to improve the height potential of girls with TS.

**Methods:** A retrospective study was carried out at Sir Ganga Ram Hospital, New Delhi, a tertiary care hospital in northern India. 27 girls were diagnosed to have Turner Syndrome from January 2008 to December 2015. History alongwith complete

clinical details including screening results for other associated abnormalities and laboratory findings were noted. All patients were given daily injections of recombinant growth hormone 0.05mg/kg/day and response was measured in terms of height gain per year. Treatment was continued till height velocity (HV) dropped to 2cm/year. Final heights and near final heights (for patients with ongoing treatment) were recorded and height gain was compared in relation to the duration of therapy.

**Results:** Fifteen patients who had received rhGH for a duration of more than 12 months were included in the study. Mean age of starting GHT was 11years with minimum age of 8y and maximum being 14.91yr. None of the patients had received estrogen replacement prior to receiving rhGH. Mean height gain was 21.64cm. Height gain showed positive correlation with duration of rhGH therapy with a p value of 0.00001, thereby showing increased benefit in height with rhGH if started at an early age. Mean height velocity in the first year of treatment was 9.7cm/year which was significantly higher than the mean height velocity of 3.75cm/year prior to GH therapy ( $p < 0.001$ ). However, HV in second year of treatment 6.42cm/yr was significantly less than HV in first year of treatment ( $p < 0.005$ ). Estrogen Replacement Therapy was added at a mean age of 15.25yr at a mean bone age of 13.1yr. Final height was known in six patients. Average final height was  $148.2cm \pm 5.06$  with the maximum height being 153.2cm.

**Conclusions:** To conclude, Growth hormone is an effective treatment for improving final height in patients with Turner syndrome with best outcome if treatment is started at an early age.



P3-859

#### LONG-TERM SAFETY OF RECOMBINANT HUMAN GROWTH HORMONE TREATMENT IN KOREAN CHILDREN: 5 YEARS' RESULT OF LG GROWTH STUDY

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**Objectives:** To evaluate the long-term safety of recombinant human growth hormone (rhGH) (Eutropin® Inj., Eutropin® AQ Inj., Eutropin® Pen Inj., and Eutropin® Plus Inj. by LG Chem, Ltd.) treatments in Korean pediatric patients.

**Methods:** LG Growth Study (LGS) is a multicenter, long-term, prospective and retrospective observational study designed to evaluate the long-term safety and effectiveness rhGH treatment (NCT01604395). This interim analysis was conducted in all short stature patients who were enrolled from Jan 2012 to Mar 2017 using a predefined statistical method to evaluate safety.

**Results:** Total 2,024 patients among 2,277 enrolled children were eligible for the analysis of safety in five short stature diagnosis (Growth Hormone Deficiency (GHD): 1,297 (64.1%); Idiopathic Short Stature: 315 (15.6%); Small for Gestational Age: 206 (10.2%); Turner Syndrome: 197 (9.7%); Chronic Renal Failure: 9 (0.4%)). They received rhGH used in LGS more than once. Almost half of the patients were male (52%), baseline chronological age was 7.99 years and Height SDS was -2.37. Mean rhGH treatment duration was 3.41 years and total treatment person-year was 6,898 years. AEs were reported in 462 (22.8%) patients and most commonly reported AEs were upper respiratory tract infection (3.2%) and headache (2.1%). Among them, 94 (4.6%) patients' AEs were considered to have relationship with the treatments. Headache (0.6%) and injection site pain (0.5%) were the major. Serious Adverse Events (SAEs) were 68 (3.4%) and Serious Adverse Drug Reactions (SADRs) were 8 (0.4%) patients. The interesting AEs were predefined and were reported as related to rhGH treatment in hypothyroidism (0.5%), scoliosis (0.3%), benign intracranial hypertension (0.1%), diabetes mellitus (0.1%), neoplasm recurrence (0.1% as SADR). Medulloblastoma was reported in one idiopathic GHD child, but not related to rhGH. AEs/1,000 treatment year was calculated as 133.48, which was comparable to those from other registry studies.

**Conclusions:** In the 5 years' interim result of LGS, there were no significant adverse events caused by rhGH in Korean pediatric patients. Cancer induced by rhGH has not been reported, but further long-term monitoring should be required for the follow-up of major adverse events.

P3-860

#### IN VIVO EVALUATION OF JR-142, A LONG-ACTING GROWTH HORMONE APPLYING A MODIFIED ALBUMIN FUSION TECHNOLOGY

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**Objectives:** Recombinant human growth hormone (hGH) has been used for the treatment of GH deficiency (GHD). Due to

its short half-life in the body, daily injection of the drug is required. To reduce this treatment burden, several long-acting forms of hGH with different structural modifications have been developed by many companies. We are currently developing a novel long-acting hGH designated as JR-142, a genetically engineered hGH fused at its C-terminus with a modified human serum albumin (HSA) at its N-terminus, which is produced by Chinese hamster ovary cells. In this study, we evaluated pharmacological properties of JR-142 in monkeys and hypophysectomized (HPX) rats.

**Methods:** We first compared pharmacokinetics of a single administration of JR-142 in monkeys with those of previously reported HSA-fused hGH, a fusion protein composed of N-terminal native HSA and C-terminal hGH, and native hGH produced in *Escherichia coli*. Next, we evaluated insulin-like growth factor I (IGF-I) inducing activity of JR-142 in comparison with a usual regimen of native hGH (once daily at 0.025 mg/kg). JR-142 was dosed once weekly at 0.2 or 0.5 mg/kg for 4 weeks. In addition, we produced rat GH fused at its C-terminus with rat albumin at its N-terminus as a surrogate molecule for JR-142, and body weight gain and bone growth were evaluated in the rat study. The surrogate molecule was dosed once weekly at 0.1, 0.2, 0.5, or 1.0 mg/kg for 4 weeks.

**Results:** In monkeys, JR-142 showed approximately 3- and 13-fold longer half-life than the previously reported HSA-fused hGH and native hGH, respectively. We also found that JR-142 dosed once weekly at 0.2 or 0.5 mg/kg for 4 weeks exhibited similar or rather higher activity on induction of IGF-I as compared to native hGH. In rat study, the surrogate molecule dosed weekly at 0.2 or 0.5 mg/kg for 4 weeks showed comparable effects on body weight gain and bone growth in HPX rats to daily treatments with native rat GH at 0.025 mg/kg.

**Conclusions:** These results suggest that JR-142 has superior pharmacokinetics to the previously reported HSA-fused hGH and that weekly treatments with JR-142 at 0.2 to 0.5 mg/kg is effective on the growth promotion of pediatric GHD for clinical use.

P3-861

#### DO LOW LEVELS OF INSULIN LIKE GROWTH FACTOR-1 (IGF-1) IN MALNUTRITION RESULT IN STUNTING?

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**Objectives:** Background: Nutritional deprivation in malnutrition results in decreased insulin like growth factor-1(IGF-1) levels through its diminished gene expression. Thus, decrease in circulating IGF- 1 leads to diversion of substrate away from growth to acute metabolic needs, affecting growth. Limited studies suggest role of serum IGF-1 as a marker of growth in malnourished children.

**Objective:** Evaluation of serum IGF-1 levels in children with acute malnutrition and its correlation with growth parameters.

**Methods:** Of sixty 6-36 months old children, thirty with weight for length/height 0 to +2 SD as controls, were evaluated after institutional ethical committee approval and parental consent. Weight, height, head circumference, mid arm circumference and weight for length/height evaluated using median WHO standards. Fasting venous sample collected for estimation of serum IGF-1 using enzyme linked immunoassay (ELISA) test. Statistical analysis done using software version SPSS 23.0.

**Results:** Mean age, weight, height in cases and controls were 16.6±9.07 and 16.3±0.89 months, 6.4±1.53kgs, 10.1±1.96 kgs and 70.8±8.48cms, 77.0±8.96cms respectively, p=0.00. Serum IGF-1 in malnourished was 82.3±24.08ng/ml and in controls 243.7±64.51ng/ml, (p= 0.00). Though there was no correlation of IGF-1 with weight (r=0.01, p=0.96 & r=0.16, p=0.39) and height (r=0.25, p=0.18 & r=0.04, p=0.82) in cases and controls respectively. Serum IGF-1 correlated positively with weight for height both in cases and controls (r=0.43 and r=0.70, p<0.05).

**Conclusions:** Serum IGF-1 was lower in malnourished children. Positive correlation of IGF-1 with weight for length/height but not with height suggests that it is good indicator of nutritional status. Therefore, IGF-1 levels by themselves alone not contributing towards stunting in malnourished children.

P3-862

#### **A NATIONAL, MULTICENTRE, OBSERVATIONAL STUDY TO ASSESS ADHERENCE AND LONG TERM OUTCOMES OF GH THERAPY IN PAEDIATRIC SUBJECTS WITH GROWTH HORMONE DEFICIENCY USING EASYPOT<sup>TM</sup> DEVICE IN SPAIN: ECOS STUDY**

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**Objectives:** To assess the adherence to GH treatment in patients with growth hormone deficiency (GHD) and its impact on clinical outcomes.

**Methods:** This national, multicentre, observational study enrolled subjects aged >2 to TM at least 3 months before the inclusion in the study (NCT01376921). Of the patients identified the ones with GHD were stratified in prepubertal and pubertal group. The primary endpoint was to assess the adherence of GH therapy (Saizen®) via easypod<sup>TM</sup> in paediatric subjects with GHD. Other objectives were to evaluate the impact of adherence on clinical outcomes and biomarkers, to identify adherence subject profiling, to assess the impact and the proportion of subjects with an adherence rate ≥85%. Adherence was measured by the mean percent of daily recorded adherence over time. Data were derived from the easypod<sup>TM</sup> device combined with physician data entry of

outcome measures and were collected in follow-up visits (at 6 months, 1, 2, 3 and 4 years after starting the treatment).

**Results:** From the total 238 subjects, data of 144 children with GHD were analyzed over a period of 4 years. The mean treatment adherence rate was high (95.2%, 95%CI: 93.3-97.0) and similar to the total population analyzed (94.5%, CI95%: 92.2-96.3). During the study visits, this rate remained high (97.0% [95.5-98.6] at 6 month and 95.9% [92.5-99.2] at 4 years) and was similar between the prepubertal and pubertal groups, in any case. Boys had a significantly lower adherence rate (94.2%) than girls (96.4%, p=0.0369). Correlation was not observed between the different growth outcomes and the adherence, except for height SDS and height velocity at 1 year, changes in height at 2 year and weight SDS at year 4; changes in BMI and in BMI SDS showed a negative correlation (at 2 year). No impact of adherence on IGF-1 status was observed. Compliance (adherence ≥85%) was high (97.2%) at 6 month and was maintained during the follow-up visits.

**Conclusions:** Data indicate that subjects with GHD treated with Saizen® via easypod<sup>TM</sup> showed a high adherence in a long period of treatment with the consequent impact in the clinical outcome which supports its use in the clinical practice.

P3-863

#### **A NEW PREDICTION SYSTEM FOR EVALUATION OF OPTIMAL FINAL HEIGHT IN CHILDREN WITH GROWTH HORMONE DEFICIENCY: IGRO**

*Ayca Torel Ergur, MD; Sevinc Odabasi Gunes, MD, Kirikkale University Faculty of Medicine, Kirikkale, Turkey*

**Objectives:** In children with growth hormone deficiency (GHD) it seems to be more useful to optimize the growth hormone therapy (GHT) dosage individually and sustain necessary dosage adjustment instead of using a standard GHT dosage in order to reach the optimal final height. Unfortunately, there is very limited technic that guide pediatric endocrinologist about this issue. However, in the last three years IGRO (International Growth Response of Optimization) has developed as an exciting new prediction system from KIGS database about this subject. In this study, we aimed to study this new prediction system; IGRO in our patients diagnosed growth hormone deficiency (GHD).

**Methods:** Six children who were diagnosed GHD in between January 2016 and January 2017 were involved in the study. Dosage of GHT was adjusted according to etiology of GHD and patients were called for follow-up visits for every 3 months in order to evaluate anthropometric measurements and laboratory test for fasting blood glucose, fasting insulin, thyroid functions, total blood count, IGF1, IGFBP3. On 3rd and 6th month of treatment IGRO was used to predict patient's height on 12<sup>th</sup> month of therapy.

**Results:** 3 girls and 3 boys, whose age was 7.75 ± 1.94 years and bone age was 4.7 ± 2.24 were involved in the study. Diagnoses of the patients were as follows: 2 total GHD, 3 partial GHD, 1 Turner syndrome. All of the cases were prepubertal. Prediction results of IGRO of our patients on 3<sup>rd</sup> and 6<sup>th</sup> month of therapy were the same so growth

hormone dosage wasn't changed. Prediction results were correlated to their actual height on 12<sup>th</sup> month of therapy except 1 patient who had total GHD.

**Conclusions:** IGRO is a very new prediction system, which has been used for a few years. Depending on our IGRO experience, instead of predicted height, final height is concluded in pubertal cases. Besides, all the prepubertal cases are not covered by the prediction system yet. However, we think if the prediction system will be improved in the future, it may be used for all of the cases and may be helpful for decision of the most effective treatment dosage in patients with GHD.

## POSTER SESSION 3

Saturday, September 16, 2017, 12:00-1:00pm

### P3 - Neuroendocrinology including hypothalamic pituitary

P3-1000 – P3-1012

P3-1000

#### NEUROENDOCRINOLOGICAL DYSFUNCTIONS OF THE PATIENTS WITH CRANIOFARENGIOMA

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**Objectives:** Childhood craniofarengiomas are rare embryonic malformations of the sellar and parasellar region with an incidence of 0.5-1/1 000 000. Despite low histological grade, its proximity to the optic nerve and hypothalamo-pituitary axis increase long term sequelae. We aimed to evaluate neuroendocrine functions pre and postoperatively in the patients with craniofarengioma retrospectively.

**Methods:** Between January 2006 and December 2016 clinical records of 22(15 boys)patients with craniofarengioma admitted pre or postoperatively were evaluated. Pre and post operatively anthropometric measurements, pituitary hormones, MRI findings, tumor localization and pathological results were recorded.

**Results:** Mean age at admission was 7,9±3.9 years. Mean follow-up time was 4.1±1,9 years. At admission complaints were head ache (50%), visual impairment (27%), short stature (18%), neurological disorders (18%) and polyuria-polydypsia (14%). Preoperatively central hypothyroidism, central adrenal insufficiency, diabetes insipidus were diagnosed in 27%, 9% and 14% of the patients respectively. Short stature and obesity were observed in 32% and 18% of the patients. Preoperatively growth hormone deficiency was not evaluated. None of the patients had pubertal delay nor advancement. In MRI tumor was sellar/suprasellar in 64%, and sellar in 36% of the patients. Tumor was resected totally in 14%, partially in 86% of the patients. Tumor size was < 2cm, 2-4 cm, and > 4 cm in 10%, 50% and 40% of the patients respectively. Pathological evaluation of the tumor revealed

adamantinomatous in 82%, papillary in 4% and mixed type in 14 %. Postoperatively short stature and obesity were observed in 64% and 32 % of the patients. Post operatively central hypothyroidism, central adrenal insufficiency, growth hormone deficiency, hypogonadotropic hypogonadism and diabetes insipidus were diagnosed in 91%, 73%, 59%, 80% and 59% of the patients respectively. Precocious puberty was observed in 1 patient. Two patients received growth hormone treatment; one stopped the treatment because of the recurrence of tumor, one still receiving.

**Conclusions:** As the survival rates, long term neuroendocrinological sequelae are increasing in the patients with craniofarengiomas. These patients should be evaluated promptly and followed by multidisciplinary teams.

P3-1001

#### NATIONAL UK GUIDELINES FOR THE INVESTIGATION, TREATMENT AND LONG-TERM FOLLOW-UP OF PAEDIATRIC CRANIOFARYNGIOMA.

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**Objectives:** Although rare, craniopharyngiomas are the commonest suprasellar tumour in childhood. Despite high overall survival, children and young people <19 years with craniopharyngiomas are at risk of multiple relapses and long-term tumour- and treatment-related neuroendocrine, cognitive and visual morbidity. We sought to provide, for the first time, a national standard for best practice based on currently available evidence for the assessment, treatment and follow-up of paediatric craniopharyngiomas.

**Methods:** Clinical questions were formulated based on a PICO (Population, Intervention, Comparison, Outcome) format by a multidisciplinary Guideline Development Group to guide systematic searches via the Ovid MEDLINE (1946-February 2017) and Cochrane Library (2016, Issue 12) databases, identifying 2023 separate research articles. Publications underwent a three-tier filtering process and 300 were reviewed using the GRADE approach. Where recommendations could not be made, a two-stage international Delphi consensus process was conducted.

**Results:** 44 clinical questions were identified, leading to 35 recommendations which were largely based on low to very low quality evidence. 30 further recommendations achieved >70% agreement via the Delphi consensus process. Important highlights include the recommendation that craniopharyngiomas are managed in tertiary paediatric centres with sufficient neuro-oncology, neurosurgery, endocrinology, radiology, pathology and neuropsychology multidisciplinary experience. At diagnosis, tumours should be graded using the "Paris" grading system and subsequent treatment tailored to avoid hypothalamic damage. Recommendations on the long-term neuroendocrine (including the safety of recombinant human growth hormone therapy), ophthalmology, and neuropsychology follow-up of survivors are also detailed.

**Conclusions:** These National Institute of Health and Care Excellence (NICE) and Royal College of Paediatrics and Child Health (RCPCH)-endorsed guidelines provide the first evidence- and consensus-based national recommendations for the management of paediatric craniopharyngioma. Through its implementation, we hope to achieve better consistency in the quality of care of such patients and improve long-term quality of survival.

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#### CHARACTERISTICS OF DYSNAETREMIAS IN PEDIATRIC BRAIN TUMORS

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**Objectives:** The postoperative course of pediatric brain tumors is often complicated by dysnaetremic conditions. Predicting which patients are at risk for these complications would improve outcomes. Copeptin has been reported as a predictor of diabetes insipidus in the adult population. We

aim to study patient characteristics and the accuracy of copeptin in predicting post-operative diabetes insipidus (DI) and syndrome of inappropriate antidiuretic hormone secretion (SIADH) in the pediatric population.

**Methods:** We performed a cohort study of consecutively enrolled pediatric neurosurgical patients at a pediatric regional referral center in Memphis, TN, USA. Patient characteristics such as demographic data, anthropometric data, tumor characteristics, prior treatment history, perioperative steroid use, diagnostic assessments for DI and SIADH, daily urine output, and pre and post-discharge endocrinopathies were extracted from the electronic medical record. Plasma and serum copeptin measurements were performed on residual blood samples. Copeptin assays are currently being performed and data is forthcoming. Logistic regression modeling will be utilized to investigate clinical characteristics and the association of post-surgery copeptin level with the likelihood of DI and SIADH.

**Results:** 17 subjects, age 1 to 17 years-old, were enrolled. All patients underwent a procedure involving the structural manipulation of the pituitary gland or hypothalamus. Surgical reasons include craniopharyngioma (41%), adenoma (24%), pilocytic astrocytoma (18%), meningioma (12%), and optic pathway glioma (6%). 9 subjects had post-operative DI (53%) and 6 had SIADH (35%). Of those patients with DI, 2 had a prior diagnosis of DI (12%) and 7 developed permanent DI (42%). Mean DI onset is 1.6 post-operative days (SD 0.73). Mean SIADH onset is 8.0 post-operative days (SD 4.98). Performance data for copeptin is forthcoming.

**Conclusions:** Dysnaetremias are common in postoperative pediatric brain tumor patients. DI onset is usually directly post-operative although definitive diagnosis may be delayed due to post-operative diuresis. In our series, SIADH occurs in almost 50% of those who develop DI, presenting with hyponatremia and interval increase in urine osmolality, with some subjects not seeing a decrease in urine output at diagnosis.

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#### POST-OPERATIVE DIABETES INSIPIDUS AND HYPONATREMIA IN CHILDREN AFTER TRANSSPHENOIDAL SURGERY: 18 YEAR EXPERIENCE.

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**Objectives:** To define the incidence and predictors of postoperative sodium alterations in pediatric patients

# ACTH SECRETING PITUITARY ADENOMA IN A CHILD WITH ROHHAD SYNDROME

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**Objectives:** We report the clinical course, biochemical and genetic results of a child with ROHHAD (Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation) syndrome associated with Cushing's disease.

**Methods:** 4.8 yr old male presented with rapid weight gain and increased appetite of 6 months duration. His weight was more than 95th percentile and BMI of 30 kg/m<sup>2</sup>. Metabolic profile showed normal fasting glucose of 5.4 mmol/L with high HbA1C of 6%. He had elevated AM cortisol of 571 nmol/L with failure of suppression of PM cortisol (496.8nmol/L) and elevated ACTH of 75 pg/ml. MRI pituitary revealed a 2 mm left-sided pituitary microadenoma. He developed an attack of Raynaud's phenomenon with flushing, sweating and weakly palpable pulses. He also had hypernatraemia (Na 151 mmol/L). The child travelled to the UK and the diagnosis of ACTH-dependent Cushing's syndrome was confirmed by inferior IPSS (peripheral: central ACTH gradient after CRH 10.2, IPSS 9.5 with left sided ACTH secretion consistent with MRI). Endoscopic transphenoidal adenomectomy was unsuccessful. Bilateral adrenalectomy was undertaken due to worsening respiratory failure. Consequently, he developed anterior pituitary hormone deficiencies and diabetes insipidus requiring replacement with growth hormone, thyroxine and desmopressin in addition to hydrocortisone and fludrocortisone. Post-operatively he had persistent hypoventilation syndrome requiring night time BiPAP support. Over a period of 2 years postoperatively, he continued to have excessive weight gain BMI reached 41kg/m<sup>2</sup>. His respiratory condition deteriorated and continuous ventilator support was needed. In addition to icy cold peripheries and bouts of sweating and flushing, he developed other signs of autonomic dysfunction including temperature instability and variability of heart rate.

**Results:** Gene panel for hypoventilation syndromes was undertaken and no detectable mutations were identified.

**Conclusions:** Based on the findings of obesity with progressive weight gain, hypoventilation, autonomic dysfunction, hypothalamic dysfunction, and abnormality in water balance, we believe that the child has ROHHAD syndrome associated with Cushing's disease. To our knowledge this is the first report of such an association.

undergoing transsphenoidal surgery (TSS) for pituitary adenomas.

**Methods:** We performed a retrospective review of 160 patients that underwent TSS for pituitary adenomas at our institution 1999 - 2017. Variables measured included daily serum sodium through post operative day 10, urine specific gravity, desmopressin (DDAVP) or salt tablet administration, fluid restriction, or seizures as a result of sodium alterations. We examined the association of diabetes insipidus (DI) or syndrome of inappropriate antidiuretic hormone secretion (SIADH) with tumor size, tumor type, number of repeat surgeries, manipulation of posterior pituitary, presence of tumor invasion, and cerebrospinal fluid (CSF) leak and drain.

**Results:** Patients were 12.9 ± 3.4 years (mean ± SD), 81 females. Ninety-two percent (n=147) had adrenocorticotropin hormone (ACTH) producing adenomas; the remaining 8% (n=12) had growth hormone (GH) producing adenomas. Thirty-nine patients had diabetes insipidus (defined as urine output >4 cc/kg/hour (ULN 300cc/h) and urine specific gravity <1.003); 35 required DDAVP; among these, 19 had hyponatremia in addition to DI, twelve patients were discharged on DDAVP. The risk of long-term need for DDAVP was significantly higher in patients that had CSF leak (p=0.007), or drain (0.025), or second surgery (0.014). Isolated hyponatremia was observed in 59 patients, 23 were attributed to SIADH, 19 to hypotonic fluids, 3 were considered part of cerebral salt wasting syndrome. All patients with SIADH were placed on fluid restriction; 1 received salt tablets. Two patients had seizures due to sodium alterations. Patients who had repeat surgery had a significantly higher incidence of DI as compared to first surgery 11/23 versus 28/137 (p=0.005). Females were more likely to develop SIADH (Table 1). The relative risk of developing DI or SIADH was 1.7 in the patients who had a CSF leak (CI 1.2-2.5, p=0.0006).

**Conclusions:** The incidence of DI after TSS was found to be 24% and SIADH 14%. Presence of a CSF leak or a second surgical intervention were risk factors for sodium alterations, females were more likely to develop SIADH.

Table 1.

Variable	DI	SIADH	DI and/or SIADH
Number of patients	24% (n=39/160)	14% (n=23/160)	38%
Gender (M vs. F)	14/39 vs. 25/39 (p=0.053)	5/23 vs. 18/23 (p=0.004)	n/a
Incidence 1 <sup>st</sup> vs. 2 <sup>nd</sup> surgery	28/137 vs. 11/23 (p=0.005)	22/137 vs. 1/23 (p=0.139)	p=0.1706
Manipulation of posterior pituitary	21/68 vs. 15/69 (p=0.224)	11/68 vs. 9/69 (p=0.604)	p=0.1664
Hormone excess (ACTH vs. GH)	35/148 vs. 4/12 (p=0.452)	19/148 vs. 4/12 (p=0.052)	p=0.0613
Tumor size (micro vs. macroadenoma)	24/121 vs. 5/20 (p=0.597)	19/121 vs. 4/20 (p=0.063)	P=0.4583
CSF leak (yes, no)	16/50 vs. 22/107 (p=0.119)	11/50 vs. 12/107 (p=0.075)	p = 0.0089
CSF drain (yes, no)	9/28 vs. 29/129 (p=0.279)	6/28 vs. 17/129 (p=0.263)	p = 0.0898
Tumor invasion into posterior pituitary (yes, no)	11/42 vs. 22/99 (p=0.611)	7/42 vs. 11/99 (p=0.366)	p = 0.3388



### SOX2 HAPLOINSUFFICIENCY IS ASSOCIATED WITH SELLAR/SUPRASellar CYST ENLARGEMENT AND SUBSEQUENT SHRINKAGE WITH RECOVERY OF NORMAL GROWTH HORMONE SECRETION

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**Objectives:** *SOX2* and *PROP1* mutations are associated with a spectrum of anterior pituitary hormone deficiencies (isolated hypogonadotrophic hypogonadism (HH) and variable multiple anterior pituitary hormones respectively). Both have been associated with development of progressive sellar/suprasellar cystic masses, possibly related to disordered Rathke cyst evolution. This case report follows longitudinal observation of such a mass in a patient with *SOX2* haploinsufficiency with HH and growth hormone (GH) deficiency.

**Methods:** Case: Patient was born with bilateral microphthalmia, birth weight 2.83kg at term. He was referred for an endocrine opinion at 17 mths for micropenis (2.5 cm) and hypoplastic scrotum. At presentation, length was -2.2 SDS, wt -2.6 SDS, testes 0.5–1 ml. Investigations confirmed euthyroid status with normal cortisol response to ACTH and low serum IGF-1 (48; ref range 57–303 mcg/L). MRI scan showed a non-enhancing pituitary lesion with suprasellar extension (8x8x11mm), suggestive of a Rathke's cleft cyst. Genetic testing revealed a heterozygous *SOX2* mutation (c.143TC>AA). Growth hormone replacement was started at 25 mcg/kg/d. Repeat scan after 16 months showed an increase in the sellar lesion (12x10x12mm).

**Results:** Patient had good clinical response to GH treatment (height SDS -0.35 at 5 years). Repeat MRI aged 5.5 years showed marked spontaneous shrinkage of lesion (4x5mm). Glucagon stimulation test showed normal peak GH (10 mcg/L) and normal peak cortisol (602 nmol/L). Serum IGF-1, off GH for 3 weeks, was normal (23nmol/L, ref range 7–27). GH treatment has been discontinued.

**Conclusions:** Sellar lesions due to *SOX2* mutation may undergo involution with recovery of anterior pituitary function. This case highlights the yet uncertain phenotypic outcome regarding anterior pituitary sufficiency and need for lifelong surveillance of functional and anatomical effect. These overlap with clinical/ imaging observations in patients with *PROP-1* mutations and common signalling pathways may be involved. Specific *SOX2* analysis in patients with significant volume Rathke pouch cysts may identify patients with related genetic underlying mechanisms – which could relate to future investigative, monitoring and potential therapeutic programmes.

### CENTRAL DIABETES INSIPIDUS IN AN INFANT WITH CONGENITAL TOXOPLASMOSIS.

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**Objectives:** Congenital toxoplasmosis (CTox) is usually asymptomatic. However acute manifestations in the neonatal period may occur, including fever, anemia, jaundice and hydrocephaly. Some infants with CTox may also present with late sequelae such as sensorineural hearing loss, chorioretinitis and microcephaly. Involvement of hypothalamic–pituitary axis is rarely reported, but when it occurs it usually affects the anterior pituitary and exceptionally the posterior pituitary. We report an infant with diabetes insipidus and CTox.

**Methods:** .

**Results:** Case Report

A 1 month 25 days old male was admitted to the emergency department due to a brief resolved unexplained event characterized by cyanosis and loss of muscular tone associated with fever. He had a history of prematurity of 32 weeks of gestational age secondary to premature labor due to cervicovaginitis, neonatal jaundice of multifactorial etiology and maternal demise secondary to presumed pulmonary embolism. At admission late neonatal sepsis with central nervous system involvement was suspected. Complete blood cell count reported 8.600 leucocytes with 26% eosinophils, cerebral spinal fluid examination showed low glucose, hyperproteinorrhachie and 16 cells of which 6% were eosinophils. Transfontanelar ultrasound and head computed tomography showed hydrocephalus and multiple parenchymal and periventricular calcifications with no evidence of lesions in the supraoptic or paraventricular tracts. Congenital toxoplasmosis was confirmed by IgG and IgM western blot assay and treatment was initiated. The clinical course was also significant for dehydration, hyponatremia and later developed hypernatremia, accompanied by an increased serum osmolality and a decreased urine osmolality. Taking into account his multiple risk factors (age, prematurity, neuroinfection and use of mechanical ventilation), and because all criteria for diabetes insipidus were met, treatment with demopressin was established with success. The remaining hormones of the hypothalamic–pituitary axis were found within normal range.

**Conclusions:** A thorough research of literature was made and disorders of the hypothalamic-pituitary axis such as central diabetes

insipidus were found to be a very uncommon form of presentation of CTox.

P3-1007

**GROWTH HORMONE SECRETING PITUITARY MACROADENOMAS IN ADOLESCENTS ,REPORT OR THREE CASES**

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**Objectives:** To describe three adolescents with pituitary macroadenoma as a cause of gigantism.  
**Methods:** We analyzed and presents three adolescents with tall stature and growth hormone secreting macroadenoma. They manifests clinically with tall stature, optic chiasm compression ,frequent headaches ,weight gain at the expense of soft tissues ,increase of hands ,feet and changes of facial appearance .Hormonal and metabolic alterations acanthosis nigricans and growth hormone and IGF1 were elevated (table 1).Nuclear magnetic resonance confirmed the diagnosis of Pituitary Macroadenoma .They underwent Pituitary surgery and received Somatoline of treatment.

**Results:** TABLE 1

Patient	age years	IGF 1 ng/ml	Tall centil	GH post ug/L	GucoaseProlactina ug/L
1	10	1054	P>95	20	103
2	15	>1600	P>95	0.9	5,8
3	15	116	p>95	>80	17

**Conclusions:** Growth hormone secreting tumors should considered in all young patients with high stature of non – clear etiology and suspicion of gigantism .

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**SUSPECTED ASSOCIATION: HYPOTHALAMIC HAMARTOMA & HYPOCALCEMIA.**

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**Objectives:** Hypothalamic hamartoma (HH) is a non-neoplastic malformation of hypothalamus attached to the Tuber Cinereum or mammillary bodies which is associated with endocrine and neurological symptoms. Hypocalcaemia and Vit-D deficiency were reported in patients with HH and were believed to be related to anti-epileptic drugs. However

in our report, we aim to raise a possible relation between HH and calcium/vitamin-D levels.

**Methods:** We report a 13-year-old girl complaining of seizures presented by uncontrolled laughter, vocalization, and tonic spasm of limbs. During infancy, her parents reported episodes of hypotonic state and vacancy of eyes. Gelastic seizures started at age of 6 years accompanied by vocalization followed by tonic seizures at night and early morning. Medical advice was not sought until 11 years when she underwent MRI and EEG which were reported as normal. Valproic acid was started. One month later she was admitted for persistent seizures. Valproic acid dosage was normal (75.47ug/ml) as well as calcium level (9.33mg/dl). She was discharged on valproic acid and phenytoin. Four months later, seizures remained frequent despite treatment. A blood test showed hypocalcaemia (6.9 mg/dl) and vitamin-D deficiency (8nmol/l); valproic acid titer was normal but phenytoin level was below the normal. Therefore, phenytoin was probably not the cause of hypocalcaemia. She was discharged on valproic acid, lamotrigine, and phenytoin; and was supplemented with vitamin-D.

**Results:** At age 13, MRI and EEG performed in another hospital were diagnostic of Hamartoma of Tuber Cinereum. She was referred to our center for hypocalcaemia. Blood tests revealed hypocalcaemia (6.8mg/dl), Vit-D deficiency (4.1ng/ml), high alkaline phosphatase (665 U/l), and high PTH (555pg/ml). Phenytoin and valproic acid levels were below normal range: 2.7ug/mL and 9.3ug/ml respectively. She was discharged on valproic acid.

**Conclusions:** In this case, etiology of seizures was diagnosed at age 13. The girl had associated hypocalcaemia and Vit-D deficiency before chronic use of anti-epileptic drugs. Although the deficiency was believed to be related to anti-epileptic drugs in previous reported cases; a relation between HH and calcium and vitamin-D levels must be raised.

P3-1009

**A HYPOTHALAMIC TUMOUR WITH NORMAL PITUITARY FUNCTION, NEUROLOGY AND FAILURE TO THRIVE**

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**Objectives:** Failure to thrive (FTT) may be a presentation for generalised lipodystrophy, which is clinically characterised by lipoatrophy, hepatomegaly, hypertriglyceridemia, insulin resistance and acromegaly features. FTT is also recognised in diencephalic syndrome, a rare presentation of hypothalamic tumours in infants and young children; associated with profound emaciation and generalised loss of

subcutaneous fat, growth acceleration, hyperkinesia and euphoria.

**Methods:** We present an 18 month old boy that was referred with significant failure to thrive from the age of 6 months and clinical features suggestive of generalised lipodystrophy. Despite having good appetite and a hyper caloric diet (1800 calories per day), his weight at presentation was -5.2 SDS, height -2.1 SDS and head circumference -2.2 SDS. His examination showed generalised loss of subcutaneous fat, pale skin, triangular face and prominent forehead. He had no hepatosplenomegaly or acanthosis nigricans, and his development and neurological examination were normal.

**Results:** Investigations showed normal baseline pituitary function and normal metabolic profile with no dyslipidaemia or glucose intolerance. His liver ultrasound, however, demonstrated an 8 cm liver with diffuse fatty changes. He had a normal microarray and was negative for Russell-Silver syndrome. DNA sample was sent to test for generalised congenital lipodystrophy. Despite an absence of neurological symptoms, a brain MRI at the age of 2.5 years revealed a large hypothalamic mass, with the histological diagnosis of a low-grade astrocytoma.

**Conclusions:** Hypothalamic brain tumours should be considered in children with persistent failure to thrive and clinical features suggestive of generalised lipodystrophy, with normal pituitary function and normal neurological examination and an absence of biochemical metabolic abnormalities.

P3-1010

#### **FACTITIOUS HYPERPROLACTINEMIA OR PROLACTINOMA? ROLE OF THE LABORATORY IMMUNOASSAY**

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**Objectives:** Pituitary adenomas have a prevalence of 2% of all intracranial tumors in children with prolactinomas being the most common. The diagnosis of prolactinoma is established by measuring serum prolactin (PRL). Rarely, immunoassays may show false elevation due to interference from nonspecific antibodies in the serum. We report a case misdiagnosed with prolactinoma due to falsely elevated serum PRL secondary to interfering antibodies.

**Methods:** A 13 year old pre-pubertal male presented with short stature, normal physical exam, without headaches or visual changes. The pituitary workup was normal except for PRL 101.8 ng/mL (normal 5-18 ng/mL) and FSH of 61.1 mIU/mL (normal 1.6- 9.7 mIU/mL, performed on Ortho Diagnostics Vitros 5600 immunoanalyzers). Brain MRI showed a 3 mm microadenoma. Oral Cabergoline was initiated and gradually increased to 1 mg twice weekly by 3 months. Although he was compliant, PRL remained high. Factitious hyperprolactinemia due to interference in the immunoassay by heterophile antibodies (HA) and/or other antibodies was suspected.

The serum sample was analysed using 1. Serial dilution (same analyzers) 2. Heterophile blocking tube (HBT, Scantibodies) and non-specific antibody blocking tube (NABT, Scantibodies) 3. Different platforms in reference lab ARUP (prolactin on the ADVIA Centaur and FSH on the Roche COBAS).

**Results:** 1) The serial dilution studies showed non-linear correlation, suggesting assay interference for both PRL and FSH. 2) PRL normalized with both HBT and NABT while FSH decreased with HBT and normalized with NABT. 3) PRL and FSH testing on different analyzers demonstrated normal values. (Table 1)

These results suggest falsely elevated prolactin and FSH due to interfering antibodies. Cabergoline was discontinued and PRL levels remained normal. The family was counseled about possibility of unexpected laboratory results in the future due to the patient's interfering antibodies.

**Conclusions:** This is a rare case demonstrating falsely elevated PRL and FSH levels due to analytic interference with specific immunoassays leading to the misdiagnosis of a prolactinoma. It is important to recognize the possibility of interfering antibodies in order to prevent unnecessary treatment.

P3-1011

#### **INCREASE IN DESMOPRESSIN DURATION OF ACTION DURING TRAMETINIB THERAPY IN A CHILD WITH OPTIC PATHWAY GLIOMA COMPLICATED BY CENTRAL DIABETES INSIPIDUS**

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**Objectives:** The objective of this report is to describe a novel association of trametinib therapy with increased duration of action of desmopressin (DDAVP) as well as to review a possible mechanism by which this association may be explained.

**Methods:** NA

**Results:** We describe a 9-year-old female with non-NF associated posterior optic pathway glioma complicated by central diabetes insipidus who experienced a significant increase in time to breakthrough thirst and polyuria from her previously stable DDAVP dosing regimen after initiating trametinib therapy. This association was replicated during multiple time points over 6 months, during which the patient held trametinib doses due to illness. When trametinib was held, the patient would experience normal DDAVP duration of action (dosed once per day). When trametinib was resumed, DDAVP duration of action would again increase (dosed once every 2-5 days). During this interval, MRI imaging performed at -3, 0, 3, and 6 months showed stable to slight increase in tumor size.

**Conclusions:** Our case illustrates an important possible interaction between trametinib therapy and the arginine vasopressin receptor 2 (AVPR2) signaling pathway, unveiled

in a patient with central diabetes insipidus on DDAVP therapy. Trametinib is a potent and specific inhibitor of the protein kinase MEK that is currently being studied for its effects in tumors containing BRAF mutations or neurofibromatosis-associated MAP kinase signaling disorder. Analysis of the AVPR2 signaling pathway suggests that MEK is deactivated as a result of ADH binding to AVPR2. Exactly what role MEK inactivation plays in principal cells of the inner medullary collecting duct is unclear, but our case suggests that this may be essential for the mobilization of aquaporin 2 (AQP2) to the apical membrane. We believe that MEK inhibitors may possess anti-diuretic properties via AQP2 activation in principle cells, possibly reflecting an important side effect of increased DDAVP duration of action in patients with diabetes insipidus. This may justify close monitoring of fluid and electrolyte balance in diabetes insipidus patients receiving trametinib as well as further study into the potential effects of trametinib on the AVPR2 signaling pathway.

P3-1012

#### LONG TERM FOLLOW UP OF PATIENTS WITH HOLOPROSENCEPHALY IN A SINGLE TERTIARY CARE CENTER

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**Objectives:** This is an observational study, conducted on children with Holoprosencephaly (HPE) followed up over a period of 35 years (mean follow up 11.66 yrs) in a single tertiary Endocrine centre. We aimed to investigate the incidence of pituitary dysfunction and to correlate this with the neuroanatomic abnormalities and phenotypic severity of HPE.

**Methods:** Medical records of 45 HPE patients (pts) were retrospectively reviewed.

**Results:** Based on clinical and MRI findings, patients were categorized into lobar (3), semilobar (17), lobar (12), middle interhemispheric fusion (MIHF) (3), spectrum HPE (6) and unclassified (4). Pituitary abnormalities were observed in the 32 pts of the first three groups, while no hormonal abnormalities were present in the MIHF and the spectrum HPE groups. The principal endocrinopathy was diabetes insipidus (DI) (n=30, mean age  $1.38 \pm 2.97$  yrs) followed by TSH (n=11, mean age  $1.37 \pm 2.26$  yrs) and ACTH (n=11, mean age  $0.42 \pm 0.59$  yrs) deficiencies. Interestingly, DI reversed in 2 pts at 7 and 11 years respectively. More than 80% of pts with ACTH or TSH deficiency also had DI. Multiple pituitary hormone deficiency (MPHD) was diagnosed in 51%. All lobar patients and 59% of semilobar and lobar patients had MPHD. Twelve patients had an isolated hormone deficiency, 9 of whom had DI. Twelve patients had growth hormone deficiency, 9 of whom had MPHD. The least common

endocrinopathy was gonadotropin deficiency (11%). Of the 11 patients followed until puberty, only 3 required pubertal induction. None of the patients had precocious puberty. Ten patients died ( $6.04 \pm 5.36$  yrs) from non-endocrine causes. Genetic testing identified Sonic Hedgehog mutation/deletion in 4 patients. Mutations in *ZIC2* (1), *FGF8* (1) and *TG1FI* (1) were also identified.

**Conclusions:** Our analysis confirmed the high incidence of DI, especially in the most severe HPE phenotypes, during the first years of life. We have also shown that DI can reverse many years after diagnosis. Despite the presence of hypothalamic abnormalities, these patients do not develop precocious puberty. Regular follow up for the evolving endocrinopathies is recommended to reduce the risk of morbidity associated with an undiagnosed endocrinopathy.

#### POSTER SESSION 3

Saturday, September 16, 2017, 12:00-1:00pm

#### P3 - Obesity, lipids, and co-morbidities

P3-1100 – P3-1142

P3-1100

#### OBESEITY TRENDS IN MULTINATIONAL PEDIATRIC POPULATION IN UAE-A WINDOW

*Deepti Chaturvedi, MD, Burjeel Hospital, Abu Dhabi, United Arab Emirates; K.K Hegde, MD, NMC Specialty Hospital, Abu Dhabi, United Arab Emirates*

**Objectives:** To study the clinical and metabolic profile of children referred to a pediatric obesity clinic in a busy secondary level hospital catering to multinational Pediatric population.

**Methods:** Obese children (n=35, boys:girls-20:15) with BMI > 95th centile for age and sex (CDC2000), without any other endocrinopathies evaluated in our Pediatric obesity clinic were included in the study. Their detailed history including nationality, mode of presentation, family history and clinical examination (SMR staging) along with biochemical parameters were retrospectively analysed for presence of risk factors for metabolic syndrome (systolic blood pressure (SBP) > 90th percentile, total cholesterol (TC) > 150mg/dl, fasting triglycerides (TG) > 100 mg/dl, high density lipoprotein - cholesterol (HDL-C) 100mg/dl)

**Results:** Age at presentation varied from 3 years to 13 years with a mean age of 8.6 years. No difference in clinical or biochemical characteristics was found based on nationality. Positive family h/o DM and Hypertension was seen in 29/35 (83%) and 18/35 (52%) children. Acanthosis was seen in 30/35 (86%). Average BMI was  $25.4 \text{ kg/m}^2$ . Mean waist and hip circumference were 86 cm and 94 cm respectively. High SBP was seen in 28% (Mean SBP-113 mm HG). High TC (91%) (mean-189 mg/dl) was the commonest biochemical risk factor followed by low HDL (57%) (Mean-50.7 mg/dl), high TG (50%) (mean-96 mg/dl) and high

FBS(7%)(Mean-94mg/dl).Mean fasting serum insulin was 18.2 micro U/ml(done in 20/35 ).Mean Hba1c was 5.54%(30/35)  
**Conclusions:** Urgent and appropriate lifestyle measures should be undertaken to control obesity in children so as to prevent development of further cardiovascular side effects and metabolic syndrome.

P3-1101

**NEW PREDICTORS AND PREVALENCE OF METABOLICALLY HEALTHY OBESITY (MHO) IN THE PEDIATRIC POPULATION**

Francesco Chiarelli, MD, University “G. d’Annunzio”, CHIETI, Italy; Marika Bagordo, MS/MA; Concetta Mastromauro, MS/MA, University of Chieti, G. D’Annunzio, Chieti, Italy; Maria Loredana Marcovecchio, MD, University of Cambridge, Cambridge, United Kingdom; Cosimo Giannini, MD, University of Chieti, G. D’Annunzio, Chieti, Italy; Angelika Mohn, MD, University “G. d’Annunzio”, CHIETI, Italy

**Objectives:** Metabolically healthy obesity (MHO) represents a subset of the obese population which, despite excessive body mass index (BMI), does not appear to present metabolic alterations. Up to now, there are no unique criteria for MHO, especially in the pediatric population. To propose a new definition for the MHO group and to assess the prevalence of MHO in a clinical based sample of obese youth.

**Methods:** Clinical and biochemical data were collected from 312 obese youth (133 males, 155 prepubertal, mean age (±SD): 10.7±3.0yrs, BMI SDS: 2.29±0.43). The definition of MHO included the presence of at least 3 of the following criteria: systolic (SBP) and/or diastolic blood pressure (DBP) <2SDS; triglycerides/HDL-cholesterol (Tg/HDL) ratio <2.27; HOMA-IR<2.03 for prepubertal and <1.97 for pubertal; ALT<40 U/L for boys and <35U/L for girls.

**Results:** 186 (59.6%) youth fulfilled the definition of MHO and 126 (40.4%) were classified in the metabolically unhealthy obesity (MUO) subset (table). MHO children were younger, had a lower BMI SDS as well as a better cardio-metabolic profile, with a lower Tg/HDL ratio and lower levels of fasting glycemia, HOMA-IR and alanine aminotransferase (ALT).

**Conclusions:** This study highlighted a high prevalence of MHO subjects who, although being obese, have not developed yet abnormal cardio-metabolic features, underlying the importance of identifying univocal criteria for MHO, so that they may be used to guide clinical decision regarding treatment urgency and intensity. Further follow-up of this population will help in understanding whether this protection will persist overtime.

VARIABLES	MHO (186, 59.6%)	MUO (126, 40.4%)	P value
Age (yr)	10.3 ± 3.04	11.2 ± 2.85	0.02
BMI SDS	2.21 ± 0.36	2.41 ± 0.49	<0.001
SBP SDS	0.97 ± 1.03	0.85 ± 0.89	0.29
DBP SDS	0.67 ± 0.70	0.66 ± 0.66	0.90
Tg/HDL ratio	1.51 [1.11-2.00]	2.57 [1.90-3.78]	<0.001
Fasting Glycemia (mg/dL)	89.8 ± 9.57	92.3 ± 8.70	0.02
HOMA-IR	2.78 [1.77-3.98]	4.34 [3.16-6.61]	<0.001
ALT (U/L)	27.8 ± 6.79	39.9 ± 20.7	<0.001

P3-1102

**CARDIOMETABOLIC HEALTH RELATES TO EDUCATIONAL OUTCOMES: A CASE-CONTROL STUDY IN ADOLESCENTS FROM A LATINO COHORT**

Paulina Correa-Burrows, PhD; Yanina Rodriguez, MSc(c), University of Chile, Santiago de Chile, Chile; Estela Blanco, MS/MA; Sheila Gahagan, MS/MA, University of California San Diego, San Diego, CA, United States; Raquel Burrows, MD, University of Chile, Santiago de Chile, Chile

**Objectives:** A case-control analysis within an ongoing cohort study explored the association of cardiometabolic markers and metabolic syndrome (MetS) with educational outcomes in the transition from high school (HS) to college education. **Methods:** At 16y, waist circumference (WC), systolic blood pressure (SBP), triglycerides (TG), HDL and glucose (Gli) were measured. A continuous score (zMetS) representing a composite metabolic risk factor profile was computed with gender-specific z-scores of WC, SBP, Gli, TG, HDL; lower values denote a healthier cardiometabolic profile. MetS was diagnosed with the NHBLI/AHA/IDF criteria. Sixty cases of MetS were identified and 180 controls were randomly selected. Data on HS graduation, grade-point average (GPA), college examination and college tests scores were collected from administrative records. Data were analyzed with multiple linear and logistic regressions, controlling sociodemographic, lifestyle and educational confounders.

**Results:** The association of zMetS, WC, and TG at 16y with the odds of completing HS and taking college exams was negative and significant. Notably, for a one-unit increase in the zMetS, we found 52% (OR: 0.48, 95%CI: 0.27-0.83) and 39% (OR: 0.61, 95%CI: 0.28-0.93) reduction in the odds of getting the HS diploma and taking college exams, respectively. The chances of HS completion and taking college exams in participants diagnosed with MetS were 13% (95%CI: 0.02-0.70) and 30% (95%CI: 0.11-0.79) that of participants with no cardiometabolic risk factors (CMRF). Compared to adolescents with no CMRF, those with MetS had lower GPA (515 vs. 461 points; P=0.002; Glass' Δ=0.55). Last, adolescents with MetS had significantly lower odds of passing the Math exam for college compared to peers with no CMRF (OR: 0.19; 95%CI: 0.04-0.95).

**Conclusions:** In adolescents from a Latino cohort, cardiometabolic health was associated with academic outcomes in the transition from secondary to higher education. MetS is known to affect cognition and raise the risk for dementia in adults. Very few studies have explored these relationships in younger age populations and even few have investigated the impact on educational outcomes. **Funding:** NHLBI-HL088530; CONICYT-PAI79140003

PLEASE SEE TABLE ON FOLLOWING PAGE

Table 1 Descriptive statistics of participants in the sample

	Number of cardiometabolic risk factors								P value <sup>2</sup>
	None (n=60)		One (n=60)		Two (n=60)		Three or more (n=60)		
	Mean or number	SD or Percentage	Mean or number	SD or Percentage	Mean or number	SD or Percentage	Mean or number	SD or Percentage	
<b>Chronological age</b>									
Age (y)	16.8	0.3	16.8	0.2	16.8	0.3	16.9	0.3	NS
<b>Sex</b>									
Males	41	31.5	42	32.3	19	14.6	28	21.5	<0.001 <sup>1</sup>
Females	19	17.3	18	16.4	41	37.3	32	29.1	
<b>Cardiometabolic profile</b>									
WC (cm)	73.6	6.1	76.8	6.1	87.2	11.4	98.3	12.1	<0.001
SBP (mmHg)	107.0	9.3	111.1	9.7	111.2	9.5	124.1	12.4	<0.001
DBP (mmHg)	66.6	5.9	68.8	6.0	70.0	8.4	76.9	8.7	<0.001
Glucose (mg/dL)	88.1	7.2	87.9	8.3	87.9	9.5	95.9	18.5	<0.001
TG (mg/dL)	67.9	22.8	77.4	31.3	86.3	37.9	176.4	74.6	<0.001
HDL (mg/dL)	50.7	7.7	35.9	9.3	37.8	6.5	35.2	7.8	<0.001
MetS (z-score)	-0.50	0.4	-0.06	0.4	0.13	0.4	1.13	0.85	<0.001
HOMA-IR	1.44	0.6	1.46	0.8	1.83	0.8	3.58	2.5	<0.001
<b>Anthropometric profile</b>									
BMI (z score)	-0.24	0.9	0.28	0.9	1.21	1.2	2.21	0.9	<0.001
Overweight (BMI z > 1 SD)	7	6.4	14	12.7	36	32.7	53	48.2	<0.001 <sup>1</sup>
Obese (BMI z > 2 SD)	0	0.0	1	1.96	16	31.4	34	66.7	<0.001 <sup>1</sup>
<b>Academic profile</b>									
HIS GPA	505.2	94.3	485.2	87.5	482.6	78.8	442.7	72.1	0.009
Completed HIS	57	28.6	51	25.6	46	23.1	45	22.6	0.011 <sup>1</sup>
Repeated a grade in HIS	18	28.1	17	26.6	20	31.3	9	14.1	NS <sup>2</sup>
Taking exams for college	33	28.5	31	26.7	34	29.3	18	15.5	0.019 <sup>1</sup>

<sup>1</sup> ANOVA with Bonferroni correction, except as indicated. <sup>2</sup> Pearson's Chi<sup>2</sup> test.

Orhun Camurdan, MD, Gazi University Medicine Faculty, Ankara, Turkey; Peyami Cinaz, Professor, Gazi University, Medical School, Ankara, Turkey

**Objectives:** This study was conducted to determine the relationship between sleep duration (SD), screen time (ST) and biochemical markers of insulin resistance in obese children and adolescents.

**Methods:** The study was carried out on 113 obese children and adolescents (53 males, 60 females) aged 9-17 who applied to Gazi University Medical Faculty Hospital Pediatric Endocrinology Department. Weekdays and weekends SD was obtained from the sleep habits questionnaire. The time spent on the screen (television, computer, mobile phone) was obtained by the questionnaire prepared by the researcher and it was grouped as ≤2, 3-4, ≥5. Insulin resistance was determined by HOMA-IR test which was calculated using fasting glucose and insulin levels. HOMA-IR > 3.16 values were taken as cut-off.

**Results:** The mean BMI Z-Score was 2.21±0.88. According to the HOMA-IR, the incidence of insulin resistance in children was 63.7%. The mean HOMA-IR was 4.34 ± 1.12. In obese individuals, the time spent in front of the screen was 3.84 ± 2.79 hours / day. HOMA-IR value was 3.87 ± 1.7 in children and adolescents who spent ≤2 hours, 3.62 ± 7.4 who spent 3-4 hours and 4.77 ± 2.4 who spent ≥5 hours in front of the screen. In the 9-13 year-old age group, HOMA-IR value was 4.82±3.15 in children who slept <8 hours, 3.05±1.30 in children who slept 8-10 hours and 3.47±2.20 in children who slept ≥11 hours. In the 14-17 year-old group, HOMA-IR values were highest (5.05±7.30) who slept <8 hours. These values were found to be 3.38 ± 1.40 and 4.22 ± 2.10 for 8-9 hours and ≥10 hours, respectively.

**Conclusions:** Homa-IR values were highest in obese children and adolescents who spent ≥5 hours in front of the screen and who sleep <8 hours. Improving SD and reducing the time spent on the screen will help prevent the risk of insulin resistance in obese children and adolescents.

P3-1105

## SLEEVE GASTRECTOMY IN PATIENTS WITH PRADER-WILLI SYNDROME AND OBESE SUBJECTS.

Danilo Fintini, MD; Alessio Convertino, MD; Sarah Bocchini, MD, Bambino Gesù Children's Hospital, Rome, Italy; Graziano Grugni, MD, Italian Auxological Institute, Verbania, Italy; Antonino Crinò, MD, Bambino Gesù Children's Hospital, Rome, Italy

**Objectives:** Prader-Willi Syndrome (PWS) results from the loss of paternally imprinted genes on chromosome 15q11-15 and is characterized by morbid obesity with difficult in losing weight only with nutritional approach. Bariatric surgery may reduce long term comorbidities and help to sustain weight loss in obese as such as in PWS population. Sleeve gastrectomy, a not malabsorptive procedure, has been used in morbid obese subjects. To date no many studies are available in PWS patients with this technique. We report 24

P3-1103

## THE EFFECT OF MEDICAL NUTRITION THERAPY ON BODY WEIGHT AND EATING HABITS IN OBESE CHILDREN AND ADOLESCENTS

Esra Doger, MD; Rukiye Bozbulut, Nutritionist; Aylin Kilinc Ugurlu, MD; Emine Demet Akbas, MD; Aysun Bideci, MD; Orhun Camurdan, MD, Gazi University Medicine Faculty, Ankara, Turkey; Peyami Cinaz, Professor, Gazi University, Medical School, Ankara, Turkey

**Objectives:** This study was conducted to analyze the effectiveness of medical nutrition therapy in the control of body weight and eating habits in obese children and adolescents.

**Methods:** The study was carried out on 55 children (20 boys, 35 girls) aged 9-18 who applied to Gazi University Medical Faculty Hospital Pediatric Endocrinology Department. Participants were divided into 9-13 and 14-18 age groups. To monitoring compliance with medical nutrition therapy, children are required to keep records of food consumption every week during the 8-week follow-up. Adherence to the Mediterranean diet was evaluated by the KIDMED index both at the beginning and at the end of the research.

**Results:** As a result of the medical nutrition therapy, in the 9-13 age group, the mean BMI in obese boys show decline from 30.9±8.9 kg/m<sup>2</sup> to 29.2±5.2 kg/m<sup>2</sup>, while the 14-18 age group drop from 35.2±3.7 kg/m<sup>2</sup> to 31.6±3.3 kg/m<sup>2</sup>. In the girls 9-13 age group with these values were; 28.8±7.1 kg/m<sup>2</sup> to 27.5±6.1 kg/m<sup>2</sup>, while the 14-18 age group dropped from 31.4±4.5 kg/m<sup>2</sup> to 29.1±3.9kg/m<sup>2</sup>. At the end of the study all children started to take regular meals. Significantly increased KIDMED points were observed at the end of study (p <0.05).

**Conclusions:** Weight gain was stopped, weight loss has been achieved and positive eating habits developed in obese children.

P3-1104

## DETERMINING THE EFFECT OF SLEEP DURATION AND SCREEN TIME ON INSULIN RESISTANCE IN OBESE CHILDREN AND ADOLESCENTS

Esra Doger, MD; Aylin Kilinc Ugurlu, MD; Rukiye Bozbulut, Nutritionist; Emine Demet Akbas, MD; Aysun Bideci, MD;

months of follow-up in PWS and obese subjects treated with sleeve gastrectomy.

**Methods:** 8 PWS (5 M; aged 17.3±6.0 yrs; range 8.1-26.8) and 11 age matched obese controls (OB; 3 M; aged 15.8±2.0; range 10.5-18.5) were included. PWS showed basal BMI, BMI SD, waist circumference, HbA1c, HOMA-IR not statistically different from OB subjects as shown in the Table. Three PWS had Type 2 Diabetes, treated with biguanides and insulin, and 2 OB showed IGT. None of pts was treated with GH. All parameters were analyzed after 12 and 24 months from surgery. Excess Weight Loss percentage (EWL%) and maximum weight loss percentage (MWL%) were calculated. Ethic Committee and informed consents were obtained.

**Results:** After 12 months from surgery Type 2 Diabetes disappeared in two PWS. OB pts with IGT normalized glycaemia. As shown in Table all PWS and OB patients showed a decrease of all considered parameters, especially during first 12 months (although not statistically significant). One PWS developed abdominal hernia one year after surgery.

**Conclusions:** Our data showed that sleeve gastrectomy in subjects with PWS, as in obese patients, improves positively BMI, and may normalizes glycemic control and insulin resistance. No statistically difference were found among parameters but this result can be influenced by the very small sample and the widespread distribution of data. These results need to be confirmed on higher number of patients with a longer follow-up.

Mean ± SD		BMI	BMI SD	CV	HbA1c (mmol/mol)	HOMA-IR	EWL%	MWL%
Basal	PWS (n.8)	45.7 ± 4.7	4.3 ± 1.5	119.4 ± 54.4	46.4 ± 20.4	11.5 ± 12.4	NA	22.9 ± 15.1
	CNT (n.11)	48.1 ± 3.8	4.0 ± 1.2	123.6 ± 49.6	34.7 ± 15.6	5.8 ± 2.2	NA	27.7 ± 10.6
12 months	PWS (n.6)	34.9 ± 6.3	2.5 ± 1.6	96.8 ± 51.0	35.5 ± 2.2	2.2 ± 1.0	23.9 ± 15.5	NA
	CNT (n.10)	35.3 ± 6.7	2.8 ± 0.8	96.6 ± 37.3	32.9 ± 10.7	2.2 ± 1.5	26.0 ± 10.0	NA
24 months	PWS (n.3)	36.3 ± 9.8	2.7 ± 1.8	105.3 ± 62.5	37.7 ± 2.8	1.9 ± 0.7	14.5 ± 24.7	NA
	CNT (n.6)	34.1 ± 8.8	2.5 ± 1.3	98.3 ± 59.6	34.5 ± 17.9	3.1 ± 1.4	29.2 ± 11.6	NA

P3-1106

### IMPAIRED HEALTH-RELATED QUALITY OF LIFE OF OVERWEIGHT AND OBESE PRESCHOOLERS

Feneli Karachaliou, PhD, Attikon University Hospital, Athens, Greece; Kyriaki Karavanaki, PhD, University of Athens Medical School, "P.&A. Kyriakou" Children's Hospital, Athens, Greece; Andri Kosta, Health visitor; Ageliki Lysikatos, Health visitor; Aristeia Pateropoulou, Health visitor, Technological Educational Institution, University of Athens, Athens, Greece; Evangelia Boudouvi, MD, Attikon University Hospital, Athens, Greece; Efthimios Kakouros, Professor, Technological Educational Institution, University of Athens, Athens, Greece

**Objectives:** There is emerging evidence that obesity may have physical and psychosocial consequences on the health of children during preschool years. TAPQOL is a feasible instrument to measure health related quality of life (HRQOL), validated in infants and toddlers. The objective of the study was to assess the impact of obesity on HRQOL of preschool children, and to compare HRQOL scores of overweight/obese with those of normal weight preschool children

**Methods:** The parents of a random general population sample of 135 preschool children (70 boys and 65 girls), aged

3 months to 4.4years (mean (sd): 3.75 (1.05) years) , in Greece and Cyprus completed the TAPQOL questionnaire. **Results:** The prevalence of overweight/obesity among preschool children was 17.3% and did not differ significantly according to gender or ethnicity. Overweight/obese preschool children compared to normal weight children had significantly higher mean scale scores on lung problems (p=0.009), sleep problems (p=0.009), motor functioning (p=0.007), social functioning (p=0.005) and communication problems (p=0.000). Overweight/obese children showed lower scale scores of liveness (p=0.027) and higher scores of anxiety (p=0.004). **Conclusions:** Quality of life health-related parameters were impaired in overweight/obese children as early as the preschool years. Parents' concerns about their preschoolers' health and behavioral problems resulting from excess weight gain, may promote their perception about weight management in this age group.

P3-1107

**NOVEL MARKERS OF HYPERINSULINEMIA IN OBESE CHILDREN BY METABOLOMICS**  
Annalaura Mastrangelolo, PhD, San Pablo CEU University, Madrid, Spain; Gabriel Á. Martos-Moreno, MD; PhD., Hospital Infantil Universitario Niño Jesús. UAM. , Madrid, Spain; Vicente Barrios, PhD, Hospital Infantil Universitario Niño Jesús, CIBEROBN, Madrid, Spain; Antonia García, PhD, San Pablo CEU University, Madrid, Spain; Julie A Chowen, PhD, Hospital Infantil Universitario Niño Jesús, CIBEROBN, Madrid, Spain; Francisco J Rupérez, PhD; Coral Barbas, PhD, San Pablo CEU University, Madrid, Spain; Jesús Argente, MD, PhD, Hospital Infantil Universitario Niño Jesús. UAM, Madrid, Spain

**Objectives:** Metabolomics can help to identify novel biomarkers that indicate pathophysiologically relevant hyperinsulinism in obese children. Here, targeted metabolomics was used to assess the suitability of these biomarkers in combination with anthropometrical and laboratory parameters for a potential clinical application. **Methods:** One hundred prepubertal (Tanner stage I) obese children (BMI>2+SDS, 50 girls/50, 50% IR and 50% non-IR in each group) underwent an oral glucose tolerance test for carbohydrate and lipid metabolism determinations. Fasting serum leptin, adiponectin and hs-CRP levels together with 30 serum metabolites (amino acids, organic acids and acylcarnitines) were quantified and their relationship explored by correlation and ROC curve analyses. **Results:** While BMI-SDS did not correlate with any of the metabolomic markers studied (indicating that BMI excess is not the main determinant of the metabolic alterations underlying IR), alanine showed the highest correlation with HOMA-IR (r=+0.58, P<0.001), serum triglycerides (r=+0.40, P<0.001) and leptin (r=+0.40, P<0.001). Moreover, in cluster with leptin, alanine had the best discriminatory power for detecting IR in obese children (AUC=0.87). Interestingly, the specific metabolite/adipokine combination with highest sensitivity for IR detection was different in girls and boys; the



combination of isoleucine/pyroglutamate and leptin (AUC=0.94) had the best discriminatory capacity for girls, and the combination adiponectin/leptin and alanine (AUC=0.86) for boys. Furthermore, changes in methionine and adiponectin levels underlying IR were differentially observed in boys and girls, highlighting the striking effect of sex in IR-mediated alterations in children, despite their prepubertal status.

**Conclusions:** This study reveals that combined sets of adipokine and metabolomic parameters can be used as specific markers of pathophysiologically relevant IR in a single fasting sample, suggesting a potential clinical tool for better identifying children at risk without using invasive protocols.

P3-1108

### IGF-1, IGFBP-3 AND INSULIN SENSITIVITY DURING WEIGHT LOSS IN CHILDREN

Niels H Birkebæk, PhD; Henning Grønbæk, Professor; Aksel Lange, PhD; Peter Holland-Fischer, PhD; Kurt Kristensen, PhD; Søren Rittig, Professor; Hendrik Vilstrup, Professor; Jan Frydlyk, MD, Aarhus University Hospital, Aarhus, Denmark

**Objectives:** In adults, increased body mass index (BMI) has a negative impact on growth hormone (GH) secretion, but the decrease in GH secretion has not unequivocally been associated with a decrease in serum insulin like growth factor 1 (IGF-1). By contrast, weight reduction studies, including diets and bariatric surgery, generally show increases in serum IGF-1 in adults. Little information on the effect of weight reduction on serum IGF-I and the correlation with change in insulin sensitivity (IS) is available in children. We studied children before and after a 10 weeks stay at a weight loss camp (WLC). We hypothesized that the diet-induced improvement in IS stimulated serum IGF-1 and the molar ratio between IGF-1 and IGF-binding protein 3 (IGFBP-3), a proxy of bioavailable IGF-1.

**Methods:** A total of 116 (65 females) obese Caucasian children with a median age of 12.3 (7-15) years were included in the study. At the WLC all children attended regular school classes, were physically active at least 1 hour every day and had a fixed diet plan with focus on reduced intake of calories. Just before attending, and after 10 weeks at the WLC, the children were exposed to a physical examination and fasting blood samples. IGF-1 and IGFBP-3 were measured by iSYS/IDS. IS was calculated using the HOMA index:  $22.5 / (\text{insulin (mU/L)} \times \text{glucose (mmol/L)})$ .

**Results:** Data are presented as mean (95% confidence interval). BMI decreased with  $3.1 \text{ kg/m}^2$  (2.9-3.3) ( $P < 0.01$ ), and IS increased with 0.22 (0.06-0.38) ( $P < 0.01$ ). IGF-1 increased with  $20 \text{ µg/l}$  (8-32) and the molar ratio of IGF-1 to IGFBP-3 with  $4.8 (2.6-6.8) \times 10^{-3}$  (both  $P < 0.01$ ), while IGFBP-3 remained unchanged. The BMI-SDS decrease was inversely correlated with the increase in IS ( $P < 0.01$ ). The increase in IS correlated with the increase in serum IGF-1 ( $P < 0.01$ ) and the increase in IGF-1 to IGFBP-3 molar ratio ( $P < 0.05$ ).

**Conclusions:** In obese children, diet-induced weight loss improved IS and serum IGF-1 towards normality, with a

positive correlation between the increase in IS and the change in IGF-1 and IGF-1 to IGFBP-3 molar ratio.

P3-1109

### MATERNAL GLUCOSE METABOLISM DURING PREGNANCY AFFECTS THE TIMING OF ADIPOSITY REBOUND IN THEIR CHILDREN

Yuta Chiba, MD; Yasuko Ogiwara, MD; Yumiko Terada, MD; Kazuko Mizutani, MD, National Center for Child Health and Development, Tokyo, Japan; Yusuke Fujisawa, MD, National Center of Child Health and Development, Tokyo, Japan; Kanako Nakao, MD; Keisuke Yoshii, PhD; Yasuhiro Naiki, PhD; Reiko Horikawa, PhD, National Center for Child Health and Development, Tokyo, Japan

**Objectives:** The timing of adiposity rebound (AR) is the predictor of obesity or metabolic syndrome in adulthood. Previous studies revealed several factors that affect AR, however, the relationship between maternal glucose and fat metabolism during pregnancy and the timing of AR is unknown. We investigated the effect of maternal HbA1c and lipid levels on the timing of AR of their offsprings.

**Methods:** 174 pairs of mothers and children (87 boys) at 5-years of age, participating in the NCCHD birth cohort were involved in this study. Children's height and weight were measured at birth, 1, 3, 6, 9-month-, and 1,2,3,4,5-year-old. The age of AR was defined as the age of the lowest BMI before increase. Pre-pregnancy maternal body weight and height data were collected from mother's health-book. Mothers' weight and height at delivery and 5 years later were also measured. Blood sampling during mid-pregnancy was performed and maternal HbA1c, TG, LDL-and HDL cholesterol, and FFA levels after overnight fast were determined.

**Results:** According to the timing of children's AR, we divided the pairs of subjects into three groups; very early AR (VE, AR before 3-year-old,  $n=32$ ), early AR (EA, AR between 3 and 4-year-old,  $n=38$ ), no rebounder (NR, no AR up to 5 years of age,  $n=104$ ). In VE group, mother's HbA1c at mid-pregnancy was significantly higher than that of NR ( $4.91 \pm 0.32\%$  (mean $\pm$ SD) vs  $4.78 \pm 0.23\%$ ,  $p=0.02$ ). VE vs ER and ER vs NR showed no significant difference in HbA1c level. TG, LDL-chol, HDL-chol, and FFA levels were not significantly different among three groups. The gain of maternal body weight during pregnancy and maternal pre-pregnancy or current BMI had no influence on the timing of AR.

**Conclusions:** The timing of AR, which may relate to the future metabolic syndrome, is affected by, at least in part, maternal glucose metabolism during pregnancy.

# INSULIN-LIKE GROWTH FACTOR RECEPTOR (IGF-1R) EXPRESSION AND PROGRESSION OF LIVER DAMAGE IN OBESE CHILDREN WITH NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

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**Objectives:** Non-alcoholic fatty liver disease (NAFLD) has evolved as the most common form of chronic liver disease in children and has become a serious public health issue. NAFLD in children is tightly associated with obesity, insulin resistance, and a number of obesity-related metabolic complications. The precise determination of the severity of the disease requires a liver biopsy with histological evaluation. The full spectrum of the disease from isolated hepatic steatosis to non-alcoholic steatohepatitis (NASH) to cirrhosis has been described in children. IGF-1 has been shown to stimulate hepatic stellate cell (HSC) mitogenesis and collagen synthesis in both cultured human and human liver tissue.

The aim of this study was to investigate the hepatic expression of IGF-1R and IGF-1 in obese children with NAFLD.

**Methods:** The expression of IGF-1R was determined by immunofluorescence (IF) in liver tissues of 45 children with NAFLD. A preliminary study of IGF-1 expression was performed in 6 patients. Three liver samples from healthy subjects were used as reference for tissue expression of IGF-1R. Expression data were correlated with histological features of NAFLD.

**Results:** In children with NAFLD, IGF-1R intensity *per area* of liver tissue was significantly related with the severity of fibrosis, being significantly higher in patients with moderate and severe fibrosis, compared to those with mild degree ( $p < 0.005$ ). The expression of IGF-1R in activated hepatic stellate cells ( $\alpha$ -SMA+ HSC) significantly increased in parallel with the progression of fibrosis ( $p < 0.05$ ). IGF-1 expression showed a similar trend, with increased IGF-1 intensity *per area* in more advanced fibrosis ( $p < 0.05$ ).

**Conclusions:** Our data suggest for the first time that IGF-1R and IGF-1 expression in liver correlates with the severity of fibrosis. In particular, the increased expression of IGF-1R in activated HSC, the main collagen-producing cells in liver, suggests that IGF signaling plays a role in the progression of liver fibrosis in obese children with NAFLD and may represent a potential therapeutic target.

## CLINICAL CHARACTERISTICS OF PEDIATRIC ADRENOCORTICAL TUMORS: A RETROSPECTIVE REVIEW OF MEDICAL CENTERS IN NORTH TAIWAN

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**Objectives:** Adrenocortical tumors are very rare in children.

The aim of this study is to review our experience in the clinical feature and laboratory data on the diagnosis of adrenocortical tumors in children.

**Methods:** From 1990 to 2015, ten pediatric patients admitted to three major tertiary medical centers in north Taipei with adrenocortical tumors were reviewed. Clinical features, imaging studies, laboratory results, as well as pathological findings were reviewed.

**Results:** The series comprised 8 girls and 2 boys, median age of 6y8m (range 1y4m - 14y8m). Virilization was the most frequent initial presenting symptom of adrenocortical tumors in female patients. Only one patient had Cushingoid appearance at diagnosis but 5 of other 9 patients without Cushingoid appearance showed evidence of corticosteroid excess at diagnosis. Six patients had elevated androgen levels with significant advanced bone age. Three patients revealed hyperaldosteronism, two of them had hypertension without hypokalemia and the other had hypokalemia without hypertension. The tumor size ranged from 3.8 to 15 cm (median 5.1 cm). Eight of ten tumors located at left adrenal gland and two of them at right side. Pathology results revealed three cases of adrenocortical carcinoma, and seven cases of cortical adenoma. Only one girl had central precocious puberty one year later after total tumor resection and two girls had secondary tumor (one osteosarcoma and one hepatic adenoma).

**Conclusions:** Our results demonstrate that adrenocortical tumors occur predominantly in females and almost always causes clinical signs. Children with virilization, Cushing syndrome, or hypertension should pay much more attention. Even though most of these patients did not had typical Cushingoid appearance at diagnosis, we found out that majority of our patients had evidence of Cushing or subclinical Cushing syndrome, which may lead our patient to have adrenal crisis when they are stressed, at admission. Since complete resection is providing for good outcome in these patients, it is important to evaluate their adrenal cortical function before surgery to avoid fatal complication.

P3-1111

## STUDY ON THYROTROPINEMIA & ITS ASSOCIATION WITH DYSLIPIDEMIA IN CHILDHOOD OBESITY

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**Objectives:** The association of subclinical hypothyroidism and obesity is still an ongoing debate. Only few studies were done on the association of subclinical hypothyroidism and dyslipidemia in overweight and obese children and have

shown varying results. Study objectives are 1) To compare serum TSH levels among overweight&obese children with age-matched controls 2) To find association between TSH, BMI and lipid profile in these children.

**Methods:** Retrospective case control study. Out of 134 overweight and obese children (cases) attending paediatric endocrinology clinic, 116 children had undergone investigations (TSH, FT4, Lipid profile). Age matched controls (n=30) were included for reference range of TSH and FT4 levels. Data on anthropometry was collected. All analysis was done using SPSS V 17.

**Results:** Among cases (n=116) 52% were males and 48% were females (p >0.05). Mean age of cases was 12.8±2.6 and controls was 13.0±2.1. Mean TSH level of cases was higher when compared to controls (4.4±0.89 Vs 1.9±0.2mIU/L; p <0.01). No significant difference observed for FT4 between cases and controls. Among cases 10.3% had subclinical hypothyroidism and 5.2% had overt hypothyroidism. Mean TSH levels of euthyroid, subclinical hypothyroid and overt hypothyroid cases were 2.59mIU/L, 6.74mIU/L and 34mIU/L respectively. No significant difference observed in FT4 levels between these groups. Mean T.Cholesterol and LDL levels were significantly higher in subclinical and overt hypothyroid group compared to euthyroid group. No significant correlation found between TSH levels, BMI and Lipid profile.

**Conclusions:**

- Overweight and obese children had significant elevated TSH levels compared to controls.
- Overweight and obese children with subclinical and overt hypothyroidism had higher mean cholesterol and LDL levels. But no significant correlation observed between TSH levels, BMI and Lipid profile.
- Large-scale data is needed to confirm our study findings.

P3-1112

**AN EASY WAY TO IDENTIFY OBESE CHILDREN AND ADOLESCENTS WITH METABOLIC RISK.**

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**Objectives:** Due to the increased prevalence of obesity in the paediatric population it is necessary to find new strategies to optimized diagnostic and therapeutic resources. Recently, triglyceride to HDL-C ratio (TG/C-HDL) is associated with a cardiometabolic risk in adults.

**Objetive:** Define if TG/C-HDL ratio is a good marker of insulin resistance in children and adolescents with obesity and its utility to identify individuals with preclinical signs of metabolic syndrome

**Methods:** Patients with overweight/ obesity defined by Orbegozo 2008 were included. Blood pressure and

anthropometric variables (height, weight, body mass index, waist circumference) were measured with standard methods. Sexual maturity was evaluated by Tanner staging. Abdominal ultrasound scan was performed to detect liver steatosis. . Biochemical data :fasting plasma glucose (FPG), 2h OGTT glucose, insulin, HOMA, lipid profile, and C-peptide were analyzed . Cut off point was considered >95<sup>th</sup> percentile of each variable . Metabolic syndrome was diagnosed according to criteria of Diabetes International Federation. SPSS.19 was used for Statistical analysis.

**Results:** Data from 110 patients (2-17 years of age ) were included, 60% of them girls y 55,4% prepubertal (Table1). The TG/C-HDL ratio  $\geq 2$  was a better predictor of metabolic syndrome ( sensitivity :100%; specificity 76.7 % ) than HOMA or insulin, without differences between sex and pubertal stage (p<0,0001). 35 patients show a TG/C-HDL ratio  $\geq 2$  of which 13 have all the criteria for metabolic syndrome. The rest of the patients had only one or more criteria or liver steatosis .

There is a statistical significant difference between TG/C-HDL ratio< or $\geq 2$  and BMI (p<0,0001), SD-BMI (p0,016), c-peptide (p<0,0001), FPG (p 0,035) and 2-h OGTT (p0,012). Patients with liver steatosis have significant higher values of this ratio (TG/C-HDL 3.35 vs TG/C-HDL 1.5 ; p00,027).

**Conclusions:** TG/C-HDL  $\geq 2$  might be an accessible, effective and methodological simple tool to detect the early stage of potential metabolic syndrome in overweight/obese children and adolescents at any age and pubertal stage, avoiding expensive resources.

Table1. Clinical and Biochemical Characteristics	Mean ( SD )	Range
Age ( years )	10,01 ( 3,01)	2,01 - 17
Body Mass Index (BMI)( Kg/m2)	27,77 ( 4,11)	19,4 - 36,98
SD BMI	4,40 ( 1,53 )	2 - 8,17
Waist Circumference( cm )	85,61 ( 11,08 )	60,0 - 113,0
TG/C-HDL	2,07 ( 1,9 )	0,28 - 13,03

P3-1113

**LEPTIN LEVELS IN HEALTHY PEPUBERAL CHILDREN WITH NORMAL WEIGHT, OVERWEIGHT AND OBESITY**

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**Objectives:** The aim of this study is to describe normal leptin levels (ELISA) in healthy prepuberal children with normal and over weight and compare values within sexes, ages, BMI and insulin levels. A cohort of obese prepuberal children was also analyzed within the same parameters

**Methods:** We included boys and girls that needed a lab workup for reassons not related to endocrine disorders. Informed consent was signed and we registered weight, height and Tanner stage of boys and girls. We also analized FSH, LH and testosterone (boys) or estradiol (girls). We separate within 2 groups: group 1:non- obese children (Zscore BMI <2) and group 2: obese children (Zscore

BMI >2). Leptin was determined by ELISA (DIA source Leptin-EASIA), and insulin with chemoluminescence (IMMULITE 2000 SIEMENS)

**Results:** A total of 83 children were studied, 49 in group 1, with normal or over weight (22 female and 27 male), and 34 in group 2, obese (18 female and 16 male). Median age was  $5.04 \pm 2.57$  in group 1 and  $7.47 \pm 1.58$  in group 2 ( $p < 0.01$ ). Median Zscore BMI was  $0.67 \pm 0.98$  and  $3.14 \pm 0.67$  in group 1 and 2 respectively. Median leptin levels in group 1 was  $1.09 \pm 0.85$  ng/ml (centile 5: 0.26 and centile 95: 2.98 ng/ml), being higher in girls than in boys (median leptin levels in girls  $1.43 \pm 0.97$  and boys  $0.76 \pm 0.58$ ),  $p = 0.01$ . In group 2, median leptin levels was  $7.9 \pm 4.43$  ng/ml, also being higher in girls (median  $9.01 \pm 4.8$  ng/ml) than boys (median  $6.56 \pm 3.6$  ng/ml), but this difference was not statistically significant. There was a positive correlation between Zscore BMI and leptin levels in both groups ( $R = 0.37$  in group 1 and  $R = 0.62$  in group 2) and between leptin and insulin levels ( $R = 0.35$  in group 1 and  $R = 0.45$  in group 2). Mean insulin levels in group 1 was  $4.07 \pm 4.7$  mIU/ml in group 1 and  $8.89 \pm 6.87$  in group 2, with no correlation between Zscore BMI and insulin levels in both groups.

**Conclusions:** Leptin levels are significantly associated to BMI in healthy and obese prepubertal children, being higher in girls. We found a positive correlation between leptin and insulin in both groups, as it is known that leptin and insulin has many different actions within the carbohydrate and lipid metabolism. It is possible that there are other factors that interact between leptin and insulin, making necessary more research in this area.

P3-1114

#### USEFULNESS OF VISCERAL FAT AREA MEASURED USING DUAL BIOELECTRICAL IMPEDANCE ANALYSIS FOR SCREENING OF METABOLIC DERANGEMENT IN OBESE CHILDREN AND ADOLESCENTS

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**Objectives:** It is very important that the evaluation of accumulation of visceral fat for management of childhood obesity. However this evaluation using CT scan is the problem of radiation, especially children. A dual bioelectrical impedance analysis (Dual BIA) instrument can determine visceral fat area (VFA) by measuring truncal impedance and surface impedance at the abdomen separately, each of which reflects truncal and subcutaneous adiposity, respectively. The aim of this study was to elucidate the usefulness of VFA measured using Dual BIA for screening of metabolic derangement in obese children and adolescents.

**Methods:** The ALT, HDL-C, TG, insulin, adiponectin, leptin levels in fasting serum, blood pressure (BP), VFA by Dual BIA in Japanese obese children (39 boys and 17 girls, at age 7 to

15) were measured. Metabolic derangements in obese children and adolescents were defined as  $BP \geq 125/70$  mmHg or  $TG \geq 120$  mg/dL or  $HDL-C < 40$  mg/dL or  $ALT > 30$  IU/L. Hyperinsulinemia was defined as insulin  $\geq 15$   $\mu$ U/mL. The relationship of VFA and each biomarker was analyzed by simple regression analyses. Usefulness of screening for obese with metabolic derangements using VFA was analyzed by ROC analysis.

**Results:** VFA had positive correlation with systolic BP, ALT, IRI, and leptin, inverse correlation with HDL-C and adiponectin. The threshold of VFA by ROC analysis for abnormal ALT or TG or HDL-C or systolic BP was  $45 \text{ cm}^2$  and that for hyperinsulinemia ( $\geq 15 \mu\text{U/mL}$ ) was  $48 \text{ cm}^2$ .

**Conclusions:** VFA measured using Dual BIA was useful for screening of the metabolic derangements associated with obese children and adolescents.

P3-1115

#### THE PROCESSING SPEED OF TASTINESS AND HEALTHINESS OF FOOD DETERMINES DIETARY SELF-CONTROL IN CHILDREN

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**Objectives:** Children live in an obesogenic environment and have ready access to high-calorie foods. A child's ability to control food desire could contribute to whether he or she will become obese, and understanding food-seeking behavior could therefore guide obesity prevention in children. Adults process taste information significantly earlier than health, which appreciably impairs their dietary self-control. However, it is not known how the ability to process taste and health information influences dietary choice in children. Our objective is to study food choice in obese and lean children, by examining the processing speed of food attributes (tastiness, healthiness) and dietary self-control.

**Methods:** 29 children [ $10.4 \pm 1.3$  y, 38% male, 48% obese (BMI  $\geq 95^{\text{th}}$ ), 52% healthy-weight (BMI  $< 85^{\text{th}}$ )] performed a neurobehavioral food choice task with computer mouse-tracking (Matlab software). Subjects rated 60 food cues (30 high-calorie, 30 low-calorie) for tastiness, healthiness, and liking. 100 food choice pairs were generated based on individual ratings for taste and health, and the child chose the item they wanted to eat using a mouse. One of the food choices was actualized at the end of the task. Mouse-trajectory analyses pinpointed when taste and health were integrated into the choice process. Self-control was deemed positive when the healthier food was chosen.

**Results:** In lean children, tastiness and healthiness were both predictors of the food choice trajectory, but taste was processed 228 ms earlier than health during choice ( $p < 0.05$ ). 33-77% of individual differences in their self-control were explained by the relative difference in processing speed of

taste and health. In obese children, tastiness became significant later in the food choice process than in lean, and healthiness was not a predictor. The processing speed of tastiness explained up to 54% of self-control (lean  $R^2 = 0.45$ ,  $p < 0.01$ ; obese  $R^2 = 0.54$ ,  $p < 0.01$ ).

**Conclusions:** Both lean and obese children exhibit a significant delay between the processing of taste and health information during dietary decision-making. Processing speed, especially in regards to tastiness, can be a strong determinant as to whether a child is successful in exerting dietary self-control.

P3-1116

#### **SIGNS OF THE METABOLIC SYNDROME ARE ALREADY PRESENT DURING PRE-SCHOOL YEARS**

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**Objectives:** The metabolic syndrome (MetS) represents a clustering of risk factors for cardiovascular disease. Our aim was to investigate whether metabolic alterations due to overweight and obesity are present in pre-school children.

**Methods:** A population-based Swedish cohort study was conducted at 6.5 years, included 188 healthy children, born at full-term. The cohort was studied with metabolic variables (high waist circumference, insulin-resistance, high triglycerides, low HDL and high blood pressure) the year before school age (6.6 (6.5-6.9) years of age). The cohort was subdivided in 2 groups based on cut-offs of BMI at 6.5 years of age: children with overweight or obesity ( $n=35$ ) and non-overweight ( $n=153$ ) according to Cole et al. For insulin resistance (IR) calculations we used HOMA-IR index  $\geq 90^{\text{th}}$  percentile (Peplies J et al. 2014). MetS were defined according to Ahrens et al (2014). ANOVA, *chi*-2 test or Fishers exact test were used for comparisons between groups.

**Results:** In total 35 (19 %) of the children had overweight or obesity. Almost 50% ( $N=13$ ) of the children with overweight and obesity were found to be insulin-resistant, as compared to 10% in the non-overweight group ( $p<0.01$ ). Only a few children had dyslipidemia at 6.5 years of age (defined as TG above the  $90^{\text{th}}$  and HDL under the  $10^{\text{th}}$  percentile for age and gender), although already at this young age there were a significant group differences with lower HDL with increasing BMI ( $p=0.025$ ). In total, 7 children had blood pressure (BP) compared to adult prediabetic values (systolic BP  $\geq 120$  mmHG and diastolic BP  $\geq 80$  mmHg) predominantly by children with overweight or obesity, (4 out of 7 children,  $p < 0.001$ ). There were 58 of all children ( $N=31\%$ ) who had a single metabolic risk factor. In total, 29 children had  $\geq 2$  risk factors, 60 % ( $N=18$ ) of those had overweight or obesity. Five children had  $\geq 3$  metabolic risk factors, all of those had overweight or obesity.

**Conclusions:** Already at pre-school age there is an abnormal metabolic profile in a substantial percentage of children influencing the risk to develop cardiovascular disease. This emphasizes the need to identify risk factors for MetS.

P3-1117

#### **IMPROVED EMOTIONAL AND BEHAVIOURAL STATUS IN MORBIDLY OBESE ADOLESCENTS FOLLOWING REVERSIBLE ENDOSCOPIC BARIATRIC PROCEDURE – DUODENAL-JEJUNAL BYPASS LINER (DJBL)**

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**Objectives:** Psychological comorbidities are an important factor in the management of obese adolescents. Study's aim was to determine psychosocial functioning before and at 12 months following reversible endoscopic bariatric procedure - DJBL.

**Methods:** Subject's characteristics are presented in Table 1. Emotional and behavioural problems were assessed by Youth Self-Report (YSR), body image and eating disorders by Multidimensional Body-Self Relations Questionnaire-Appearance Scales (MBSRQ-AS) and Eating Disorder Examination Questionnaire (EDE-Q 6.0). Impact of obesity on psychosocial functioning was assessed by Obesity-related Problems scale (SOS-OP). Wilcoxon's signed-rank test and Mann-Whitney U test were used for statistical analysis.

**Results:** As shown in Table 1 DJBL group didn't differ to controls in physical or psychological characteristics at baseline. BMI and WC decreased in DJBL group and insulin sensitivity improved at 12 months. Emotional and behavioural problems improved, while appearance orientation increased.

**Conclusions:** In addition to reduction in body weight and improved metabolic status in morbidly obese adolescents that underwent DJBL procedure, an improvement in emotional and behavioural problems was reported; especially in regard to perceived attention problems and internalizing symptoms. These changes are considered favourable for continued conservative management following DJBL removal.

P3-1118

#### **INCREASE OF BODY MASS INDEX (BMI) FROM AGE 1.5 TO 3 YEARS AUGMENTS THE DEGREE OF INSULIN RESISTANCE CORRESPONDING TO BMI AT 12 YEARS OF AGE**

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**Objectives:** Excess body fat (adiposity) is an important independent risk factor for development of insulin resistance in adults and children. Some obese children do not develop metabolic comorbidities of obesity, whereas some children are more metabolically sensitive to adiposity. The mechanism underlying this phenotype is not explained by adiposity levels, although metabolic sensitivity to adiposity may differ between ethnic groups. To interpret this mechanism, we

hypothesized that an increase in body mass index (BMI) from about 1.5 to 3 years old, a period normally characterized by a decreased or stable BMI, may augment insulin resistance corresponding to BMI at adolescent age. To elucidate the relationship between homeostatic model assessment of insulin resistance (HOMA-IR) and BMI levels at 12 years of age in groups based on an increase or decrease in BMI from age 1.5 to 3 years.

**Methods:** All 192 children (101 boys and 91 girls) in a birth cohort in Japan were enrolled in the study. At 12 years of age, fasting blood samples were collected for determination of plasma glucose and insulin. Insulin resistance was determined by calculating HOMA-IR as fasting glucose (mmol/l)  $\times$  fasting insulin (mIU/l) / 22.5. The participants were divided into groups by gender and based on an increase, stable or decrease in BMI from age 1.5 to 3 years.

**Results:** Regression coefficient of log-transformed HOMA-IR per log-transformed BMI in groups based on an increase, stable or decrease in BMI from age 1.5 to 3 years were 0.29, 0.33 and 0.23, respectively, in boys and 0.30, 0.23 and -0.32 in girls. The augmented degree of log-transformed HOMA-IR per log-transformed BMI was significantly higher in girls who had a BMI increase from 1.5 to 3 years compared to those who showed a decrease in BMI or stable BMI.

**Conclusions:** This study suggests that children, and particularly girls, who show an increase of BMI from 1.5 to 3 years, a period normally characterized by a decreased or stable BMI, are more prone to developing insulin resistance at 12 years of age.

P3-1119

#### ONE-CARBON METABOLITE LEVELS IN BREAST MILK AND INFANT POSTNATAL GROWTH

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**Objectives:** Adverse perinatal events, including maternal overweight and rapid growth, increase long-term risk for obesity and metabolic disease. Early nutrition is a crucial factor in determining infant postnatal growth. However, how specific breast milk analytes modulate growth and determine long-term risk remains unknown. Here, we quantified one-carbon metabolism-related analytes in breast milk, and determined potential associations with maternal obesity and infant postnatal growth.

**Methods:** We studied 34 exclusively breastfeeding mother-infant dyads across a range of maternal BMI (18.5-47.2 kg/m<sup>2</sup>) at 1 month after birth. Our main outcome for infant

growth was weight-for-length z-score (WLZ), adjusted for birth WLZ, gestational age, maternal age, and pre-pregnancy BMI. We used a mass spectrometry-based approach to quantify choline, betaine, methionine, s-adenosylmethionine, s-adenosylhomocysteine, cystathionine, 5-methyltetrahydrofolate, and homocysteine in milk, and applied multivariate regression to determine potential associations.

**Results:** Maternal overweight or obesity (OWO) resulted in higher infant WLZ at 1 month compared to normal weight (NW) mothers. One-carbon metabolites were not associated with maternal pre-pregnancy BMI. Among all metabolites, betaine was significantly correlated to infant WLZ ( $\beta$ std=-0.37,  $p=0.041$ ). This correlation was particularly strong in infants from OWO mothers ( $n=19$ ,  $\beta$ std=-0.80,  $p<0.001$ ), while no association was observed in NW mothers ( $n=15$ ,  $\beta$ std=0.06,  $p=0.908$ ). Milk betaine content also correlated to other growth parameters in infants from OWO mothers, including ponderal index ( $\beta$ std=-0.75,  $p=0.002$ ), and no correlation was observed to head circumference or body composition measures.

**Conclusions:** Here, we performed the first comprehensive profiling of one-carbon metabolites in human breast milk, and found a significant association between low betaine levels and infant accelerated early growth. Given that rapid postnatal growth is a strong and potentially modifiable risk factor for future obesity, our results suggest a link between low milk betaine content and long-term metabolic risk. Further studies are warranted to assess whether milk betaine plays a role in shaping growth and determining future risk.

P3-1120

#### CHILDREN WITH NORMAL BODY MASS INDEX MAY HAVE AN INCREASED WAIST TO HEIGHT RATIO

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**Objectives:** To investigate the association between body mass index (BMI) and waist to height ratio (WHtR) in children from a Swedish birth cohort study.

**Methods:** The setting was a population-based longitudinal birth cohort, The Halland Health and Growth Study (H<sup>2</sup>GS) comprising 1541 full term children (750 boys and 791 girls) followed prospectively with measurements of weight, height and waist circumference. Children were classified as having normal-/underweight or overweight/obesity at 60 months of age according to BMI cut-off values by IOTF, and as having normal,  $\leq -1$  standard deviation (SD) or  $\geq +1$  SD in WHtR according to Swedish reference values. Chi-Square tests were made for group comparisons between children classified according to BMI and to WHtR respectively.

**Results:** Overweight/obesity according to BMI was to a high proportion associated with a high WHtR, where 101/172 (59%;  $p<0.001$ ) children with overweight/obesity according to BMI had a high ( $\geq +1$  SD) WHtR (Table 1). However 118/1369 (9%;  $p<0.001$ ) of children with normal-/underweight according to BMI also had a high WHtR, representing 54% of all children with a high WHtR.

**Conclusions:** Among the children with increased WHtR approximately half of them had a BMI representing normal-/underweight. Several studies have shown that an increased WHtR can indicate a potential risk of health problems associated with waist adiposity like the metabolic syndrome, and cardiovascular disease, and children with such risks may be missed if they are only followed with BMI.

**Table 1** Association between body mass index (BMI) and waist to height ratio (WHtR) in children classified at 60 months as having normal-/underweight or overweight/obesity according to BMI cut-off values by IOTF, and as having normal,  $\leq -1$  standard deviation (SD) or  $\geq +1$  SD in WHtR according to Swedish reference values.

N=1541	WHtR $\leq -1$ SD	WHtR normal	WHtR $\geq +1$ SD
BMI normal-/underweight	793 (58%)	458 (34%)	118 (9%)
BMI overweight/obesity	12 (7%)	59 (34%)	101 (59%)

P3-1121

**DISSECTING FACTORS INFLUENCING POSTNATAL GROWTH DURING EARLY INFANCY: A PROSPECTIVE COHORT STUDY OF INFANTS IN SHANGHAI**

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**Objectives:** It has been reported that parent's anthropometric parameters pre- or peri-pregnant period could affect fetal, infancy, childhood growth pattern; however the research results are not completely consistent. We aimed to evaluate the associations of offspring early growth using successive data from birth to 24 months with pre-pregnancy BMI, weight, and height of mother and father, maternal gestational weight gain, and gestational week.

**Methods:** After exclusion of cases that did not fulfill the inclusion criteria or were not willing to participate, we finally included 3475 pregnant mother and 3475babies. Weight and length of these infants were examined at birth and at ages 1, 4, 6, 9, 12, 18, and 24 months respectively. Both paternal height, weight and maternal pre-pregnancy weight, height were measured at the pre-pregnancy clinic visit. Maternal gestational weight was measured at each pregnancy clinic visit.

**Results:** Parental pre-pregnant BMI played the most important role in their offspring's body size after 6 months age. The total gestational weight gaining during pregnancy of the mother steadily explains nearly a quarter ( $25\pm 5\%$ )of the relative importance of children's weight. The effect of gestational week on the baby's body size disappeared soon after birth. However, the importance of gestational week declined over time whereas height of the parent became the determination factors for the children's height after 6 months

of age and the weight of the parents is the major factor influencing the children's weight after 6 months of age.  
**Conclusions:** Our study showed that there exists a strong association between parental pre-pregnancy BMI and the child's body size after 6 months. Intervention programs of children's overweight or obesity seem to be started from the pre-pregnancy period and parent's healthy life style will reduce prevalence of children's obesity.

P3-1122

**DOSAGE OF THE TYPE 1 INTERCELLULAR ADHESION MOLECULE (ICAM-1) AND CORRELATION WITH CARDIOVASCULAR RISK INDICATORS IN OVERWEIGHT ADOLESCENTS**

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**Objectives:** To evaluate if there is a direct correlation between the intercellular adhesion molecule type 1 (sICAM-1) and cardiovascular (CV) risk factors.

**Methods:** A cross-sectional study was conducted in a sample of 61 overweight or obese adolescents (42 girls and 19 boys). We evaluated anthropometric measurements, lipid profile, oral glucose tolerance test (oGTT), carotid íntima media mean and brachial artery blood flow velocity were performed by ultrasound and dosages of sICAM-1by ELISA.

**Results:** Patients had a mean (SD) chronological age of 0.7 years (2.4) and BMI expressed in SDS (SD) of 2.6 (0.6). No patient was diagnose with diabetes. The studied population presented a mean (SD) of the carotid íntima media thickness of 0.5 cm (0.01), brachial artery flow velocity (SD) of 105.7 (36.9), serum concentration of sICAM-1 (SD) of 218ng/dL (356.9), insulin sum (SD) of 484 (250). There was no correlation between the values os sICAM-1 and non-HDL cholesterol, brachial artery blood flow velocity and sum of insulin. We found a negative correlation between the brachial artery blood flow velocity and sum of insulin (resistance = - 0.274;  $p = 0.034$ ).

**Conclusions:** In this group, the patients presented several elevated values of CVS risk factors, such as increased BMI expressed in SDS, the carotid íntima media thickness, non-HDL cholesterol and sum of insulin, but we did not find any correlation between those and the values of sICAM-1. However, the negative correlation between sum of insulin and brachial artery blood flow velocity could suggest the early onset of endothelial dysfunction.



METABOLIC COMORBIDITIES IN 1300 OBESE CHILDREN AND ADOLESCENTS: INFLUENCE OF RACE, BODY COMPOSITION AND ADIPOKINE LEVELS

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**Objectives:** Ethnic background and socioeconomic factors are involved in the development of childhood obesity and its comorbidities, which are also influenced by adipokine production and body fat content and distribution. Our aim was to study the metabolic features, serum adipokine levels and body fat content and distribution of 1300 obese children, analyzing the influence of race.

**Methods:** Whole cohort: We determined BMI, glycemia, insulinemia, HbA1c, lipid profile, uric acid and calculated HOMA and WBISI in 1300 patients (986 Caucasians/247 Latinos/67 other).

Extended study: In 150 patients (50% Caucasians/Latinos; 50 prepubertal/100 pubertal; 50%/sex) liver ultrasonography, DXA [Hologic QDR4500W] and abdominal MRI [Phillips® Achieva1.5T] were performed, calculating the trunk/lower limb (T/LLfr; DXA) and visceral to subcutaneous abdominal fat ratio (Vis/SQfr; MRI). Serum leptin, soluble leptin receptor (sOBr) and total (T) and high molecular weight (HMW) adiponectin (ADP) levels were quantified.

**Results:** There were no inter-ethnic differences in BMI-SDS, mean fasting glucose or the prevalence of T2DM, IGT and IFG, which were 2 (0.1%), 114 (9%) and 82 (6.5%), respectively. Latinos (both prepubertal and pubertal) had higher triglyceride and insulin levels and HOMA, similar WBISI, and lower HDL and uricemia than Caucasians (Table).

T/LLfr was higher in pubertal Latino females than in Caucasians (0.21±0.07 vs. 0.16±0.05, p<0.05) and the T/LLfr was higher in pubertal Latinos in both sexes (p<0.01). T/LLfr correlated positively with HOMA and triglycerides (p<0.05 and <0.01, respectively) and negatively with HDL and T- and HMW-ADP (p<0.05), but not with leptin or sOBr.

Liver steatosis (LS) prevalence was higher in Latinos (χ2: 8.69; p<0.01), both prepubertal (33.3% vs. 16.0%) and pubertal (31.4% vs. 8.0%) patients. Patients with LS had higher T/LLfr(p<0.05), HOMA and triglyceride levels (p<0.05) and lower WBISI (p<0.01) and HDL (p<0.05) than those without LS.

**Conclusions:** Latino obese children show a higher trend towards central fat distribution than Caucasians, associating

higher insulin resistance, dyslipidemia and prevalence of liver steatosis.

PLEASE SEE TABLE ON FOLLOWING PAGE

	Total cohort (n=1300)		p value	Caucasians (n=986)		Latinos (n=247)		p value (inter-ethnic)	
	Prepubertal	Pubertal		Prepubertal	Pubertal	Prepubertal	Pubertal	Prepubertal	Pubertal
n	603 (53.3%)	607 (46.7%)	NS	525 (53.2%)	461 (46.8%)	130 (52.6%)	117 (47.4%)	NS	NS
Sex	F 263 (38.0%) M 340 (62.0%)	F 351 (57.8%) M 256 (42.2%)	p<0.001	F 192 (36.4%) M 333 (63.6%)	F 271 (58.8%) M 190 (41.2%)	F 56 (43.1%) M 74 (56.9%)	F 66 (56.4%) M 51 (43.6%)	NS	NS
Age (years)	8.26 ± 2.54	12.98 ± 1.97	p<0.001	8.47 ± 2.38	13.10 ± 1.94	7.66 ± 2.82	12.93 ± 2.05	<0.05	<0.01
BMI-SDS	4.21 ± 1.52	3.77 ± 1.43	p<0.001	4.14 ± 1.42	3.71 ± 1.36	4.36 ± 1.64	3.81 ± 1.39	NS	NS
Glucose (mg/dl)	91.65 ± 7.00	93.44 ± 6.70	p<0.001	91.34 ± 7.08	93.27 ± 6.70	92.83 ± 6.58	94.17 ± 6.85	NS	NS
HbA1c (%)	5.45 ± 0.34	5.47 ± 0.30	NS	5.45 ± 0.34	5.45 ± 0.30	5.43 ± 0.34	5.53 ± 0.28	NS	NS
Insulin (μU/ml)	11.78 ± 6.94	17.19 ± 10.74	p<0.001	11.47 ± 6.37	16.51 ± 10.44	13.01 ± 8.46	18.88 ± 11.39	<0.05	<0.05
HOMA	2.70 ± 1.05	4.01 ± 2.66	p<0.001	2.63 ± 1.56	3.85 ± 2.63	2.99 ± 1.86	4.43 ± 2.67	<0.05	<0.05
WBISI	3.97 ± 2.07	3.11 ± 1.68	p<0.001	4.10 ± 2.18	3.17 ± 1.69	3.81 ± 1.62	3.10 ± 1.70	NS	NS
LDL-C (mg/dl)	99.72 ± 25.31	93.36 ± 24.27	p<0.001	99.67 ± 25.03	93.56 ± 24.42	101.97 ± 27.58	93.16 ± 24.30	NS	NS
HDL-C (mg/dl)	47.33 ± 11.10	43.93 ± 9.84	p<0.001	47.83 ± 10.85	44.50 ± 9.89	45.34 ± 11.56	40.94 ± 9.51	<0.01	<0.001
Triglycerides (mg/dl)	74.64 ± 44.34	65.63 ± 53.60	p<0.001	72.75 ± 43.51	62.69 ± 53.78	82.61 ± 45.90	97.2 ± 54.40	<0.01	<0.01
Uric acid (mg/dl)	4.47 ± 0.92	5.28 ± 1.31	p<0.001	4.51 ± 0.89	5.30 ± 1.05	4.30 ± 0.92	5.11 ± 1.12	<0.05	<0.05

Table: Demographic, anthropometric and metabolic characterization of the entire cohort according to their ethnic background, sex, and pubertal status, including inter-ethnic comparisons. Abbreviations: BMI: Body mass index; F: Female; M: Male; NS: Non significant.

--EFFECTIVENESS, SAFETY AND METABOLIC EFFECTS OF CARBOHYDRATE RESTRICTION IN THE MANAGEMENT OF OBESITY IN ADOLESCENTS AFTER 1 YEAR FOLLOW-UP

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**Objectives:** Changes in diet macronutrient proportions could be useful in the management of obese adolescents. Carbohydrate restriction (CH-R) could induce a shift in substrate use, determining changes in body composition and metabolism. The aim of this study was to evaluate the effect of CH-R on body composition, CH and lipid metabolism in obese adolescents.

**Methods:** We recruited 111 obese Caucasian (+4.58±1.84 BMI-SDS) adolescents (14.50±1.76 years; 64% females), comparing CH-R diet (CH=10% of daily intake 4 months; 30% 4th to 8th month and 52% later; n=55) vs. no CH restriction diet (CH-N) [52%], n=56), after 6 (total n=94) and 12 months (total n=40). BMI, body composition (bioimpedanciometry Tanita® BC-420MA), glycemia, insulinemia, lipid profile, uric acid and 25-OH-Vitamin-D were studied.

**Results:** Groups were comparable at baseline. At 6M: both groups reduced their BMI-SDS and fat mass (p<0.001), with CH-R inducing a greater fat mass reduction (p<0.05) and a higher rate of high weight loss ([HWL, >10% weight loss] 57.8 vs. 18.4%; χ2 15.59; p<0.001) with a decrease in body water (p<0.01) and estimated muscle mass (p<0.001) absent in CH-N. HOMA improved only in CH-R (p<0.05), whereas vitamin-D increased in both groups (p<0.001), without intra- or intergroup differences in lipid profile or uric acid levels, but with transient hyperuricemia at 3M in CH-R (Table).

**Between 6 and 12M:** both groups partially regained BMI (p<0.05), with a parallel increase in muscle mass and body water, but only CH-N increased body fat (p<0.05). At 12M, HWLs were 45% in CH-R vs. 20% in CH-N (χ2 2.85; p=0.09). HOMA decreased in CH-N (p<0.05), resulting in no difference in HOMA between groups at 12M. A decrease in LDL/HDL

ratio was observed only in **CH-R** ( $p<0.05$ ), with no change in triglyceride/HDL ratio or uric acid. Vitamin-D levels returned to baseline values in both groups (**Table**).

**Conclusions:** 1) Diet **CH-R** results in a greater fat mass reduction in obese adolescents after 6 and 12 months of treatment and is not associated to a higher rate of weight regain in the first year.

2) Improvement in insulin resistance is an early event under **CH-R** and delayed under **CH-N**, although achieved at 12M in a similar fashion with both dietary approaches.

	CH-R diet Intragroup significance	CH-N diet Intragroup significance	Intergroup Significance
BMI (SDS) B to 6M 6 to 12M	-1.74 ± 1.03; $p < 0.001$ +0.54 ± 0.58; $p < 0.05$	-1.03 ± 0.95; $p < 0.001$ +0.34 ± 0.63; $p < 0.05$	$p < 0.001$ NS
FAT MASS (Kg) B to 6M 6 to 12M	-10.03 ± 5.77; $p < 0.001$ -0.22 ± 10.46; NS	-5.00 ± 4.38; $p < 0.001$ +1.73 ± 4.20; $p < 0.05$	$p < 0.05$ $p < 0.05$
MUSCLE MASS (Kg) B to 6M 6 to 12M	-3.57 ± 10.21; $p < 0.05$ +0.97 ± 1.33; $p < 0.01$	+0.42 ± 6.05; NS +1.27 ± 1.69; $p < 0.01$	$p < 0.001$ NS
BODY WATER (Kg) B to 6M 6 to 12M	-1.20 ± 2.92; $p < 0.05$ +0.73 ± 1.05; $p < 0.05$	-0.30 ± 1.52; NS +0.85 ± 1.38; $p < 0.05$	$p < 0.01$ NS
HOMA B to 6M 6 to 12M	-0.99 ± 1.94; $p < 0.05$ -0.13 ± 1.16; NS	-0.51 ± 2.06; NS -0.91 ± 1.80; $p < 0.05$	NS NS
URIC ACID (mg/dl) B to 6M 6 to 12M	-0.22 ± 0.83; NS +0.20 ± 0.99; NS	-0.23 ± 0.78; NS -0.18 ± 0.52; NS	NS NS
25OH-vitaminD (ng/ml) B to 6M 6 to 12M	+4.10 ± 9.28; $p < 0.001$ -2.98 ± 12.27; NS	+4.47 ± 8.45; $p < 0.001$ -4.58 ± 9.05; $p < 0.05$	NS NS

**TABLE:** Changes (delta) in the studied parameters between baseline (B) and 6 months (B to 6M; n=94) and between 6 and months (6 to 12M; n=40). Intra- and intergroup significance level for the changes observed in all parameters in the defined time interval are shown. **Abbreviations:** BMI: Body mass index; **CH-N:** No carbohydrate restriction; **CH-R:** Carbohydrate restriction; **N:** Non significant.

P3-1125

**BIRTH WEIGHT AND METABOLIC SYNDROME IN A GROUP OF OVERWEIGHT AND OBESE CHILDREN IN NORTHEAST MEXICO**

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**Objectives:** Determine the prevalence of low birth weight and high birth weight in 2-16 year old overweight and obese children with and without the metabolic syndrome in northeast Mexico

**Methods:** We conducted a retrospective study from patients of an obesity clinic in a hospital in Monterrey, Mexico from October 2013 to April 2016. We included children between ages 2–16 years with diagnosis of obesity or overweight. Exclusion criteria included patients with incomplete anthropometric or laboratory data, extreme low birth weight (LBW) ( Birth weight information was reported in the first consultation. Weight was recorded in kilograms and height recorded in centimeters. BMI was calculated (weight (Kg) /Height(m<sup>2</sup>)). Abdominal circumference was measured and blood samples were retrieved after 12-hour fasting by laboratory experts within the hospital. Low birth weight (LBW) was defined as 4000 grams for newborns. MS was defined as 3 or more of the following criteria: Triglycerides

≥110 mg/dl, low HDL-c Boys≤40 mg/dl, girls ≤40 mg/dL, abdominal obesity by waist circumference ≥p90, hypertension ≥p90 for age, gender and fasting glucose ≥100 mg/dl according to ADA criteria or HOMA ≥2.5.

**Results:** From the 624 patients we excluded 50 patients, and 574 were included. MS was identified in 330 (57.5%) patients. LBW was reported in 33 patients, 5.7% of the total population. In the MS group 20 (6.1%) patients reported LBW compared with 13 (5.3%) patients in the group without the MS. High birth weight was reported in 74 patients, 12.8% of the total population. In the MS group 45 (13.6%) patients had high birth weight compared with 29 (11.9%) patients in the group without the MS.

**Conclusions:** A higher prevalence of MS was reported in this study group compared to other reports. Although a higher prevalence of high birth weight than LBW was found; patients with the MS had higher prevalence of both than patients without the MS.

P3-1126

**TITLE: DIETARY THERAPY COMPLIANCE OBESE CHILDREN IS IMPROVED BY USE OF SPECIALLY DESIGNED WEBSITE.**  
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**Objectives:** Success in changing lifestyle is the first step in preventing and reversing metabolic syndrome in youth. In tightly controlled settings, a low-fructose diet improves insulin resistance and hepatic steatosis. Whether fructose-restriction can be effective in the real-world setting remains unclear.

**Purpose:** To determine whether provision of a tailored, interactive website enhances 6-month compliance with low-fructose (LF) and standard healthy diets (SH) in obese adolescents.

**Methods:** Adolescents ages 11-17 years with BMI >95th%tile, were stratified by sex and ethnicity and randomized to intervention (LF) or control (SH) diets. LF diet: limit fructose to < 25 grams/day. SH diet: standard healthy diet. Adolescents and adult guardians were instructed to log in weekly to a healthy eating website to view daily dietary tips, recipes, blog entries, discussion groups and LF and SH diet resources and to to complete a food frequency questionnaire. A registered dietitian assessed compliance at baseline and 6 months using 24-hour recall. Primary outcome measure was percentage of subjects who met dietary goals. Web usage was measured by page hits for each login over the course of the study.

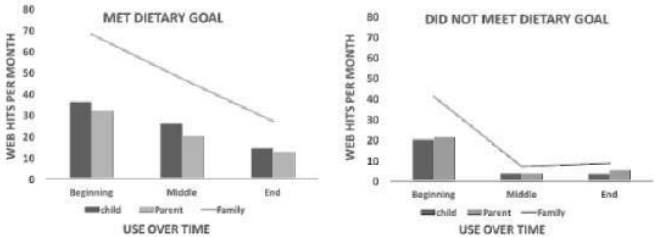
**Results:** Twenty subjects (8 LF, 12 SH) completed the study. No significant difference in BMI change between LF and SH. The LF group demonstrated both improved dietary compliance and higher overall web use (Table 1). Website usage was higher in those who met dietary goals, but decreased over time. (Fig 1a, 1b).

**Conclusions:** Provision and usage of an interactive healthy eating website improved long-term compliance with dietary recommendations, particularly when subjects who were asked to follow a difficult intervention such a LF diet. However, while the LF group had a higher compliance rate, this group also had higher drop out. Family participation had significant impact on both the web use as well as compliance. These findings suggest that provision of an interactive website may be a helpful addition to institution of long-term lifestyle-altering diets in adolescents.

**Acknowledgements:** NIH (K12 HD055894, T32 DK077586 )

Characteristics and Web Use in Study Subjects		
	Control	Intervention
Age (years)	14.3 (11.5-16.5)	14.2 (11.7-16.7)
Sex (% Female)	66%	88%
Average change in BMI-Z score over 6 months	-0.1	-0.1
Met Dietary Goal (%)	58%	75%
Average Child Total Web Use (# Hits Over 6 months)	97.1	270.1
Average Parent Total Web Use (# Hits Over 6 months)	87.6	191.6

**Table 1:** There was no statistical difference in age, BMI change or overall web use between intervention and control groups. Sex was statistically different between groups.



**Figure 1:** In both the intervention and control groups, average website use by individual subjects, parents and combined (family) was higher compared to website use in subjects that did not meet their dietary goal.

P3-1127

**RELATION BETWEEN SCHOOL DIET AND OBESITY IN PRIMARY SCHOOL CHILDREN**

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**Objectives:** Childhood obesity is a public health problem in the country, the school meal could be one of the factors that lead to this disease. this study was designed to verify the incidence of obesity using the body mass index (BMI) in primary school children (6 to 10 years old) and to assess the menus of two schools, one public and one private, using as base the guidelines for the age group in the manual of the Brazilian Ministry of Education.

**Methods:** Cohort study, quantitative, including students of two schools in the city of Cascavel – PR, one public and the other a private school, randomly chosen. All participants had their weight and size measured in order to calculate BMI. The nutritional diagnosis was established according to the categories of the World Health Organization (WHO) in underweight, eutrophic, overweight and obese child. Using the monthly menu supplied by each school, the nutritional composition of the everyday food was calculated according to the “Brazilian Food Database”, and then an average was made with each nutritional content of the 4 weeks on the

menu. These values were compared with those recommended by the National Education Development Fund (“FNDE”).

**Results:** A total of 139 students were assessed, 27 from a private school and 112 from a public school, with ages ranging from 6 to 10 years old, with a balanced gender composition (71 males and 68 females). According to the results, 39.3% of the school children were overweight or obese in the public school, and 29.6% in the private school. Comparing the nutritional status of both schools, statistically significant differences (x = 1.48; p = 0.477) were not identified between them. Regarding the school meal menu, both public and private schools provided meals with nutritional values above the recommended by FNDE.

**Conclusions:** there were high percentage figures of overweight and obese school children, regardless of school type, and above what was expected. Both schools presented high calorie level menus, carbohydrates, proteins and lipids above the recommended level and an amount of fibers lower than the stipulated by the FNDE, which can make a substantial contribution to the high overweight and obesity levels found in this population.

P3-1128

**INCREASED LEVELS OF THE APOPTOSIS MARKER APO-1/FAS IN OBESE CHILDREN AND ADOLESCENTS WITH FURTHER ELEVATIONS DURING AN ORAL GLUCOSE TOLERANCE TEST (OGTT)**

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**Objectives:** Introduction: Apo-1/Fas(CD95), a glycosylated surface protein which belongs to TNF/NGF receptor’s superfamily causes rapid induction of apoptosis in cells with increased sensitivity. Elevated Fas expression in adult obese and diabetic patients correlates with systemic and skeletal muscle insulin resistance and endothelial dysfunction. The Apo1/Fas pathway seems to contribute to insulin resistance via changes in the secretion pattern of cytokines

Objective and hypotheses: To investigate the correlation of apoptotic marker Apo-1/Fas with biochemical measurements during an OGTT in obese and lean children

**Methods:** 50 Greek children (7-16 yrs. old) participated in the study. 30% of the children were lean (BMI<85%) and 70% were obese (BMI>95%). At baseline, lipid profiles and IGF-1 were measured. During the OGTT, glucose, insulin and Apo-

1/Fas (measured by ELISA) were calculated at time points: 0', 30', 60', 90', 120', and 180'.

**Results:** The obese children and adolescents had a positive correlation between Apo-1/Fas and insulin levels at  $t=0'$  ( $p=0.016$ ) and  $t=120'$  ( $p=0.035$ ) with a progressive increase of Apo1/Fas during the OGTT [maximal increase (167%) at  $t=90'$ ]. In contrast, in the lean children and adolescents a progressive decrease of the Apo-1/Fas was found during the OGTT [maximal decrease (28%) at  $t=90'$ ]. Additionally, in the obese children and adolescents, Apo-1/Fas was positively correlated with triglyceride ( $p=0.007$ ) and IGF-1 ( $p=0.023$ ) levels and negatively correlated with HDL cholesterol levels ( $p=0.040$ ).

**Conclusions:** Our study suggests that Apo-1/Fas levels rise with increasing insulin and triglyceride and IGF-I levels in obese children and adolescents, possibly putting them at a greater risk for cell apoptosis and endothelial dysfunction. It is of interest that even short-term elevations in insulin, as seen during the OGTT test, cause an increase in Apo-1/Fas levels. More studies need to be conducted to see if short-term Apo-1/Fas level increases in obese children on high glycemic index food diets may further increase their risk for metabolic disorders.

P3-1129

#### ASSOCIATIONS BETWEEN MEASURES OF ADIPOSITY AND CARDIAC AUTONOMIC FUNCTION IN CHILDREN WITH A FAMILY HISTORY OF OBESITY (QUALITY COHORT)

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**Objectives:** Visceral adiposity is associated with decreased heart rate variability (HRV) in adults and adolescents, but studies are limited in pre-pubertal children. We examined the association between adiposity indices and HRV in a large sample of children, adjusting for potential confounders, including lifestyle habits and fitness.

**Methods:** Data are from the QUALITY cohort (630 children aged 8-10 years with a parental history of obesity). Adiposity indices include: waist-to-height ratio, obesity (BMI percentile  $>97.7^{\text{th}}$ ile) and % fat mass (Dual energy X-ray absorptiometry). HRV indices were derived from Holter ECG recordings: SDNN (standard deviation normal to normal), RMSSD (root mean square of the successive differences), PNN50 (percentage of successive normal sinus RR intervals/50 ms), ln transformed Low (ln-LF) and High frequency (ln-HF), and LF/HF ratio. Confounders include: age, sex, Tanner stage (assessed by nurse), moderate-to-vigorous

physical activity (minutes; accelerometry), self-reported screen time (minutes), and fitness (peak oxygen consumption). Multivariable linear regression models adjusted for all covariates.

**Results:** Obesity was associated with lower ln-HF (back-transformed B [95%CI] =0.79 [0.63, 0.99]), lower RMSSD (B=-4.56 [-8.86, -0.27]); lower PNN50 (B=-5.32 [-9.08, -1.55]) and greater LF/HF ratio (B=0.49 [0.29, 0.68]). Similarly, waist-to-height ratio was associated with lower ln-HF (back-transformed B = 0.35 [0.13, 0.95]); lower RMSSD (B=-23.32 [-42.42, -4.22]); and lower PNN50 (B=-26.03 [-42.76, -9.29]) and greater LF/HF ratio (B=1.83 [0.97, 2.70]). Likewise, % fat mass was associated with lower ln-HF (back-transformed B=0.44 [0.22, 0.90]); lower RMSSD (B=-19.52 [-32.97, -6.06]); lower PNN50 (B=-21.16 [-32.94; -9.38]) and greater LF/HF ratio (B=1.50 [0.89, 2.11]). No other indices of HRV were associated with adiposity.

**Conclusions:** Adiposity is associated with decreased parasympathetic activity (ln-HF, RMSSD and PNN50) and a sympathetic-parasympathetic imbalance (LF/HF ratio) in children. These relations are independent of potential confounding determinants of HRV. Longitudinal studies exploring these pathways are needed.

P3-1130

#### GENDER DIFFERENCES IN OBESITY-RELATED METABOLIC AND CARDIOVASCULAR DERANGEMENTS IN OVERWEIGHT/OBESE CHILDREN: A CROSS-SECTIONAL CLINIC-BASED STUDY FROM SRI-LANKA

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**Objectives:** To determine metabolic and cardiovascular derangements in overweight/ obese Sri Lankan children, and explore for any gender-based differences in complication rates

**Methods:** Overweight/obese children aged 5-15 years, presenting to the University Paediatric Obesity Clinic, Lady Ridgeway Hospital for children, Colombo from September 2015 to September 2016 were screened. Metabolic complications were defined as: dysglycaemia: impaired fasting glycaemia (IFG) fasting glucose 100–125 mg/dl, impaired glucose tolerance (IGT) 2-h post glucose blood sugar 140–199 mg/dl, insulin resistance: fasting insulin  $>17\text{mIU/ml}$ , 2h insulin  $>150\text{mIU/ml}$ , HOMA-IR [fasting insulin (microU/L) x fasting glucose (nmol/L)/22.5.]  $>2.5$ ; dyslipidemia: total cholesterol  $\geq 200\text{mg/dl}$ , LDL  $\geq 150\text{mg/dl}$ , HDL  $<40\text{mg/dl}$ , triglycerides  $\geq 150\text{mg/dl}$ ; and liver derangement: ALT  $>40\text{IU/l}$ . Height, weight, waist circumference and blood pressure (BP) was measured and birth weight obtained from clinical records. Rate of complications were compared by gender using chi square tests. Logistic regression was used to adjust for the effect of age, birth weight and BMI Z score (BMIZ).

**Results:** 197 children were studied (boys=132, girls=65). Mean age was  $9.5 \pm 2.4$ , birth weight  $3.1 \pm 0.5$ , and BMIZ  $2.76 \pm 0.9$ . Boys had greater waist circumference (85cm vs 80cm,

P=0.001) and tendency towards higher BMIZ (2.8 vs 2.5, p=0.07). However, girls had higher rates of insulin resistance (elevated fasting insulin 44 % vs 18 %, p=0.001, elevated 2h insulin 37% vs 15%, p=0.003, high HOMA-IR 70% vs 38%, p<0.001), IGT (17% vs 6%, p=0.03) and dyslipidemia (low HDL 63% vs 44%, p=0.02, hypertriglyceridemia 29% vs 13%, p=0.02) These differences remained even after adjusting for BMIZ, age and birth weight. Girls also had higher systolic(S) BP than boys (SBP 102 vs 98 mmHg, p=0.03, diastolic BP 66 vs 63 mmHg, p=0.07).

**Conclusions:** Overweight/obese Sri Lankan girls had higher rates of obesity-related metabolic complications compared to boys. This finding is concerning, especially given the impact of the health of the girl-child on the future generation too. Underlying reasons need to be explored further.

P3-1131

**CORTISOL AWAKENING RESPONSE AND FASTING MORNING CORTISOL MAKE DISCORDANT PREDICTIONS ABOUT MARKERS OF METABOLIC SYNDROME.**

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**Objectives:** Chronic amplification of the hypothalamic-pituitary-adrenal axis (HPAA) from psychological stress may predispose to ectopic fat (EF) deposition and metabolic syndrome (metS). The relationship of self-reported stress, chronic HPAA activation, EF, and biochemical indicators of metS in overweight children remains unclear. This study examines whether laboratory measures of HPAA activity correlate with self-reported stress, increased EF, insulin resistance (IR), and dyslipidemia in overweight children.

**Methods:** Cross-sectional study of 44 ethnically diverse girls and boys ages 8-18 years with BMI > 85th percentile. Exclusion criteria: chronic glucocorticoids or medication for diabetes, IR or dyslipidemia. Adrenarche and puberty were assessed by DHEAS and LH respectively. Stress was assessed by the Perceived Stress Scale (PSS) and the Positive and Negative Affect Schedule (PANAS-C). Chronic HPAA activation was assessed by salivary fasting morning cortisol upon first waking, and by the 30-minute cortisol awakening response (CAR: rise in cortisol in the first 30 minutes after waking). MetS was assessed by fasting insulin, glucose, triglycerides, HDL and non-HDL cholesterol. EF was assessed by DXA.

**Results:** CAR correlated positively and significantly with fasting insulin (correlation 0.67, P < 0.05), and a positive trend was found between CAR and non-HDL-C (correlation 0.53, P < 0.15). In contrast, higher waking cortisol correlated negatively and significantly with both fasting insulin (correlation -0.71, P < 0.03) and non-HDL cholesterol (correlation -0.68, P < 0.04). PSS and PANAS-C scores did not correlate with salivary cortisol or EF

**Conclusions:** In a group of overweight children, increased HPAA reactivity assessed by salivary CAR, but not salivary waking cortisol, predicted IR and possibly dyslipidemia. Lack of concordance between cortisol measures and between biological and survey assessments of psychological stress

indicates that further work is needed regarding how best to assess chronic stress in children. Validation of these results with analysis of additional subjects may inform whether interventions to reduce chronic stress might reduce the risk of metS. Work supported by NIH – T32 DK077586.

Table 1: Correlation Analysis (nonparametric Spearman's rank correlation coefficient)

COMPARISON		CORRELATION	L95% CI <sup>1</sup>	U95% CI <sup>2</sup>	P-VALUE
Waking Salivary Cortisol	vs: Insulin	-0.71	-0.93	-0.04	0.0297
	vs: Non-HDL-C	-0.68	-0.92	0.02	0.0433
	vs: Ratio Abdominal Fat to Total Fat	-0.43	-0.82	0.30	0.2292
	vs: PANAS-C	0.16	-0.53	0.72	0.6602
	vs: PSS	-0.06	-0.66	0.59	0.8649
Morning Salivary Cortisol Rise	vs: Insulin	0.67	-0.03	0.92	0.0473
	vs: Non-HDL-C	0.53	-0.23	0.88	0.1451
	vs: Ratio Abdominal Fat to Total Fat	0.27	-0.44	0.76	0.4591
	vs: PANAS-C	0.11	-0.56	0.69	0.7713
	vs: PSS	0.26	-0.45	0.76	0.4775

1: Lower 95% confidence bound 2: Upper 95% confidence bound

P3-1132

**ALTERED EXPRESSION OF BILE ACID RELATED GENES AND INCREASED DUCTULAR REACTION IN LIVER OF OFFSPRING EXPOSED TO MATERNAL HIGH FAT DIET**

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**Objectives:** Exposure to a poor nutritional environment in utero, including high fat diet (HFD), can increase the risk of developing non-alcoholic fatty liver disease (NAFLD) in offspring. Animal models of maternal HFD exposure show that offspring develop steatosis, inflammation and fibrosis in the liver. The mechanism of how this chronic injury develops is not clear. The goal of the current study was to evaluate the impact of maternal HFD exposure on bile acid metabolism and transport.

**Methods:** Female C57Bl6 mice were fed a control diet (CD, 10% kcal from fat) or HFD (60% kcal from fat) for 8 weeks and bred with lean males. Dams were continued on the same diet with offspring maintained on either CD or HFD for 12 weeks. Histology, gene, and protein expression analyses of liver from offspring were performed.

**Results:** Offspring exposed to perinatal HFD and then placed on CD (HFD/CD) at weaning show evidence of fibrosis, increased alpha-smooth muscle actin positive stellate cells and cytokeratin-19/beta-catenin positive ductular reaction. Liver from HFD/CD offspring show increased levels of total liver bile acids compared to CD/CD. There is also decreased expression of multiple genes involved in bile acid metabolism and transport in HFD/CD liver.

**Conclusions:** Perinatal HFD exposure induces pathologic changes in liver of offspring that persist into adulthood including fibrosis and ductular proliferation. These findings are associated with increased liver bile acids and altered expression of genes important in bile acid metabolism and transport. This study provides preliminary evidence that cholestasis may exist in these offspring and is a potential etiology for the pathology that is observed in the adult offspring.

### POSTNATAL HIGH FAT DIET FEEDING INDUCES OBESITY AND PRECOCIOUS PUBERTY IN C57BL/6J MICE PUPS: NOVEL MODEL OF OBESITY AND PUBERTY.

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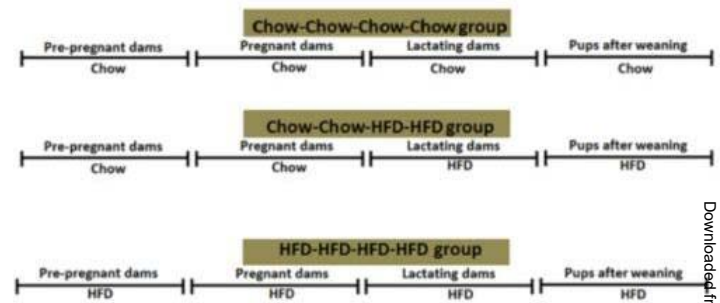
**Objectives:** To develop a novel animal model of postnatal high fat diet (HFD) induced obesity before puberty onset was the objective of the current study.

**Methods:** C57BL/6J mice and two diets, HFD (60% fat) and control chow (12% fat) were used. Experimental design of diet intake is summarized in Fig 1. Weight gain and vaginal canalization (VC) were used as markers of obesity and puberty onset respectively. After perfusion, peritoneal white adipose tissue (WAT) from male and brains from female pups were collected. WAT and body weight (BW) were measured to know about fat deposition and obesity while brains were used for the immunohistochemistry of kisspeptin. Student's Un-paired t-test, one way ANOVA and two way ANOVA were used for different comparisons. P value less than 0.05 ( $P < 0.05$ ) was taken as significant difference.

**Results:** HFD feeding has increased BW in mice pups (Tab1, Fig 2). Furthermore, HFD was more potent to increase BW in male than female pups at postnatal day 40 [P-40] (Fig 3) but not at P-19 and P-24 (Tab1, Fig 2). Interestingly, HFD feeding increased the weight of peritoneal and subcutaneous WAT (Fig 4). Additionally, HFD feeding induced precocious puberty (Fig 5) and increased hypothalamic kisspeptin expression in female pups (Fig 6). Interestingly, HFD induced parental obesity and precocious puberty have no synergistic effects on HFD induced pups obesity and precocious puberty (Fig 7). Most importantly, our results suggest that body weight/fat may not trigger puberty onset during HFD feeding but it may be the diet composition that induces earlier VC (Tab 3, Fig 8).

**Conclusions:** In the current study, for the first time we developed obese animal model of C57BL/6J pups before puberty onset with precocious puberty and opened a new

window for pediatric endocrinologists to explore postnatal HFD induced children obesity or/and precocious puberty and their mutual interaction. Our animal model fulfils the face and construct validity of postnatal HFD induced obesity and precocious puberty. C57BL/6J mice represent heterogeneous human population therefore, the current study support the use of this novel model to explore postnatal diet induced children obesity, obesity related metabolic complications and precocious puberty.



**Fig. 1** Three groups of animals were used in the current study. Chow-Chow-Chow-Chow group (C-C-C-C) [dams n=3, pups (male n=17, female=11)] = Dams were feeding on control diet before and during pregnancy and after delivery and their pups were feeding on control chow after weaning. Chow-Chow-HFD-HFD group (C-C-H-H) [dams n=3, pups (male n=17, female n=17)] = Dams were feeding on control chow before and during pregnancy but feeding on HFD after delivery, pups were feeding on HFD after weaning. HFD-HFD-HFD-HFD group (H-H-H-H) (dams n=3, pups female n=8) = Parents were already obese and undergone through precocious puberty by feeding on HFD, dams were feeding on HFD before and during pregnancy and after delivery, pups were also feeding on HFD after weaning. C-C-C-C (control) and C-C-H-H (HFD obese) groups were used to compare the effects of HFD feeding on weight gain and puberty onset while H-H-H-H group was used to study the synergistic effects of parental obesity and precocious puberty on HFD induced weight gain and precocious puberty in pups.

P3-1134

### LONG-TERM FOLLOW-UP OF GONADAL DYSFUNCTION IN MORBIDLY OBESE ADOLESCENT BOYS AFTER BARIATRIC SURGERY

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**Objectives:** There is a known relationship in adult males between elevated body mass index(BMI) and hypogonadism. It was previously reported by this group that morbidly obese adolescent males prior to bariatric surgery had evidence of gonadal dysfunction that was negatively associated with BMI, waist circumference(WC), and HOMA-IR. Our aim was to evaluate the effects of weight loss on gonadal dysfunction two years after bariatric surgery (gastric banding) in obese adolescent males.



**Methods:** Fifty-four of 87 males (age  $16.2 \pm 1.2$  yrs) enrolled at the Center for Adolescent Bariatric Surgery at Columbia University Medical Center were found to be hypogonadal (low total testosterone,  $<200$  ng/dL for Tanner stage 4 and  $<350$  ng/dL Tanner 5). This group had a greater BMI compared to the rest of the cohort ( $p=0.04$ ). 16/54 males had long-term hormonal data available for analysis at  $T_0$ =pre-surgery,  $T_1$ =1 yr post-surgery, and  $T_2$ =2 yrs post-surgery. Two sample t-tests, chi-square tests, linear mixed models, and regression analysis of testosterone and metabolic data were performed. These 16 were compared with the remaining 38 participants (only long term weight data available) at all points with no statistical difference noted between groups (BMI, weight loss).

**Results:** In  $n=16$ , there was a statistically significant decrease in BMI, weight, WC, and percent excess weight loss at  $T_1$  and  $T_2$  compared to  $T_0$ . There was no significant change in LH or FSH levels or the number of patients who were classified as hypogonadal over time ( $p=0.383$ ). Mean total testosterone at  $T_0$ ,  $T_1$ , and  $T_2$  was 267.63 ng/dL, 303.81 ng/dL, and 368.47 ng/dL, respectively. While only a trend towards increasing testosterone was noted between  $T_0$  and  $T_2$  ( $p=0.069$ ), there was a statistically significant negative correlation between BMI and testosterone after 2 years ( $p=0.003$ ,  $r=-0.81$ ). No associations between testosterone and other metabolic syndrome risk factors were found.

**Conclusions:** While a significant increase in testosterone was not found two years after bariatric surgery, the negative relationship between BMI and testosterone persisted, suggesting that there may be an optimal threshold for testosterone production with respect to BMI. Long term studies are needed to further evaluate the effect on body composition, fertility, and overall sense of well-being.

P3-1135

#### SUCCESSFUL MULTIDISCIPLINARY MANAGEMENT AND USE OF GLP-1 RECEPTOR AGONIST FOR MORBID OBESITY IN ADOLESCENT PRADER-WILLI SYNDROME

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**Objectives:** Prader-Willi syndrome (PWS) is a genetic multisystem disorder caused by a loss of expression of paternally derived genes on chromosome 15q11-13 region. Progressive obesity and its complication lead to increase morbidity and early death in patients with PWS. Although growth hormone (GH) therapy is known to treatment for PWS, management for morbid obesity in adolescent and adult PWS is still limited. Herein, we report a successful management for an adolescent PWS with morbid obesity without surgery.

**Methods:** An 18-year-old girl was presented with dyspnea and abdominal cellulitis. This subject was diagnosed with

PWS at 14 years of age and both type 2 diabetes and hypertension were diagnosed 2 years ago. At visit, this subject's height, weight and body mass index (BMI) was 143 cm, 145 kg, and  $71 \text{ kg/m}^2$ . She could not walk and sit alone due to joint pain and massive cellulitis on abdomen and legs. The antibiotics was administered and daily calorie was restricted to 800 kcal/day for 1 week, however, weight was increased to 161 kg and dyspnea was aggravated.

**Results:** The mechanical ventilation was applied for 20 days and calories were restricted to 200 kcal/day. The weight loss of 26 kg was achieved and extubation was done successfully. The level of IGF-1 and IGFBP was 34.5 ng/mL and 1680 ng/mL, respectively. The cocktail test was performed and revealed hypopituitarism including GH and gonadotropin deficiency. The low dose of GH, estrogen and glucagon-like peptide 1 (GLP1) receptor agonist was started and aquatic rehabilitation was applied. At discharge, she was able to walk and the subject's weight and BMI was 104kg and  $50.8 \text{ kg/m}^2$ , respectively. After one year of GLP1 agonist, her BMI was maintained to  $47.3 \text{ kg/m}^2$  and this subject was satisfied with 600kcal/day.

**Conclusions:** We applied the aggressive calorie restriction, GH therapy, aquatic rehabilitation and GLP-1 agonist to adolescent PWS with morbid obesity and achieved incredible weight reduction of 60kg for 2 months. Also, maintenance of weight reduction and reduced appetite during GLP-1 agonist administration was observed in our case. The multidisciplinary team management is important to improve PWS patient outcome despite of critical morbid obesity and GLP-1 agonist may be effective to maintain weight reduction for adolescent and adult PWS.

P3-1136

#### CAN OBESITY ASSOCIATED WITH LEPR GENE MUTATIONS BE TREATED WITH FLUVOXAMINE? A CASE REPORT

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**Objectives:** In human, hypothalamic leptin pathway is activated following the systemic release of the adipokineleptin (LEP) and its subsequent interaction with the leptin receptor (LEPR) located on the surface of neurons of the arcuate nucleus region of the hypothalamus. Despite the use of leptin therapy in congenital leptin deficiency, it is useless in LEPR mutations. Fluvoxamine maleate is a selective serotonin re-uptake inhibitors agent and it is used for obsessive-compulsive disorders. Fluvoxamine breaks leptin resistance by reducing stress at the level of endoplasmic reticulum, It also reduces appetite as a side effect. Taking into account these effects, we started fluvoxamine after receiving approval from the family.

**Methods:** A four-month-old girl admitted to polyclinic with the complaint of an abnormal rapid weight gain immediately after birth. She was fed only with breast milk and had no other complaints. She was born with cesarean/section as 3000gr and 50cm. There was no evidence other than global obesity on physical examination. Laboratory tests did not



have any features other than central hypothyroidism. Sodyum-L-tiroxin was started at a dose of 75mcg/m<sup>2</sup>/day. Leptin levels were measured due to continued abnormal weight gain despite the normal free T4 level in the control after two weeks. Leptin level was found very high (>30ng/ml). Genetic analysis revealed a previously unidentified homozygous mutation in the LEPR gene [p.P639L (c.1916C>T)]. There are no drugs known to be effective in LEPR mutations. When she was 12 month old, the efficacy of fluvoxamine and the side effects were explained to the family and started at 1 mg/kg day after receiving approval. No effect was observed at this dose. The dose was increased to 2 mg/kg/day. No any side effect or effect was observed except severe appetite reduction.

**Results:** The changes in height, weight and BMI of the patient before and after the treatment are given in the table 1. **Conclusions:** Although there are no drugs known to be effective at present for the treatment of obesity associated with LEPR gene mutations, Fluvoxamine seems to be effective in the short term. However, in order to make a definite interpretation, the results should be observed in more patients and longer time.

Age (month)	Weight (kg)	Height (cm)	BMI (kg/m <sup>2</sup> )
Birth	3000gr	50	12
4	10,2	63,8	25
5	11,7	65,1	27,6
8	16,1	71,6	31,4
11	20,1	78,2	32,9
12	23	79	36,8
15	22	82	32,7

P3-1137

**OBESITY IS A STRONG RISK FACTOR FOR THE DEVELOPMENT OF RESTLESS LEGS SYNDROME AND POOR SLEEP QUALITY IN CHILDREN AND ADOLESCENTS**

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**Objectives:** Adult epidemiological studies have suggested that the rate of restless legs syndrome (RLS) in the general population may range from 5% to 15%. The aim of this study was to investigate the prevalence of RLS in a community sample of obese adolescents aged 10-16 years and its association with sleep quality and health-related glucose metabolism markers.

**Methods:** The study group comprised 144 obese and overweight children aged 10-16 years (mean BMI: 30.5±0.5) and the control group consisted of 66 age-matched healthy children (mean BMI: 18.7±0.2). The RLS Questionnaire devised by the International RLS Study. Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality, where a score >5 indicated poor sleep quality.

**Results:** The prevalence of RLS was higher in the obese group (21.7%) than the overweight (3.4%) and lean groups (1.5%) (p<0.001). The prevalence of a poor PSQI score was higher in the obese group (37.3%) than the lean group (24.2%, p<0.001). The obese with RLS group had poorer sleep quality

scores than the non-RLS obese group. BMI was significantly correlated with the total PSQI score of obese children (p **Conclusions:** RLS is common in obese children and it may be associated with altered sleep quality. Therefore, obese children with RLS need to be assessed in respect of support required to improve sleep quality.

P3-1138

**IMPACT OF CHANGE IN ADIPONECTIN AND PAI-1 LEVELS IN CHILDHOOD OBESITY ASSOCIATED WITH EOSINOPHILIC INFLAMMATION OF THE AIRWAY AND WHOLE BODY**

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**Objectives:** Childhood obesity has been suggested to be a risk factor for bronchial asthma. However, the pathological association between body fat accumulation and eosinophilic inflammation in the airway is not well known. We examined the relationship between clinical factors of obesity and eosinophilic inflammation on the basis of fractional exhaled nitric oxide (FeNO) measurements and peripheral blood eosinophil(B-Eo) counts.

**Methods:** In this study, 41 children (age:6-15 years, mean age:10.0years) attending our outpatient clinic were enrolled. Children with diabetes mellitus, any endocrine disease, or using corticosteroids inhalers were excluded. We measured the height, weight, waist circumference, blood pressure, and FeNO levels of each subject. Blood samples were examined for B-Eo count, IgE, AST, ALT, γ-GTP, TG, HDL-Chol, MDA-LDL, uric acid, insulin, BS, hs-CRP, leptin, adiponectin, and PAI-1 level in the morning after an overnight fast. The relationships between these values and FeNO or B-Eo counts were then analyzed. The statistical analysis was performed using JMP pro12. This study was approved by the ethics committee of Tokyo Women's Medical University.

**Results:** The mean BMI-z score of the 41 children was 1.87. No single correlation between FeNO or B-Eo counts and the BMI-z score was found. FeNO was high (>35ppb) in 8 cases and normal (<35ppb) in 33 cases. Adiponectin was significantly lower in the high FeNO group than in the normal FeNO group (6.5µg/mL vs 8.1µg/mL, P<0.02). A negative correlation between B-Eo counts and adiponectin (r=-0.34, P<0.05) and a positive correlation between B-Eo counts and PAI-1 levels was found (r=0.42, P<0.01). A multiple regression analysis revealed that age, leptin/adiponectin, AST/ALT, uric acid, hs-CRP and B-Eo counts were selected for the FeNO model (R<sup>2</sup>:0.60, P<0.0002), while MDA-LDL/LDL, LDL, AST/ALT, BS and IgE levels were selected for the B-Eo model (R<sup>2</sup>:0.35, P<0.022).

**Conclusions:** Our data demonstrated that the change in adipocytokines such as adiponectin and PAI-1 associated with childhood obesity were strongly related with eosinophilic inflammation in the airway and whole body.

# NEONATAL OVERFEEDING IN MICE PERMANENTLY PROGRAMS OBESITY THROUGH EARLY ADIPOCYTE HYPERTROPHY

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**Objectives:** Epidemiological and clinical data show that rapid weight gain early in life is strongly associated with childhood overweight/obesity. However, the specific molecular mechanisms that lead to such long-lasting effects remain poorly characterized. In this study we aim to gain insight into the mechanism of early adipose tissue accrual that leads to permanent obesity.

**Methods:** We have previously developed a mouse model of neonatal overfeeding and accelerated growth rate by litter size reduction (Small Litter (SL)=4 pups/dam; Control (C)=8 pups/dam). Mice from SL developed increased adiposity as early as 7 days, and remained obese through adulthood. These mice developed many features of the metabolic syndrome as adults, including insulin resistance and hepatic steatosis, despite normalizing his food intake after weaning. We performed histologic studies to determine adipocyte size and gene expression.

**Results:** Increased adiposity in SL mice was characterized by adipocyte hypertrophy (C=2973±444  $\mu\text{m}^2$ ; SL=7501±315  $\mu\text{m}^2$ ;  $p<0.05$ ), which persisted until adulthood. In agreement, expression of lipogenic genes (*Fasn*, *Scd1*, *Srebf1*) was increased, whereas the expression of adipogenic factors remained unaltered (*Pparg*, *Cebpa*, *Fabp4*). Conversely, neonatal undernutrition, rear in Large Litters (LL=12 pups/dam), resulted in the opposite phenotype with reduced fat mass and a more favorable metabolic profile. Adipocyte size was reduced and expression of lipogenic genes was down-regulated whereas adipogenic markers were increased. Hypertrophic obesity, which is associated with insulin resistance, is in part induced by impaired recruitment and differentiation of new adipocytes. In agreement, SL mice showed decreased expression of *Suvar39* and *Dlk1*, and upregulation of *Wisp2* which inhibits adipogenesis and has been linked to hypertrophic obesity. Conversely, in LL mice, *Wisp2* expression was reduced and *Suvar39* and *Dlk1* up-regulated in adipose tissue.

**Conclusions:** Our data suggests that excessive nutrient availability during lactation results in storage of the energy surplus via lipogenesis, leading to adipose tissue hypertrophy. Furthermore, rapid early hypertrophy determines adipose tissue dysfunction and metabolic derangements throughout life.

# ARE WE DOING ENOUGH?: ASSESSING PRACTICE PATTERNS AND IDENTIFYING CHALLENGES TO PROVIDING HEALTHY LIVING COUNSELLING AT A TERTIARY LEVEL CARE PEDIATRIC HOSPITAL IN CANADA

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**Objectives:** Childhood obesity rates are increasing and treatment has been largely ineffective. Pediatric healthcare providers (HCP) have a key role to play in prevention. The study objective was to gather pediatric HCP views on: (i) barriers and facilitators to providing healthy lifestyle counselling (HLC) during clinic visits; (ii) current practice patterns and knowledge of healthy active living recommendations; and (iii) preferred methods for improving knowledge and skills related to HLC.

**Methods:** A needs assessment survey, designed based on themes from the literature and reviewed by key stakeholders, was distributed via email to 705 HCPs at a large tertiary care pediatric center in Canada. Descriptive statistics and thematic analysis were performed.

**Results:** Response rate was 31% (40% physicians, 17% nurses, 25% allied health, 16% social workers/psychologists, 2% other). Most HCPs self-reported assessing height (82%) and weight (89%) at least half of the time; however, only 56% calculated body mass index (BMI) half of the time and 26% reported that BMI was useful only when the patient was already overweight/obese. Physical activity (69%) and sugary drink intake (80%) were assessed more frequently than screen time (52%), junk food (44%), and fruit/vegetable intake (51%). Although 88% of participants provided HLC, only 46% believed they were meeting their patient's needs, and 40% reported moderate/high levels of confidence when discussing weight issues. Barriers to counselling included: time constraints, finding the "right time," poor perceived self-efficacy, and having unhealthy personal lifestyle habits. Factors that might facilitate HLC included: additional human resources, a hospital environment that supports healthy habits, and the ability to refer patients to community-based programs. Most (90%) respondents believed they could improve their HLC skills, and 81% were interested in additional training.

**Conclusions:** We report a gap in pediatric HCP practice and low confidence in discussing weight issues. Next steps will be to develop a toolkit that will address the barriers and knowledge gaps, with the aim of increasing HCP capacity to integrate HLC into their daily practice.

# RELATIONSHIP BETWEEN IMMUNE PARAMETERS AND NON-ALCOHOLIC FATTY LIVER DISEASE IN OBESE CHILDREN

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**Objectives:** To investigate the relationship between immune parameters and non-alcoholic fatty liver disease (NAFLD) in obese children.

**Methods:** A total of 117 obese children and 209 healthy non-obese children were studied as the obese and control groups. Depending on the severity of NAFLD, the obese group was divided into subgroups 1 (without NAFLD), 2 (with simple fatty liver) and 3 (with steatohepatitis). Glycometabolism, lipometabolism and immune parameters were measured.

**Results:** In the obese group, body mass index (BMI), waist and hip circumferences, fasting insulin, homeostasis model of assessment for insulin resistance (HOMA-IR), triglyceride, total cholesterol, low density lipoprotein cholesterol (LDL-C), apolipoprotein (Apo)B/ApoA1, alanine aminotransferase, uric acid, white blood cells, neutrophils percentage, platelet and interleukin (IL)-6 were significantly higher than those in the controls ( $P < 0.05$ , respectively), while lower high density lipoprotein cholesterol and lymphocyte percentage were noted ( $P < 0.05$ , respectively). The difference of IL-10 was marginal between the control and obese groups ( $P = 0.07$ ). Moreover, IL-6 in the subgroup 3 was higher than those in the control group and subgroup 1 ( $P < 0.05$ , respectively). IL-10 in the subgroup 3 was higher than those in the control group, subgroup 1 and 2 ( $P < 0.05$ , respectively). Logistic regression analysis showed that BMI, LDL-C, HOMA-IR and IL-10 were independent factors of NAFLD ( $P < 0.05$ , respectively).

**Conclusions:** These results support a low-grade chronic inflammation in obese children. Moreover, obesity, dyslipidaemia and IR are risk factors while IL-10 may be a protective factor for NAFLD.

P3-1142

# PSEUDOTUMOR CEREBRI: DIFFERENTIAL DIAGNOSIS OF HEADACHE IN OBESE PATIENTS

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**Objectives:** Relate the cases of four patients followed-up in our Obesity Clinic in the Pediatric Endocrinology Department that were diagnosed with Pseudotumor cerebri (PTC).

**Methods:** Review of patient charts that follow up in our Obesity Clinic in the Pediatric Endocrinology Department.

**Results:** Four patients followed-up in our Obesity Clinic in the Pediatric Endocrinology Department were diagnosed with PTC. Their median age was 13 years (range 11-16), three females and one male, BMI 32-44,8 kg/m<sup>2</sup>.

They presented with daily mild to moderate headache associated with nausea, vomiting, blurred vision. One patient developed seizure. All patients were submitted to a complete lab evaluation which was normal. They underwent CT scan and MRI of the head which were also normal. Only one patient had a previous diagnosis of central venous thrombosis. CSF pressure was elevated, with values ranging from 32 to 40cmH<sub>2</sub>O (normal below 20cmH<sub>2</sub>O) with normal biochemical tests and culture. Neurologic evaluation was normal and fundoscopic exam showed papilledema in three of the patients.

Diagnosis of PTC and atypical PTC (patient with no papilledema) was made due to severe obesity. Treatment with acetazolamide was initiated in all the four patients. After on average of six months of treatment all patients presented clinical improvement and since they were also being treated for obesity, reduction in their BMI allowed gradual dose decrease in acetazolamide until total suspension in three patients. The one male patient who had only partial clinical improvement did not lose weight and had laparoscopy sleeve gastrectomy indicated. After the surgical procedure he had significant weight loss (37,4% of the weight) and showed full recovery of PTC.

**Conclusions:** Although it is a rare condition, in our casuistic four of 400 patients had diagnosed. PTC has to be investigated in obese children with headache using complementary exams and ophthalmological evaluation. The severe obesity is a challenge for the pediatrician because the management includes life style modification, pharmacological intervention, and eventually surgery.

## POSTER SESSION 3

Saturday, September 16, 2017, 12:00-1:00pm

## P3 - Puberty

## P3-1300 – P3-1331

P3-1300

# INCOMPLETE CENTRAL PRECOCIOUS PUBERTY SHOWING LOW GRADE OF LH RESPONSE TO GnRH : LHCGR GENE ANALYSIS AND GnRH AGONIST TREATMENT.

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**Objectives:** To investigate LHCGR gene polymorphism clinical characteristics in girls with incomplete CPP, showing peak LH < 5 IU/L on GnRH stimulation test.

**Methods:** 102 girls with incomplete CPP and 100 normal adult women were enrolled in this study. GnRH agonist treatment outcome were analyzed. All subjects underwent LHCGR gene analysis and compared between patient groups and controls. In 102 patients group, auxological data and gonadotropin level were analyzed. Out of them, 75 patients completed GnRH agonist treatment, treatment outcomes were analyzed too.

**Results:** Total seven polymorphism were found in this study. Two missense mutations were found in patients group. The g.48698754 G/A (Glu->Lys) and g.48688613 G/A (Arg->His) mutation was found in each two patients. One missense mutation, g.48694236 A/G (Asn->Ser) and one synonymous mutation, g.48688732 T/C were found in both groups. Two missense mutations and one insertion were found in controls, g.48687721 C/A (Asp->Glu) was novel mutation. GnRH agonist treatment increased predicted adult height from  $154.52 \pm 5.78$  to  $163.48 \pm 5.19$  in 75 patients with incomplete CPP.

**Conclusions:** Incomplete CPP has associated with LHCGR gene polymorphism. GnRH agonist treatment improved predicted adult height in girls with incomplete CPP.

P3-1301

#### ANALYSIS OF SLEEP-WAKE BEHAVIOR IN PATIENTS WITH PRECOCIOUS AND DELAYED PUBERTY

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**Objectives:** Biological rhythms play a fundamental role in regulation of physiological processes and behavior and are evolutionary conserved in plants, invertebrates, vertebrates and humans. Circadian rhythms are endogenously regulated and entrained by rhythmic environmental factors. In the last few years, large human cohort studies revealed a biphasic shift of the chronotype with chronological aging during adolescence with a continuous shift towards a later time until approximately 19.5 years in female and approximately 21 years in male. Thereafter, the individual's timing of sleep-wake behavior becomes earlier again. However so far it is not known, if and to which extent this shift in human chronotype might be related to pubertal hormonal changes during adolescence.

**Methods:** We analyzed chronotype of 61 patients with either precocious or delayed pubertal development by using

established questionnaires (Munich ChronoType Questionnaire and Children's Chronotype Questionnaire) and compared these results with 309 age and sex-matched controls. These questionnaires use the midpoint of sleep on free days corrected for the sleep time accumulated over the workweek (MSFsc) as a proxy for chronotype.

**Results:** Patients with precocious puberty had a significant later chronotype compared to the control group (precocious central puberty:  $2.5 \pm 1.1$  MSFsc (hh:min); premature pubarche:  $(2.4 \pm 1.0$  MSFsc (hh:min); control group:  $2.2 \pm 0.6$  MSFsc (hh:min)). However vice-versa patients with a delayed pubertal development had a significant earlier chronotype ( $4.02 \pm 0.84$ , MSFsc (hh:min)) in relation to the control group ( $4.28 \pm 1.4$  MSFsc (hh:min)).

**Conclusions:** So far the chronotype shift during adolescence was only observed as a correlation between the chronological age and the individual sleep-wake behavior. This study provides evidences for a significant impact of pubertal hormonal changes during puberty on chronotype. Further studies will be necessary to elucidate the exact mechanism how pubertal hormones can modify the internal clock as the suprachiasmatic nucleus.

P3-1302

#### INSULIN SENSITIVITY IN GIRLS WITH CENTRAL PRECOCIOUS PUBERTY AT DIAGNOSIS, 6 AND 12 MONTHS OF GnRH ANALOGUE TREATMENT

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**Objectives:** To evaluate BMI and metabolic parameters in Central Precocious Puberty girls at diagnosis and during GnRHa treatment.

Background: Puberty is associated with a physiological decline in insulin sensitivity (IS). Overweight and obesity are common among girls with Central Precocious Puberty (CPP). Early menarche and CPP have been considered as risk factors for long term obesity and cardiovascular diseases. Concern has been raised by the potential impact of GnRH analogues (GnRHa) treatment on body weight and metabolic profile.

**Methods:** Prospective longitudinal study of 17 girls with CPP evaluated at diagnosis (Tanner 3; median age: 7.8 years (5.7-8.5) at 6 and 12 months on GnRHa therapy. Oral glucose tolerance test (OGTT) was performed in all of them; glucose and insulin levels (Cobas e411, Roche) were measured at 0, 30, 60, 90 and 120 minutes. Surrogates estimates of IS (HOMA-IR, G/I, QUICKI) were calculated and evaluated according to our normal local cutoff. Matsuda Index was also calculated from OGTT. Fasting lipid profile was also evaluated. ANOVA for repeated measurements was used to evaluate changes in BMI, fasting insulin and lipids throughout treatment.

**Results:** At diagnosis, 10/17 patients were overweight (OW) or obese (OB). Six patients (3 with normal weight) had 2 impaired indices for IS (HOMA-IR and G/I). In OGTT, 5 OW/OB patients showed hyperinsulinemia. Matsuda index was low in 2 patients at diagnosis. During GnRHa treatment, no significant changes were observed in BMI, fasting insulin, or Matsuda index compared to baseline. Only four patients at diagnosis had dyslipidemia. Among them, 2 patients presented hypertriglyceridemia that persisted at the end of treatment in only one.

**Conclusions:** Our cohort of CPP girls showed a high frequency of OW and OB as well as high prevalence of insulin resistance. GnRHa seems not to have a major impact on BMI or metabolic profile during the studied period. Further studies will be necessary to determine long term metabolic risk in these patients.

P3-1303

#### EVOLUTION OF PREMATURE THELARCHÉ

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**Objectives:** Premature thelarche(PT) is defined as isolated breast development in girls

The aim of the study was to identify the outcome of PT in our population and to identify clinical, radiological and hormonal parameters that could distinguish between non-progressive PT and apparent PT which progresses to CPP – “progressive PT”.

**Methods:** All patients referred for possible PT from January 2007 to September 2016 were included. Outcome was categorized as regressive, persistent or progressive (precocious puberty). Clinical, hormonal and radiological parameters were compared in the groups of non-progressive and progressive PT.

**Results:** Of 283 girls referred for early sexual maturation, 108 presented with PT. Median age at onset was 1 (0-7) years while median age at diagnosis was 2 (0.41-8.5) years. At diagnosis 42% of the girls were under 2 years of age; mean(SD) height 0.28 (0.88) SDS, BMI 0.45 (0.90) SDS. Forty-five patients were lost to follow up. The course in the remaining girls was: regression in 18 (17%) with median (range) age 2(1-6.4) years, mean (SD)period until regression1.57 (1.08) years; persistence of pubertal signs in 40 (37%), age at diagnosis 2.1 (0.7-7.5) years, duration of follow-up 1.75 (1.29) years; and progression to CPP in 5 (5%), age at diagnosis 2.9 (1.7-7) years, duration of progression to CPP 1.8 (0.1) years. Girls with progressive PT were taller and heavier at diagnosis than those with non-progressive PT – Height SDS 0.80±0.6 vs 0.25± 0.9 SDS and BMI SDS 1.7±0.9 vs

0.6±0.9 but these differences were not statistically significant. Basal/peak LH at the time of CPP in the 5 patients with progressive PT was 1.9 ±1.7/26 ±16 mIU/ml.

**Conclusions:** In our population, the course of PT is rarely regressive (17%), the most common outcome being the persistence of pubertal signs. The difference in height and BMI between the progressive and non-progressive forms of PT is probably real but larger patient numbers are needed to confirm this finding. Since evolution toward CPP may happen after many years we recommend clinical follow-up in girls with persistent PT until the normal age of puberty.

P3-1304

#### A NOVEL SMARTPHONE APP MEASURING SPEAKING VOICE FREQUENCY IS A NON-INVASIVE METHOD TO DETERMINE THE ONSET OF PUBERTY IN BOYS

Gary Butler, MD, University College London Hospital, London, United Kingdom; David Howard, PhD, Royal Holloway, University of London, London, United Kingdom; Martin Ashley, PhD, Edge Hill University, Lancashire, United Kingdom

**Objectives:** At present there is no reliable way to determine the onset of puberty in boys by non-invasive means. Previous methodologies had assigned stages of voice maturation by frequency analysis and assigned stages but these methods could not be translated into clinical practice. A validated method of directly comparing voice frequency changes with the onset of puberty is needed.

**Methods:** A novel app ('SpeechTest' App store) was developed in iOS to evaluate the fundamental speaking frequency SF0 (Hz). A simple counting task from 20-0 backwards allowed a reading of the mean voice pitch to be determined. After full ethical permission, 62 boys aged 10-17 years attending endocrinology or urology clinics and who required staging of puberty or genital examination for clinical reasons were invited to participate.

**Results:** The fall in SF0 negatively correlated ( $r = -0.54$ ) with the increase in mean testicular volume (TV). An arbitrary 200Hz threshold was associated with TV around 5ml. (6ml 174.2 Hz SD 27.5;  $p < 0.001$ ). Those boys with measured SF0 above 200Hz had a lower testicular volume (5.3 SD 2.9ml) compared with those in whom the SF0 was lower (8.4 SD 3.5ml;  $p < 0.001$ ).

**Conclusions:** A simple App measuring speaking voice frequency and applying a threshold of 200Hz could therefore be considered as a non-invasive guide to the onset of puberty in boys when clinical examination is not required or possible. It also paves the way for larger scale studies on the onset of male puberty.

# LONG TERM EFFECT OF GONADOTROPIN-RELEASING HORMONE ANALOGUE TREATMENT ON GLUCOSE AND LIPID METABOLISM AND FUNCTION OF HYPOTHALAMIC PITUITARY GONADAL AXIS IN CHINESE GIRLS WITH ICPP

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**Objectives:** The aim of this study was to observe the influence of gonadotropin-releasing hormone analogue (GnRHa) treatment on

body mass index (BMI), glucose and lipid metabolism, hypothalamic pituitary gonadal axis (HPGA) function in Chinese

girls with idiopathic central precocious puberty (ICPP) after withdrawal.

**Methods:** The girls, who were treated with GnRHa for two years and had withdrawn, were enrolled in our study. The data of

height, weight, BMI, fasting blood glucose (FBG), blood lipid, insulin, serum hormones associated with the HPGA, and the volume of uterine and ovarian were obtained at withdrawal, the first and second year after withdrawal respectively.

**Results:** A total of 65 girls with ICPP were studied. Compared with withdrawal, BMI, insulin, homeostasis model assessment index of insulin resistance, triglyceride, luteinizing hormone, follicle stimulating hormone, sex androstenedione, estradiol and the volume of uterine and ovarian at the first and second year after withdrawal were increased significantly ( $P < 0.05$ ), but the level of BMI-Z score, FBG, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, hormone-binding globulin did not change significantly ( $P > 0.05$ ).

Dehydroepiandrosterone sulfate and testosterone at second year after withdrawal were significantly higher than those at withdrawal ( $P < 0.05$ ). After withdrawn for (14.16±6.70) months, 32 girls emerged menarche, whose average

ages were (11.86±0.75) years old.

**Conclusions:** HPGA function of ICPP girls who had treated with GnRHa gradually recovered after withdrawal. The treatment of GnRHa

has been found no influence on weight status, but might increase the level of insulin and androgen. Further follow-ups of these patients will clarify whether this phenotype persists and if it will have important long-term implications regarding increased risk of polycystic ovary syndrome (PCOS) or metabolic complications.

# IS THE USE OF GNRH ANALOG ALONE CAPABLE OF IMPROVING FINAL HEIGHT IN PATIENTS WITH A LATE ONSET PRECOCIOUS PUBERTY?

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**Objectives:** The treatment of central precocious puberty (CPP) with GnRH analogues (GnRHa) is well documented in the literature in children with early onset (younger than 6 years old), however there is no consensus as to the improvement of final height in patients treated older. The aim of this study was to evaluate the impact of the treatment GnRH analog alone on the final height in girls diagnosed with central precocious puberty after 6 years old treated in our service in a 10 years period.

**Methods:** We retrospectively analyzed medical records (2005-2015) of girls with CPP who started treatment with GnRHa between 6 and 10 years old and had the final height documented. Anthropometric and laboratory data were collected at beginning of the treatment, during the follow-up and after the final height was established.

**Results:** Among the 472 patients screened in our service for precocious puberty, 34 were selected. Many patients were excluded due to other comorbidities or diagnosis. The mean age of thelarche onset in the studied population was  $6.9 \pm 0.7$  SD years. Treatment started at the age of  $8.4 \pm 0.7$  SD years, lasting for  $2.1 \pm 0.7$  SD years, the initial monthly dose of leuporelin was 3.75 mg, and 4 patients had the need for 7.5 mg/month. The bone age median was 11 years. There was no significant difference between the predicted initial height/ZE and the final height in these patients ( $158.3 / -0.88$  vs.  $157.5 / -0.85$ ,  $p = 0.62$ ), neither between body mass index at the start of the treatment and at the end of it ( $1.04$ - $0.73$ ) or the target height ( $n = 24$ ,  $150$  vs  $148.5$ ,  $p = 0.3$ ).

**Conclusions:** GnRHa treatment in the studied population, even in older girls allowed patients to reach the midparental height, but without improvement of the final height when compared to the initial predicted adult height by the Bailey-Pinneau method.

# RETROSPECTIVE REVIEW OF SUPPRELIN THERAPY

Luong V Doan, MD; Alicia Lowes, DO, Akron Children's Hospital, Akron, OH, United States

**Objectives:** Patients on histrelin acetate (Supprelin) therapy with adequate suppression were compared with patients demonstrating breakthrough symptoms. Variables between the two groups were compared to correlate higher risk factors for failure with supprelin, which may minimize unnecessary therapy.

**Methods:** A retrospective cohort of 52 patients with precocious puberty, treated with supprelin therapy between 2006 and 2016 were divided into a non-failure group (n=38) and failure group (n=14). Failure was defined as advancing signs or biochemical evidence of pubertal progression from start of therapy. Adequately suppressed patients were classified as the non-failure group. Variables reviewed were age, gender, weight, body mass index (BMI), tanner staging, bone age, number of implants, luteinizing hormone, follicle stimulating hormone, and estradiol or testosterone levels at time of placement and break through.

**Results:** The failure group had a greater baseline BMI at the start of therapy compared to the non-failure group (mean: 20.48 vs 17.93,  $P=0.0186$ ). The failure group also had a greater change in BMI (mean: 3.19,  $P=0.0225$ ) compared to the non-failure group (mean: 1.09,  $P$  value 0.0129) during therapy. 78.5% of the failure group experienced failure within 2 implants. The difference between bone age and chronological age was greater at baseline in the failure group than the non-failure group (mean: 2.47 vs 1.75, with  $P=0.0693$ )

**Conclusions:** BMI and changes in BMI during therapy were identified as factors that positively correlated with supprelin therapy failure. This suggests that a higher dose may be beneficial for individuals that exceed a threshold weight. A greater difference between baseline bone age and chronological age was also found in the failure group. The higher  $P$  value for this may be due to our small sample size. A greater difference between bone age and chronological age is suggestive of prolonged exposure to gonadotropins. This may cause certain individuals to become more resistant to suppression. These findings positively support that the standardized dose used in supprelin therapy is inadequate for all patients with precocious puberty and that there are certain individuals with increased risk for failure with supprelin.

P3-1308

#### THE INFLUENCE OF GONADOTROPIN RELEASING HORMONE AGONIST TREATMENT ON THE BODY WEIGHT AND BODY MASS INDEX IN GIRLS WITH IDIOPATHIC PRECOCIOUS PUBERTY AND EARLY PUBERTY

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**Objectives:** This study aimed to investigate the influence of gonadotropin releasing hormone agonist (GnRHa) treatment on the weight and body mass index (BMI) of girls who were diagnosed with idiopathic central precocious puberty(CPP) or early puberty(EP).

**Methods:** Patients who were younger than 8 years of age at diagnosis were classified as CPP and patients aged between 8 years and 9 years at diagnosis were classified as EP. Of 129 patients, 34 were diagnosed with CPP and 95 were diagnosed

with EP. The patients were divided according to pretreatment weight status into normal weight group, an overweight group, or an obese group.

**Results:** No significant changes were observed with respect to the weight standard deviation score (SDS) before and after 1 years, 2 years of treatment, respectively ( $P>0.05$ ,  $P>0.05$ ) in all patient groups. No significant changes were observed in relation to the BMI SDS before and after 1 year, 2 years of treatment, respectively ( $P>0.05$ ,  $P>0.05$ ) in all patient group. Depending on the degree of obesity, differences with respect to the weight SDS and BMI SDS were observed.

**Conclusions:** BMI SDS increased in the GnRHa-treated patients as a whole group, but was not statistically significant. But BMI SDS increased significantly in the normal weight group after 2 years of GnRHa treatment. So, GnRHa treatment may affect the change of BMI SDS depending on degree of obesity.

P3-1309

#### A NOVEL HOMOZYGOUS MISSENSE MUTATION IN IGSF10 CAUSES NORMOSMIC HYPOGONADOTROPIC HYPOGONADISM

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**Objectives:** Complete Hypogonadotropic hypogonadism has been suggested as an extreme phenotype of significantly delayed puberty. Although no genetic etiology was so far suggested for classical delayed puberty, IGSF10 heterozygous mutations have been recently suggested to significantly contribute to this phenotype. Herein, we identify and characterize a homozygous variant in the IGSF10 gene as the cause of hypogonadotropic hypogonadism in a male patient.

**Methods:** Whole exome sequencing was performed in a healthy 18-year-old male born to consanguineous parents presenting with classical normosmic hypogonadotropic hypogonadism. A western blot analysis of skin fibroblasts from the proband is conducted in order to explore protein expression.

**Results:** Using whole exome sequencing, we have identified a rare novel homozygous missense point mutation in the IGSF10 gene in our proband, at chr3:151,156,359, c.C5990T,P1997L. The mutation is located in the 6th and last exon of the IGSF10 gene. IGSF10 is an important factor in the migration of GnRH neurons from the nasal placode to the hypothalamus in the early embryonic life in both mice and humans.

**Conclusions:** Our findings suggest that mutant IGSF10 can result in normosmic hypogonadotropic hypogonadism in males. Pathogenic variants of the gene may interrupt



migration of the GnRH neurons and thus cause permanent HH.

P3-1310

#### USING BASAL LUTEINIZING HORMONE (LH) AS FIRST-LINE INVESTIGATION TO DIAGNOSE CENTRAL PRECOCIOUS PUBERTY

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**Objectives:** The gold standard for the diagnosis of central precocious puberty is measuring the gonadotropins after stimulation by Gonadotropin-Releasing Hormone (GnRH) or a GnRH agonist. However, GnRH stimulation testing is time-consuming, costly and invasive. With the development of more sensitive LH immunoassays, basal LH has been proposed as first-line diagnostic tool for central precocious puberty. The objective of the study is to evaluate if basal LH can be used to diagnose central precocious puberty, and to determine the appropriate cut-off for diagnosis.

**Methods:** We performed a retrospective analysis on the data collected for patients evaluated for precocious puberty who had undergone a GnRH stimulation test in our centre from October 2011 to October 2016. Basal LH was measured using chemiluminescent immunoassay with a minimum detectable concentration of 0.2 IU/L. GnRH stimulation test was considered positive for central precocious puberty if the peak LH level was higher than 5 IU/L. Using logistic regression models, receiver operating curves (ROCs) were generated to evaluate the sensitivity and specificity at each cut-off value of basal LH.

**Results:** 57 GnRH stimulation tests were reviewed. There were 52 females and 5 males. 32.7% of females and 100% of males had positive GnRH stimulation tests. Using the Youden's J index, the optimal cut-off value was  $>0.55$  IU/L with a sensitivity of 72.73% (95% confidence interval 49.78 - 89.27%) and a specificity of 91.43% (95% confidence interval 76.94 - 98.2%). The area under the curve was 0.8409 with a p value of  $<0.0001$ .

**Conclusions:** Using the data from our centre, we propose a working algorithm for a future prospective study: For a basal LH of less than 0.2 IU/L, we will not proceed with GnRH stimulation testing. For a basal LH of between 0.2 to 0.6 IU/L, we will monitor for pubertal progression, and proceed with GnRH stimulation test if puberty progresses. For a basal LH of  $\geq 0.6$  IU/L, we will proceed with GnRH stimulation testing. This working algorithm has the potential to reduce our current number of GnRH stimulation tests by 67%.

P3-1311

#### DIFFERENCES IN CLINICAL AND BIOCHEMICAL PARAMETERS BETWEEN THREE DIFFERENT TRIPTORELIN FORMULATIONS IN GIRLS WITH PRECOCIOUS PUBERTY

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**Objectives:** Determine clinical and biochemical response to three different doses of Triptorelin Pamoate  
Evaluate bone age progression in the three groups  
Evaluate possible differences in growth velocity in three different doses of Triptorelin

Compare weight gain between the three groups

**Methods:** Girls diagnosed with precocious puberty or advanced puberty where randomly assigned to treatment with Triptorelin Pamoate 3.75 mg IM every 28 days, 11.25 mg IM every 90 days or 22.5 mg IM every 180 days. At diagnose bone age, pelvic US and gonadotropins were measured. Visits were scheduled every 3 months. LH and FSH were measured at 3-9-12 and 18 months. Bone age and pelvic US every 6 months.

**Results:** 329 girls were included. 110 patients were assigned to 3,75 mg of Triptorelin Pamoate every 28 days (group A), 109 patients to 11.25 mg of Triptorelin Pamoate every 90 days (group B) and 110 patients to 22,5 mg of Triptorelin Pamoate every 180 days (group C).

2 patients in group A, 4 patients in group B and 1 patient in group C were not included in analysis due to adherence problems.

Mean follow were 26 months ( $25.2 \pm 8$ ). LH at diagnosed was 1.98 mIU/ml for group A, 2.0 mIU/ml for group B and 1.6 mIU/ml without differences between the three groups. Growth velocity was higher in group C (6.2 cm/year) compared with group A (5.8 cm/year) and group B (5.3 cm/year). Weight gain was also higher in group C (4.85 kg/years in group C, 3.9 kg/years in group A and 4.18 kg/year in group B). Mean bone age at diagnoses was similar between groups (Group A 9.3 years, group B 9.5 years in group C 9,4 years) and progression was not different between groups. Pelvic US did not reveal differences between groups.

Age of menarche was 11.1 months after finalizing treatment in group A, 12.1 months after finalizing treatment in group B, and 12.2 after finalizing treatment in group C.

No severe adverse effects were observed. Headache and dizziness were the most frequent complains in all groups without significant differences

**Conclusions:** Our study revealed that weight gain was higher in patients using 22.5 mg of Triptorelin pamoate. Growth velocity was also higher in this group probably related to higher LH values. Bone age did not differ between groups and age of menarche was similar in 11.25 mg and 22.5 groups.

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Group (n)	Mean Age (Years)	LH (base) (mIU/ml)	LH 24 months (mIU/ml)	FSH (base) (mIU/ml)	FSH 24 months (mIU/ml)	Growth velocity (cm/year)	Weight gain (kg/year)
3,75 mg every 28 days (108)	8,36 ±0,8	1,98 ±0,5	0,71 ±0,3	3,8 ±1,2	0,4 ±0,4	5,8 ±1,1	3,9 ±1,3
11,25 mg every 90 days (105)	8,41 ±0,9	2,0 ±0,3	0,82 ±0,2	3,3 ±0,9	0,6 ±0,8	5,3 ±0,8	4,18 ±1,7
22,5 mg every 180 days (109)	8,33 ±0,6	1,6 ±0,5	1,0 ±0,3	3,0 ±1,0	0,6 ±0,5	6,2 ±1,0	4,85 ±1,7

P3-1312

### SEXUAL MATURATION AND SICKLE CELL ANEMIA: WHAT ABOUT CHILDREN ATTENDING A REFERENCE CARE UNIT IN CAMEROON?

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**Objectives:** Our study evaluates the pubertal development of children with Sickle cell Anemia(SCA) compared to healthy children in the Mother and Child Center in Cameroon.

**Methods:** Through a case-control study, each child aged 8 to 18 years with SCA was matched to a healthy control. Clinical features as height, weight, body mass index, body composition and sexual maturation were assessed. Hormonal measurements were performed for Follicle Stimulating Hormone, Luteinizing Hormone and sexual steroids (estrogens/ testosterone) at Robert Debré application Hospital in Paris with radio-immunologic assays. We looked into association between severity criteria of SCA and delayed puberty through multivariate analysis.

**Results:** Delayed puberty was reported in 27.3% of girls and 10% of boys with SCA. Median age of menarche was delayed to 2 years compared to controls. SCA patients had low free fat mass compared to controls ( $p = 0.03$ ). Abnormal levels of gonadotropins and sexual steroids were reported in cases. History of severe infection, acute chest syndrome as well as low hemoglobin level were associated with delayed sexual maturation in children with SCA.

**Conclusions:** Delayed puberty was frequent in children with sickle cell Anemia. Sexual maturation was affected by severity of the disease.

P3-1313

### CLINICAL AND PARACLINICAL CHARACTERISTICS IN GIRLS WITH PRECOCIOUS PUBERTY

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**Objective:** Describe some clinical and paraclinical characteristics aiming to orient early diagnosis of puberty forms in our current medical actuality.

**Methods:** Cross-sectional descriptive retrospective study on 51 girls diagnosed of precocious puberty at the Pediatric Center from March 2000 to March 2014.

**Results:** There was a clear difference of age at the diagnosis moment, mean age of peripheral precocious puberty group was  $4 \pm 2,8$  years, younger statistically significantly than that of central precocious puberty group. Bone age advanced over chronological age significantly (by more than 1 year) was also a manifestation of central precocious puberty. There was a clear difference of the uterus – ovaries sonographic index between two groups. There was a clear difference of gonadic axis hormon concentration: basic FSH, LH serum levels between two groups. *Basic serum LH level* increased significantly,  $p < 0,0001$  in central precocious puberty group. We also used low dose aGnRH dynamic test to differentiate peripheral precocious puberty and central precocious puberty. Post – test serum LH level,  $LH/FSH > 1$  were different clearly between two groups.

**Conclusions:** Clinically, age at mammary gland appearance characteristics was an important data valuable to orient early diagnosis of puberty forms; bone age advanced over chronological age significantly (by more than 1 year) was also a manifestation of central precocious puberty. Paraclinically, a pelvic ultrasound was a medical test with highly diagnosis value but required well – trained and highly skilled technician and how to prepare for the exam. Quantitative method of basic LH serum level by 2<sup>nd</sup> generation immune assays could be used to evaluate maturation level of gonadotropic axis. It is possible to use low dose aGnRH dynamic test to differentiate central precocious puberty and peripheral precocious puberty.

P3-1314

### AGE AT MENARCHE IN LEBANESE GIRLS

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**Objectives:** For many years, Lebanese pediatricians and gynecologists are following American and European norms for the normal age at menarche. Up until today, there are no published studies about the age at menarche in Lebanon. In

view of this, we conducted a cross-sectional study, in different regions of Lebanon, to determine the age at menarche and to find out factors affecting its onset.

**Methods:** Data was collected by self-administered questionnaires including birth date, address, gestational age, birth weight, breastfeeding, current weight and height, consanguinity, father's profession, nationality, physical activity, diet, tobacco use, age at breast budding, age at menarche and mother's age at menarche. Questionnaires were distributed to girls between 10 and 21 years old, in different private and official schools, chosen randomly in 5 provinces in Lebanon: Beirut, North Lebanon, Mount Lebanon, South Lebanon and Beqaa. Questions were completed by the girls and their mothers at home after informed consent.

**Results:** More than 4247 papers were distributed and a sample of 2090 girls who have attained menarche was obtained. Results of the study were analyzed using SPSS version 20.00 and showed that the mean age at menarche in Lebanon is  $11.84 \pm 1.30$  years whereas the mother's mean age at menarche is  $12.49 \pm 1.45$  proving that the age at menarche in Lebanon has been decreasing over the last several years. In addition, significant correlations ( $p < 0.05$ ) of the age at menarche with the maternal age at menarche, body mass index, region, season and diet were found.

**Conclusions:** The age at menarche in Lebanon is 11.84 years and we found that the most important factors affecting its onset are: maternal age at menarche, body mass index, region and season. Early menarche in Lebanese girls is associated with high BMI as in many countries such as Europe, North America, Kuwait and India. When it comes to the seasons; most of the Lebanese girls get their menarche in the summer season. The Lebanese capital has the higher mean of normal age at menarche than the other Lebanese regions assembled. As for the relation between daughter and mother menarche, our study showed that the girl and the mother have a very close age at which menarche occurs.

P3-1315

#### **PREMATURE SEXUAL MATURATION AS BENIGN AND PATHOLOGICAL CONDITIONS – A 5 YEARS EXPERIENCE IN A SINGLE TERTIARY CENTER**

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**Objectives:** To evaluate a large cohort of boys and girls referred with signs of early puberty and to differentiate cases of precocious puberty as a pathological condition (central and peripheral precocious puberty) versus benign conditions of sexual precocious maturation (early normal variant, premature telarche, premature adrenarche).

**Methods:** Retrospective study of a cohort of 492 boys and girls evaluated in a single tertiary center for precocious sexual maturation between 2012 - 2016. Based on hormonal basal and dynamic tests (GnRH agonist test) and imaging studies, patients were classified as: Early normal variant (ENV): puberty onset at 8-9 years in girls / 9-10 years in boys or puberty onset before 8 years in girls / 9 years in boys and stimulated LH  $< 5$  mIU/mL; Premature telarche (PT): B2-5 P1 before 8 years and stimulated LH  $< 5$  mIU/mL; Premature adrenarche (PA): P2-P5 B1/G1 and stimulated LH  $< 5$  mIU/mL (excluding non-classical congenital adrenal hyperplasia, CAH); Peripheral precocious puberty (PPP): B2 before 8 years in girls, G2 before 9 years in boys, suppressed gonadotropins, increased sex steroids, imaging studies (excluding CAH); Central precocious puberty (CPP): B2 before 8 years in girls, G2 before 9 years in boys, stimulated LH  $> 5$  mIU/mL or basal LH  $> 0.9$  mIU/mL, increased sex steroids.

**Results:** Of all patients, 90.3% ( $n=444$ ) were girls. Diagnostic distribution was: 21.5% had ENV of pubertal onset, 20% had PT, 35% had PA, 21% had CPP and 2.5% had PPP. For each studied year, precocious puberty as a pathological condition (CPP and PPP) was around 25% of total referred cases of precocious sexual maturation. Of cases with benign conditions (ENV, PT, PA), the majority were PA (46.4%). PA had an increasing annual trend in our series. Children with PA had the highest body mass index among all groups. Age at diagnosis in both types of precocious sexual maturation, pathological and benign, overlapped between 5 and 7 years of age.

**Conclusions:** Opposed to precocious puberty as a pathological condition, PA reveals an ascending annual trend amongst benign conditions of premature sexual maturation. Overlapping age interval between pathological and benign types of precocious maturation imposes a testing protocol and follow-up.

P3-1316

#### **OUTCOMES OF GIRLS WITH IDIOPATHIC CENTRAL PRECOCIOUS PUBERTY TREATED WITH 1- AND 3-MONTH GONADOTROPIN-RELEASING HORMONE ANALOG FORMULATIONS**

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**Objectives:** To compare anthropometric and reproductive data between girls with central precocious puberty (CPP) after treatment with 1- and 3- month GnRH analog.

**Methods:** Retrospective analysis of medical records of girls with idiopathic CPP treated with 3-mo leuporelin  $11.25$  mg ( $n = 22$ ; age at onset of treatment:  $8.3 \pm 1.9$  years) and girls treated with 1-mo leuporelin  $3.75$  mg ( $n = 27$ ; age at onset of treatment:  $8.2 \pm 2.5$  years) who were followed up to adult height (AH). Anthropometric (adult height and body mass index) and reproductive data (menarche, the pattern of menstrual cycles, and hormonal profile) were evaluated.

**Results:** The mean duration of treatment was  $2.8 \pm 0.5$  yr and  $2.5 \pm 1.3$  yr in 3- and 1-mo leuprorrelin group, respectively. The AH of girls treated with 3-mo leuprorrelin was  $162.4 \pm 6.3$  cm/SDS  $0.2 \pm 1$ , all of them reached AH within target height range ( $159.7 \pm 6.1$  cm/SDS  $-0.3 \pm 1$ ). The AH of girls treated with 1-mo formulation was  $159.2 \pm 5.1$  cm/SDS  $-0.5 \pm 0.8$ , also within target height range ( $159.5 \pm 4.9$  cm/SDS  $-0.5 \pm 0.8$ ). No side effects were observed in this cohort. A higher prevalence of overweight/obesity was identified in 1-mo leuprorrelin compared with 3-mo leuprorrelin group at adulthood (60% vs 40%, respectively). The interval between the end of treatment and menarche was similar in both groups ( $1.2 \pm 0.4$  yr and  $1 \pm 0.5$  in 3-mo and 1-mo group, respectively). A higher rate of regular menstrual cycles was obtained in those girls treated with 1-mo leuprorrelin compared with girls treated with 3-mo leuprorrelin (81% vs 69%, respectively). Gonadotropin and estradiol levels were normal in all patients. Clinical or laboratory findings of hyperandrogenism were detected in only two patients (one in each group).

**Conclusions:** All patients with CPP treated with both leuprorrelin formulations reached normal adult height. A higher prevalence of overweight/obesity in girls treated with 1-mo leuprorrelin and the higher prevalence of irregular menstrual cycles informed by patients treated with 3-mo leuprorrelin might suggest differences of the two formulations in the long-term outcomes. The underlying mechanism to explain these findings must be further explored. Finally, both formulations were safe and effective for treatment of CPP in girls.

P3-1317

#### EFFECTS OF SUBCUTANEOUS KISSPEPTINE-10 ADMINISTRATION ON SEXUAL DEVELOPMENT OF SPRAGUE DAWLEY RATS DURING LATE GESTATIONAL PERIOD: A DOSE RESPONSE STUDY.

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**Objectives:** How pre-natal kisspeptine-10 administration effects early and late reproductive developments in female rats.

**Methods:** Kisspeptin-10 was administered as sub-chronic subcutaneous dose at three different dosage regimens: Kp(10 pg/kg), Kp(1 ng/kg) and Kp(1 µg/kg), during late gestational period (GD 7 to GD 21) on daily basis. Body Weight (B.W), Anogenital Distance (AGD), Nipple Counting, External Signs of Puberty Onset (P.O), Estrous cyclicity and Tissue histology of ovaries and analysis of hormones were investigated.

#### Results: Abbreviations:

Body weight: B.W  
Ovarian weight: O.W  
Pubertal onset: P.O  
Post-natal day 1: P1  
Primary Follicles: P.F  
Preantral Follicles: P.A.F  
Antral Follicles: A.F  
Corpus Lutea: C.L

No difference in AGD and nipple number at P-1 and at P.O (Tab 1). B.W at P1-14 decreased and O.W at P.O increased in Kp(10pg/Kg) while no change in B.W at P1-14 and O.W at P.O in Kp(1 ng/kg) and Kp(1µg/kg). No change in B.W and O.W in all groups except decrease in O.W in Kp(1 ng/kg) at P75. No change in the uteri, (Tab 2, 3).

No ( $p < 0.05$ ) change in P.F at P.O and at P-75. ( $p < 0.05$ ) reduction in P.A.F in Kp(10 pg/kg) and Kp(1ng/kg) but no ( $p < 0.05$ ) change in Kp(1µg/kg) at P.O, also no ( $p < 0.05$ ) change at P-75 in all groups. ( $p < 0.05$ ) decrease in A.F in Kp(1µg/kg) with no ( $p < 0.05$ ) change in other groups at P.O, while ( $p < 0.05$ ) reduction at P-75 in Kp(10 pg/kg) but no ( $p < 0.05$ ) change in other groups. In C.L no ( $p < 0.05$ ) change in all groups at P.O, while at P-75, Kp(10pg/kg) and Kp(1ng/kg) has ( $p < 0.05$ ) decline with no change in Kp(1µg/kg). A.F ( $p < 0.05$ ) increased in Kp(10 pg/kg) and Kp(1µg/kg) while no change in Kp(1ng/kg) at P.O, Whereas at P-75, ( $p < 0.05$ ) decrease in Kp(1µg/kg) while no change in other groups, Tab 4, 5, fig 4, 5. No ( $p < 0.05$ ) difference in testosterone concentration neither at P.O nor at P-75. Estradiol ( $p < 0.05$ ) increased in Kp(1µg/kg) at P.O but no ( $p < 0.05$ ) change in other groups at P.O and at P-75. Progesterone has no ( $p < 0.05$ ) difference at P.O and at P-75, Tab 7. Estrous cyclicity has changed accordingly to the treatment with kp-10, Tab 6, Fig 7.

**Conclusions:** The study reveals that continuous administration of kisspeptin does not lead to an early maturation but may impair reproductive cyclicity and hormonal secretions.

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Table 1: Relative anogenital distance (AGD), evaluated at postnatal day 1 (PND 1) and pubertal onset and nipple counting at postnatal day 13 (PND 13), from female offspring exposed prenatally to different doses of Kisspeptin-10.

	Anogenital distance (cm)		Nipple Retention <sup>a</sup>
	Pubertal onset	PND 75	
Control	2.08±0.09	1.14±0.05	13(12-14)
Kp-(10 pg/kg)	1.92±0.05	1.2±0.04	12(10-14)
Kp-(1 ng/kg)	2.19±0.12	1.2±0.06	13(11-16)
Kp-(1 µg/kg)	1.77±0.10	1.26±0.02	12(12-14)

Note: Values are expressed as mean±SEM. One-way ANOVA with an a posteriori Dunnett's test. Values are expressed as median (Q1-Q3). Kruska-Wallis with an a posteriori Dunn (Bonferroni) test.

Table 2: Body weight (g) and net weight gain (g) at postnatal day 1 to postnatal day 75 (PND 1-PND 75) of female offspring after maternal Kisspeptin-10 exposure.

	Weight Gain From PND1-PND14 (g)	Body Weight (g)		Net Weight Gain (g)
		Pubertal Onset	PND 75	
Control	15.84±0.30	99.8±1.53	190.5±2.38	184.29±2.39
Kp-(10 pg/kg)	13.72±0.600*	103.6±6.95	178.6±1.75	173.21±1.79
Kp-(1 ng/kg)	14.10±0.37	99.6±5.36	176.25±5.43	169.92±0.67
Kp-(1 µg/kg)	16.16±0.72	112.6±2.32	184.83±8.34	178.59±8.33

Note: Values are expressed as mean±SEM. One-way ANOVA with a posteriori Dunnett's test. Significant difference indicated by \*p< 0.05.

In group 1 (CPP)-The mean basal LH was  $3.7 \pm 1$  IU/L, basal FSH was  $4.54 \pm 1.2$  IU/L, basal estradiol was  $30.99 \pm 7.3$  pmol/L, peak LH was  $15.1 \pm 4.3$  IU/L, peak FSH was  $16.2 \pm 3.9$  IU/L, 120 min estradiol was  $114.7 \pm 20.5$  pmol/L, basal LH/FSH ratio was  $0.7 \pm 0.22$ , and peak LH/FSH ratio was  $2.49 \pm 0.6$ . In group 2 (PT)-The mean basal LH was  $0.39 \pm 0.07$  IU/L, basal FSH was  $3.23 \pm 0.86$  IU/L, basal estradiol was  $9.89 \pm 2.59$  pmol/L, peak LH was  $8.29 \pm 1.44$  IU/L, peak FSH was  $24.17 \pm 1.7$  IU/L, 120 min estradiol was  $15 \pm 4.35$  pmol/L, basal LH/FSH ratio was  $0.17 \pm 0.04$ , peak LH/FSH ratio was  $1.02 \pm 0.51$ .

**Conclusions:** The most common etiology of precocious puberty in girls was idiopathic central precocious puberty and premature thelarche, while in boys they were neurogenic central precocious puberty and CAH. GnRH stimulation test is a useful test to diagnose precocious puberty in children.

P3-1319

# KARYOTYPE, AMH, FSH AND ULTRASOUND AS PREDICTIVE FACTORS OF SPONTANEOUS PUBERTY AND PREMATURE OVARIAN INSUFFICIENCY IN TURNER GIRLS

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**Objectives:** To investigate the value of genetic, clinical and ultrasound features able to predict the onset of spontaneous puberty and to monitor ovarian function in post-pubertal Turner girls (TS) at risk for premature ovarian insufficiency (POI), to create a specific clinical route allowing them to preserve their potential fertility.

**Methods:** All TS girls (n= 65) were recruited from the Department of Pediatrics, San Raffaele Hospital of Milan. Serum Anti Mullerian Hormone (AMH) levels were determined using the AMH Gen II ELISA kit (Beckman-Coulter). According to their karyotype TS patients were divided into three groups: 45,X (n=21), 45,X/46,XX (n=11) and miscellaneous without Y chromosome material (n=33). Pubertal development was established according to Tanner criteria.

**Results:** The prevalence of spontaneous puberty was higher in Turner girls with mosaic karyotype than in girls with monosomia or miscellaneous karyotype. AMH strongly correlated with ovarian status: AMH level was significantly higher in 45,X/46,XX karyotype than in girls with monosomic or miscellaneous karyotype and significantly higher in girls with spontaneous pubertal onset than in girls with induced puberty. AMH cut off level of 0.42 ng/ml well predicted absent puberty in prepubertal Turner syndrome girls. A cut off-level of FSH value as 10 mIU/ml (in girls aged almost 10 years) well discriminated Turner girls with normal ovarian function against those with POI. Interestingly AMH and FSH values were negatively correlated. Detecting follicles at pelvic trans-abdominal ultrasound was strongly correlated to the onset of spontaneous pubertal development and significantly correlated with AMH values.

**Conclusions:** This study confirms that it is possible to discriminate four factors that could help pediatric

P3-1318

## ETIOLOGY, CLINICAL FEATURES AND BIOCHEMICAL PROFILE OF CHILDREN WITH PRECOCIOUS PUBERTY, 5 YEAR STUDY IN A TERTIARY HOSPITAL IN INDIA

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**Objectives:** To evaluate etiology, clinical and biochemical profile of precocious puberty in a cohort of Indian children

**Methods:** In this case-series study, 111 girls and 13 boys with precocious puberty referred to Department of Endocrinology at Manipal Hospital, Bangalore were examined from Oct 2011 to Oct2016.

**Results:** The mean age of girls and boys was  $6.03 \pm 2.9$  years and  $5.2 \pm 1.34$  years respectively. Height  $\geq 2$  SDS was observed in 60 % of the cases at presentation. BMI distribution by groups showed: 48 % girls normal weight, 16 % overweight and 36 % obese. Based on etiology, patients were classified in three categories of Central precocious puberty, peripheral precocious puberty and normal variant puberty. CPP was identified in 44 girls (39.6 %) and 5 boys (38.5%). PPP was identified as the etiology of 5.4 % (6 girls) and 46 % (6 boys) of precocious puberty in girls and boys respectively. Ovarian cysts in 2 girls, McCune-Albright syndrome in 2 girls and non classical CAH in 1 girl were identified as the etiology of peripheral precocious puberty. 3boys with peripheral precocious puberty were diagnosed with CAH and 2boys were diagnosed with adrenal carcinoma. Normal variant puberty was diagnosed in 54.9 % of girls and 18.1 % of boys.

endocrinologists to predict which girls with Turner syndrome will develop spontaneous puberty and among them which girls are at risk of POI and need a close follow-up. These factors are: karyotype, FSH, AMH, follicles at the pelvic trans-abdominal ultrasound. The evaluation of AMH levels could become a fundamental tool for physicians to monitor ovarian function in Turner girls with spontaneous pubertal onset, at risk of POI.

P3-1320

#### THE FUNCTION OF HYPOTALAMO-PITUITARY-GONADAL AXIS AFTER CHILDHOOD HIGH-RISK NEUROBLASTOMA TREATED WITH HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM-CELL TRANSPLANTATION

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**Objectives:** Poor prognosis of childhood high-risk neuroblastoma (HR-NBL) has previously limited the study of long-term endocrine outcome. While increasing the number of survivors, the intensive multimodal therapy with autologous stem cell transplantation includes alkylating chemotherapy and radiotherapy which both may adversely affect gonadal function. The aim of this study was to evaluate the function of hypothalamo-pituitary-gonadal (HPG) axis and fertility in long-term survivors of HR-NBL.

**Methods:** A cohort including all Finnish adult and adolescent (n=21; 9 males) long-term (>10 yrs) survivors of HR-NBL was examined at a median age of 22 (16-30) years. The control group comprised 20 age- and sex-matched healthy young adults. Serum LH, FSH, estradiol/testosterone and inhibin B concentrations were measured, and the use of sex-hormone substitution and number of offspring were recorded. We also retrospectively investigated pubertal timing and history of pubertal induction therapy. Mann-Whitney U test was used for statistical analyses.

**Results:** Puberty had been hormonally induced in 5/21 HR-NBL survivors (1 boy, 4 girls) due to delayed/absent pubertal development; none presented with precocious puberty. At the time of examination, 10/12 female and 3/9 male survivors were on estrogen/testosterone substitution due to gonadal failure. Basal LH concentrations did not differ significantly from controls (median 6.2 vs 4.2 IU/l, p=0.16), while median FSH was higher among the survivors (10.1 vs. 4.6 IU/l, p=0.024). Estradiol concentrations were similar in survivor and control females (0.22 vs. 0.13 nmol/l, p=0.61). Male survivors had smaller testicular size (8.5 vs. 40 ml, p<0.001) and lower inhibin B levels (<10 vs. 170 ng/l, p>0.001) compared with control males. Altogether 3 survivors (1 male, 2 females) had children; all with history of spontaneous puberty and without hormone substitution or total-body irradiation.

**Conclusions:** Dysfunction of HPG axis is common in both males and females after childhood HR-NBL and should be

addressed in the follow-up of the growing group of long-term survivors.

P3-1321

#### SERUM AMH AND INHIBIN B LEVELS BETWEEN BEFORE AND DURING TREATMENT WITH GNRH AGONISTS IN GIRLS WITH CENTRAL PRECOCIOUS PUBERTY

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**Objectives:** In girls with central precocious puberty (CPP), the hypothalamic-pituitary-gonadal axis is prematurely activated. If the girl is treated with GnRH agonist (GnRH-a), gonadotropins levels become suppressed. We aimed to evaluate whether serum antimüllerian hormone (AMH) and inhibin B levels are affected in girls with CPP and whether pituitary suppression by GnRH-a affects serum AMH and inhibin B levels.

**Methods:** Thirty-six girls who were diagnosed with CPP by GnRH stimulation test followed during GnRH-a treatment. We analyzed serum AMH and inhibin B levels before, 6 and 12 months after initiation of treatment. To investigate whether AMH and inhibin B levels were affected in girls with CPP, baseline levels were compared with levels in age-matched healthy girls (n=35).

**Results:** Before treatment, serum AMH levels (mean±SD) in girls with CPP showed no significant difference compared with levels in controls (7.5±6.8 vs 7.1±2.4 ng/mL, P=0.742). However, serum inhibin B levels in girls with CPP were significantly higher than that in controls (66.7±51.4 vs 16.4±7.9 pg/mL, P<0.001). After 6 months of treatment, AMH declined to 5.3±3.7 ng/mL (P=0.016) and inhibin B also decreased to 37.8±29.4 pg/mL (P<0.001). The AMH and inhibin B levels were more suppressed after 12 months of treatment (AMH: 4.4±3.2 ng/mL, P<0.001, inhibin B: 22.5±19.8 pg/mL, P<0.001). Serum AMH levels were not correlated with basal LH, basal FSH, peak LH, peak FSH, Estradiol and inhibin B levels.

**Conclusions:** In girls with CPP, serum AMH levels are not affected while serum inhibin B levels are elevated compared with levels in controls. The partial suppression of AMH by GnRH-a treatment suggests that AMH has partial dependence to gonadotropin. Further studies including the result after discontinuation of treatment are needed to prove our results.

P3-1322

#### RESTORATION OF OVULATION AFTER UNILATERAL OOPHORECTOMY IN AN ADOLESCENT WITH MCCUNE-ALBRIGHT SYNDROME

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**Background:** McCune-Albright syndrome (MAS) is characterized by endocrine hyperfunction, polyostotic fibrous dysplasia and café-au-lait spots. The most frequent endocrine presentation is gonadotropin-independent precocious puberty due to autonomous ovarian function. It is caused by a post-zygotic activating somatic mutation of the GNAS1 gene, which is variably expressed in tissues. Persistent autonomous ovarian function in MAS is associated with the development of multiple dominant follicles, premature luteinization and anovulatory infertility.

**Methods:** N/A

**Results: Case presentation:** Patient presented at 6 months with peripheral precocious puberty with vaginal bleeding, breast development, elevated estradiol levels and suppressed gonadotropins. She was treated with aromatase inhibitors and estrogen receptor antagonist (Tamoxifen) until age 10. Menses subsequently resumed within a year. During medical suppression, she had estradiol levels >200 pg/mL (prepubertal <14). She never developed café-au-lait spots; however at age 16 was found to have an asymptomatic focus of fibrous dysplasia on her sphenoid bone. Her adult height is 144.2 cm (~0.1 percentile), and her calculated midparental height is 158 cm (~25 percentile).

She had persistent menorrhagia and anemia despite cyclic progesterone treatment. Her estradiol levels were >1000 pg/mL with undetectable gonadotropins. Serial pelvic ultrasounds demonstrated persistently enlarged right ovarian cyst. Laparoscopic right ovarian cystectomy pathology confirmed the presence of a missense point mutation at codon 201 substituting Arg with His on the GNAS1 gene, constitutively activating the Gs protein.

Subsequent ovarian ultrasounds revealed recurrent right ovarian cysts, with normal left ovarian imaging. Given her ongoing menorrhagia despite high dose progestins, a right salpingo-oophorectomy was performed to remove the autonomous ovarian tissue. Post-operatively, the patient had normal levels of estradiol and unsuppressed gonadotropins. Her menses occur monthly for 5 days only.

**Conclusions:** Our patient had normal levels of estradiol and resumption of normal menses after oophorectomy. Surgical resection may be an option for the control of unilateral autonomous MAS disease.

P3-1323

#### PROTEIN-TRUNCATING MUTATION IN “GENE A” IN A GIRL WITH CENTRAL PRECOCIOUS PUBERTY: IMPLICATIONS FOR A NOVEL GAIN-OF-FUNCTION MECHANISM OF G-PROTEIN COUPLED RECEPTORS

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**Objectives:** The human genome encodes approximately 750 G-protein coupled receptors (GPCRs). Previously reported pathogenic gain-of-function mutations of GPCR genes invariably encoded receptors with excessive signal transduction activity. Although *in vitro* assays demonstrated that an artificially created inactive mutant of the GPCR “A” exerted paradoxical gain-of-function effects when co-transfected with wildtype proteins, such a phenomenon has not been observed *in vivo*. Here, we report a protein-truncating mutation in “gene A” identified in a patient with precocious puberty.

**Methods:** Clinical and molecular analysis of a 3.5-year-old girl with central precocious puberty and functional assessment of the identified mutation.

**Results:** The girl exhibited early breast budding and accelerated statural growth. Clinical examinations demonstrated advanced bone age, elevated serum estradiol, and gonadotropin hyperresponses to GnRH. Sequence analyses identified a heterozygous frameshift mutation in “gene A”. The mutant mRNA escaped nonsense-mediated decay and generated a truncated GPCR lacking two transmembrane domains and the carboxyl terminal tail. The mutant protein was less frequently expressed on the cell surface than the wildtype protein and retained no *in vitro* signal transduction activity; however, co-transfection of the mutant with wildtype proteins resulted in markedly exaggerated ligand-induced Ca<sup>2+</sup> responses.

**Conclusions:** The results indicate that certain inactive mutants of the GPCR “A” can lead to central precocious puberty by enhancing the functional property of coexisting wildtype proteins. Considering the structural similarity among all GPCRs, this paradoxical gain-of-function mechanism may also underlie other human disorders.

P3-1324

#### AN UNCOMMON CAUSE OF PRECOCIOUS PUBARCHÉ. – A CHALLENGING DIAGNOSIS.

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**Objectives:** Precocious pubarche (PP) is generally due to alterations in adrenal synthesis (congenital adrenal hyperplasia), adrenal tumor or idiopathic. We present a clinical case of a young girl with PP due to a rare source.

**Methods:** A case report is described

**Results:** A 1,7 year-old girl was referred due to presence of pubic hair and enlargement of clitoris one month earlier associated with one acne and gain of stature (3 cm) and weight (1.5 kg), since then. Her previous medical history (gestation, birth record, and follow-up) was uneventful. On physical exam: 13.5 kg and 89.5 cm, B1P2 with mild enlarged clitoris. Initial exams: FSH: 0.2 UI/L ; LH < 0.1 UI/L ; ACTH: 59 pg/mL (7 - 63); Cortisol: 13.7 µg/dL; Estradiol: 0,6 ng/dL; 17 OH Progesterone: 262 ng/dL; Abdomen and Pelvic US:



normal. Additional exams revealed: 17 OH Progesterone: 421 ng/dL (< 100) ; Androstenedione: 75 ng/dL (< 50); DHEA-S: 25 µg/dL (< 19); **Testosterone (T): 743 ng/dL (< 40)**; IGF-1: 415 ng/mL (44 - 356); IGFBP-3: 5330 ng/mL (700 - 3500). At 1.9 years old an ACTH test was performed with no elevation of 17 OHP and other adrenal hormones but, persistence of elevated T levels (781 ng/dL). At 2 years old, (seven months after her initial symptoms) her physical exams showed 19.1 kg (z: 6.41); 96.5 cm (z: 2.5); M1P2-3, hoarse voice, more acne and muscle hypertrophy of upper and lower limbs, as a clinical progression of her persistent elevated T levels. Although DHEA-S levels were normal a MRI scan of abdomen and pelvic region was performed and a mass was shown at left ovarian region. She was submitted to laparoscopic procedure and a 2.8 cm tumor was removed. Histopathologic evaluation revealed an **ovarian steroid cell tumor, not otherwise specified**. One month later, T level dropped to 9 ng/dL, and she is progressively decreasing her hyperandrogenic features, but still on follow up.

**Conclusions:** Although rare, it is important to remember ovarian tumor as a cause of hyperandrogenism in girls with precocious pubarche and intervene promptly in order to avoid late diagnosis in these patients.

P3-1325

#### **TESTOTOXICOSIS WITH ESCAPE INTO CENTRAL PRECOCIOUS PUBERTY: IS GnRH AGONIST TRULY NEEDED?**

*Tracy Patel, MD, Baylor College of Medicine, Houston, TX, United States*

**Objectives:** To describe the case of a boy with testotoxicosis who was not treated with GnRH agonist after escape into central precocious puberty (CPP).

**Methods:** Case Report

**Results:** A 2.8 yo male presented for evaluation of premature pubarche, enlarged phallus & accelerated growth velocity (GV). Serum testosterone (T) was 201 ng/dL with prepubertal LH level. Bone age (BA) was advanced at 6 yrs. Molecular genetics confirmed an activating mutation of the LH receptor. He was treated with flutamide & letrozole with decline in GV, slowing of progression of virilization & skeletal maturation (SM). T levels ranged from 179 to 332 ng/dL. At 5.4 yrs he had increase in testicular size. T levels had increased to 479 ng/dL. LH was elevated, consistent with CPP. E2 was suppressed. GV & SM were stable. Decision was made to forego addition of GnRH agonist & he was closely monitored. From age 5.4 to 8.1 yrs, he had increase in testicular size as expected in CPP. T levels ranged 409 to 669 ng/dL. However GV remained stable, ranging 3.2 to 6 cm/yr, with no evidence of accelerated SM. E2 remained undetectable. At 8.5 yrs his GV increased to 8.8 cm/yr & testes were 12 cc. Bone age was 12.5 yrs with acceleration in SM. Predicted adult height remained stable. T level had increased to 999 ng/dL with E2 12 pg/mL. Lupron was initiated with subsequent decline in T levels, ranging 403 to 710 ng/dL, suppression of E2 & slowing of GV.

**Conclusions:** Testotoxicosis is a rare disorder characterized by increased T production independent of LH stimulation.

Various treatment options exist, with combination of androgen receptor (AR) antagonist and aromatase inhibitor gaining favor in recent reports. Regardless of treatment modality, escape into CPP is common. This is the first report to my knowledge where GnRH agonist was not immediately initiated after biochemical escape into CPP was detected. Clinically the patient remained stable for nearly 3 years. It can be argued that the increase in T caused by secondary CPP in the setting of supraphysiologic T levels may not have clinical consequence in the context of good inhibition of the AR and aromatase activity. Parameters such as GV, rate of SM, and E2 levels may be better determinants when considering GnRH agonist therapy.

P3-1326

#### **IS IT EXTREME POLYCYSTIC OVARIAN SYNDROME OR A TUMOR?**

*Sonalee J Ravi, MD; Melanie Cree-Green, MD, University of Colorado School of Medicine, Aurora, CO, United States; Nicholas Gilman, MD, Denver Health, Denver, CO, United States*

**Objectives:** Polycystic Ovarian Syndrome (PCOS) is a common cause of elevated androgens in adolescent girls and is diagnosed based on clinical and/or biochemical evidence of hyperandrogenism in the presence of persistent oligomenorrhea once other potentially pathologic causes of hyperandrogenism or oligomenorrhea are ruled out.

**Methods:** A 12 year old Tanner III breast and Tanner V pubic hair, pre-menarchal female presented with severe hirsutism (Ferriman-Gallwey Score of 22), clitoromegaly and excessively deep voice. We present here her initial presentation after 2.5 years of symptoms, dynamic hormone testing to exclude rare causes of hyperandrogenism, and presentation after 6 months of therapeutic follow-up.

**Results:** Her initial evaluation was notable for a 46,XX karyotype, pubertal but not significantly elevated FSH and LH with LH:FSH ratio >2, and pubertal progesterone, estrone and estradiol. Her 2pm 17-hydroxyprogesterone was high normal (128 ng/dL). 250mcg ACTH stimulation testing showed baseline 17-hydroxypregnenolone, 11-deoxycortisol, dehydroepiandrosterone, androstenedione, and testosterone all > 2-3 times the upper limit of normal and not consistent with a single enzyme defect, with minimal stimulated elevations. Abdominal and pelvic imaging did not reveal a tumor. A dexamethasone suppressed ACTH test was performed and adrenal androgens were suppressed whereas ovarian androgens were not. Metabolic labs were notable for elevated fasting (39 µIU/mL) and post-prandial (>300 µIU/mL) insulins. After 3 months of daily 20 mcg estrogen containing oral contraceptives, 100 mg spironolactone and 2000 mg metformin, all baseline concentrations decreased to normal however the patient had not yet attained menses. She was increased to a 30 mcg estrogen oral contraceptive and continued on spironolactone and metformin. After 6 months of total estrogen therapy the patient had decreased

hirsutism, and menarche though no change in the pitch of her voice.

**Conclusions:** This case demonstrates severe clinical findings of PCOS, with initial labs suggesting of congenital adrenal hyperplasia or a tumor. This testing however was negative despite extreme findings and biochemical and clinical findings resolved with estrogen treatment.

Table 1: Hormone Measurements

Hormone measurement	Initial labs	Pre-ACTH stimulation	Post ACTH Stimulation	Post-Dexamethasone suppression	ACTH stimulation Post-Dexamethasone	Post 3 months OCPS
<b>Androgen Pathway</b>						
DHEA (<202 ng/dL)		582	585	193	465	74
DHEA-S (32-248 ug/dL)	208			94	95	
Androstenedione (28-230 ng/dL)	413	734	517	438	457	40
Total Testosterone (6-50 ng/dL)	121	148	144	162	154	8.4
Free Testosterone (0.9-6.8 pg/mL)	21					
Dihydrotestosterone (4-22 ng/dL)		17	17			
<b>Glucocorticoid Pathway</b>						
17-OH Pregnenolone (44-235 ng/dL)		1047	1362	53	1023	52
17-Hydroxyprogesterone (<129 ng/dL)	128	187	236	108	171	16
11-deoxycortisol (12-158 ng/dL)		177	193	<10	123	20
Cortisol (2.5-25 ug/dL)	20.4	21	31	<1	23	39
<b>Mineralocorticoid Pathway</b>						
Progesterone (10-856 ng/dL)		23	40	10	31	<10
11-Deoxycorticosterone (2-19 ng/dL)		26	39	3.6	23	2.4
Plasma Renin Activity (0.5-3.3 ng/mL)	2.69					
<b>Non-Adrenal</b>						
Sex Hormone Binding Globulin (17-155 nmol/L)	32					
FSH (1.2-11 mIU/mL)	3.6					
LH (0.1-11 mIU/mL)	9.9					
Prolactin (1.9-25 ng/mL)	9					
Estradiol (7-170 pg/mL)	45.4	47	47			
Estrone (15-105 pg/mL)		89	71			

P3-1327

**PREMATURE OVARIAN FAILURE IN AN ADOLESCENT WITH ECTRODACTYLY, ECTODERMAL DYSPLASIA SYNDROME**

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**Objectives:** We present a case of an adolescent female with Ectrodactyly, Ectodermal Dysplasia and Cleft Lip/Palate (EEC syndrome) who developed premature ovarian failure, which has not previously been reported in association with this syndrome.

**Methods:** A 14 year 7 month old female with EEC syndrome presented with secondary amenorrhea. Menarche was at age 12 years. She had regular menses for 13 months, becoming lighter and shorter before ceasing at age 13 years 5 months. On exam she was underweight. She had ectrodactyly, split hands and feet. Scalp and eyebrow hair was thin, and body was hairless. Hearing aids were in place. There was adontia as

well as dysplastic teeth with caries. Surgical scars of cleft lip and palate repair were noted. Breasts were tanner 5 but small and flaccid. Pubic hair was absent. Vaginal introitus was unestrogenized.

**Results:** Labs revealed FSH 151.9 mIU/mL, LH 41.6 mIU/mL, and Estradiol <5 pg/mL. On imaging, the uterus appeared pre-pubertal, right ovary was not visualized, and the left ovary was small at 1.1cc. Unilateral right sided hydroureter with hydronephrosis was noted. Genetic testing confirmed a mutation in the TP63 gene consistent with EEC3 syndrome. Testing for known causes of ovarian failure was unremarkable. The patient was diagnosed with premature ovarian failure and estradiol therapy initiated.

**Conclusions:** EEC syndrome is a rare autosomal dominant disease characterized by split hands, hearing loss, malformed hair, teeth and nails, and cleft lip/palate. It affects approximately 1.5 in one million births. Genitourinary anomalies are common, presenting as cystic kidneys, megaureter, or ureteroceles. Reproductive anomalies are rare. Transverse vaginal septum and imperforate hymen have been described. Central hypogonadism has been reported, in addition to other pituitary deficiencies, but primary gonadal failure has not been reported.

Premature ovarian failure occurs in only 0.01% of women under the age of 20. Known causes of premature ovarian failure include Turner syndrome, Fragile X premutation, autoimmune oophoritis, and infection. These etiologies were not identified in our patient. This is the first reported case of premature ovarian failure as a feature of EEC Syndrome.

P3-1328

**HEMATOSPERMIA IN 2 ADOLESCENTS; SHOULD WE WORRY?**

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**Objectives:** We report the clinical aspects of 2 adolescents patients with hemospermia

**Methods:** The two patients were brought because their mothers noted blood stains on his underpants interpreted as "sleep nocturnal ejaculation" (wet dream). Both were not sexually active and he denied masturbation. No history of trauma or dysuria, no history of hemorrhagic disease or medication in the previous year

**Results:** The 1st patient had unremarkable physical and genital examinations. Blood pressure (BP) was within the normal range. He was in mid puberty (pubic hair Tanner stage 4; testicular volume 10 ml bilaterally; total testosterone 11.5 nmol/L). Urine analysis and culture were normal. After the second episode, he was treated with ciprofloxacin for ten days. A third episode occurred 10 days after having stopped therapy. A pelvic MRI scan was requested. The MRI documented a cyst located along the midline of the prostate with a size of 3 x 2 mm suggesting Müllerian duct cyst or prostatic utricular cyst. MRI T1-weighted images revealed a hemorrhagic focus in the right seminal vesicle and ejaculatory duct. Thee patient had no further episodes for 10 months.

The 2nd patient had history of treatment at the age of 9 years with leuprolide for precocious puberty associated with pineal cyst, which was stopped at the age of 11 years. His physical and genital examinations were unremarkable. The BP was normal as well as linear growth. His testicular volume was 15 ml, bilaterally; and total testosterone 12.67 nmol/L. Urine analysis and culture, serum prostate specific antigen (PSA) (0.6 ng/ml), renal and bladder ultrasound were normal. Hematospermia recurred with an incomplete penile tumescence during a medical examination. The seminal fluid was brown in color with an apparent normal viscosity. . Trans rectal ultrasound (TRUS) was not accepted by the patient. MRI showed high-intensity signals on T1-weighted suggested a hemorrhagic focus in the right seminal vesicle. After 10 months reated MRI confirmed the previous diagnosis. Hematospermia recurred 5 times during 3 years of follow-up. **Conclusions:** In adolescents with hematospermia the duration and recurrence of hematospermia and the presence of associated symptoms should influence the decision for further evaluation. MRI improves visualization and diagnosis.

P3-1329

#### **PRECOCIOUS PUBERTY IN RESOURCE LIMITED SETTINGS; DESCRIPTIONS AND FINDINGS FROM CASES IN A TERTIARY REFERRAL CENTRE**

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**Objectives:** The objectives of the study were to describe the cases of precocious puberty which presented to a tertiary referral centre in Botswana over a 6 year period from 2010-16 by reviewing their clinical presentation, diagnosis , management and outcomes.

**Methods:** This was a retrospective charts review of all individual cases of precocious puberty which presented to the Paediatric Endocrinology clinic at a tertiary referral centre in Botswana in the period between 2010-2016. The demographic profile, clinical presentation, diagnosis, management and outcomes were captured during the regular clinic visits as routine part of clinical care during the aforementioned period. The information was retrospectively studied to characterize the cases and their outcomes.

**Results:** From 2010 to 2016, there were 9 cases of precocious puberty that were diagnosed at a tertiary referral centre in Botswana. There were 8 females and 1 male. The median age for the group was 6.5 years. The most common mode of clinical presentation was the development of pubic hair followed by breast enlargement and rapid growth. The basic investigations that lead to the confirmation of the diagnosis included the Bone Age X Ray, Follicle Stimulating Hormone(FSH) levels, Leutenizing Hormone(LH) levels and Estradiol/Testosterone levels. Of the 9 cases, 8 had central precocious puberty which was successfully treated with Gonadotropin-releasing Hormone(GnRH) analogue, leuprolide. One case had peripheral precocious puberty of unknown

cause which spontaneously resolved without any medical treatment

**Conclusions:** Precocious puberty tend to present late(median age 6.5 years) in our setting compared to reports from high income setting where the median age at diagnosis was 5.3 years. The diagnosis and successful management of precocious puberty is feasible in our setting with limited resources.

P3-1330

#### **A SECULAR TREND OF AGES AT MENARCHE AND SPERMARCHE IN KOREAN ADOLESCENTS OVER A DECADE: USING THE KOREA YOUTH RISK BEHAVIOR WEB-BASED SURVEY (KYRBS) 2006-2015.**

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**Objectives:** It is noted that spermarche begins at SMR 3 in boys and menarche begins at SMR 3-4 in girls. While previous studies have demonstrated that the mean age of menarche has been declining constantly, little is known about secular trend in mean ages of both menarche and spermarche in Korean population. The objective of this study is to reveal the pubertal trend in age at menarche and spermarche in Korean adolescents over the past decade since 2006.

**Methods:** Data collected from the KYRBS between 2006 and 2015 were used for the analysis. KYRBS is a cross-sectional, nationwide school-based web survey with a stratified multistage probability sampling design. It has a national representative sample of Korean students in Grades 7-12 and is conducted annually. Students completed self-administered survey during the regular school hours under the supervision. We conducted a cross-sectional analysis of self-reported age at menarche and spermarche. Descriptive statistics were calculated to demonstrate the general characteristics of the study population.

**Results:** The sample size of a survey varies from 68,043 to 75,643 of which approximately 52-3% are boys and 46-47% are girls. Through years, the minimum average age of the study population is 14.94 (SD, 0.02) in 2006, and the maximum is 15.15 (SD, 0.02) in 2010. Timing of menarche and spermarche tends to shift downward; while increases of 5.43% and 0.16% in experiencing menarche and spermarche, respectively, were observed in Grade 7, decreases of 3.57% and 5.43% in experiencing menarche and spermarche respectively, were observed in Grade 9. In addition, the mean age at menarche in 2015 was 12.241 years which showed a decrease from 12.457 years in the 2005. The mean age at spermarche in 2015 was 12.997 years, which showed a notable decrease from 13.148 years in the 2005.

**Conclusions:** We have found the ages at menarche and spermarche have been falling in the Korean adolescents for the last 10 years. Further analysis including potential risk factors of early menarche and spermarche needs to be

performed to identify underlying causes of these secular trends in the Korean adolescents.

P3-1331

#### **SUBNORMAL GROWTH VELOCITY AND RELATED FACTORS DURING GnRH ANALOG THERAPY FOR IDIOPATHIC CENTRAL PRECOCIOUS PUBERTY**

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**Objectives:** Decline of subnormal growth velocity (GV) and related factors during gonadotropin-releasing hormone analog (GnRHa) therapy for idiopathic central precocious puberty (ICPP) are unclear. We investigated the incidence of subnormal growth velocity, associated factors and clinical effects in patients with GnRHa therapy for ICPP.

**Methods:** The records of 50 girls were investigated, who had diagnosed ICPP and had started GnRHa treatment before the age of 8. Subnormal GV frequency, related factors and effects on final height (FH) during GnRHa therapy were investigated.

**Results:** During the treatment, a significant decrease in the annual GV and GVSDS of the patients is observed over the years ( $p:0.02$  and  $p:0.001$  respectively). 16(32%) patients' GV never decline below  $-1$  SDS, while 19(38%) patients' dropped 1 time, 15(30%) patients' dropped 2 times below  $-1$  SDS. The age of detection of subnormal GV was median 9.9(4.9-10.9). Patients with pubic hair at diagnosis were found to have an increased risk of subnormal GV ( $p:0.016$ ). There was a significant negative correlation between basal LH level at diagnosis and the first and second year GVSDS ( $p:0.012$  and  $0.017$ ). A significant negative correlation between the BA at diagnosis and the 1st year GV, 3rd year GV and GVSDS, and 4th year GVSDS ( $p<0.005$ ) is also observed. LH suppression had significantly increased during treatment ( $p:0.001$ ).

**Conclusions:** It should be considered that during GnRHa treatment the risk of subnormal GV is high at 3rd year of treatment, in patients with pubic hair at diagnosis, have high baseline and peak LH at diagnosis, advanced BA and excessive LH suppression on follow-up.

## **POSTER SESSION 3**

**Saturday, September 16, 2017, 12:00-1:00pm**

### **P3 - Sex differentiation/gonads and disorders of sex development**

**P3-1500 – P3-1539**

P3-1500

#### **PHENOTYPIC, HORMONAL AND MOLECULAR GENETIC CHARACTERISTICS OF 5-ALPHA REDUCTASE TYPE 2 DEFICIENCY PATIENTS: A MULTICENTER STUDY FROM TURKEY**

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**Objectives:** To present the genotype-phenotype correlations and clinical characteristics of patients with genetically confirmed 5-alpha reductase type 2 deficiency (5ART2D) and to determine the diagnostic value of testosterone/dihydrotestosterone (T/DHT) ratio, which is currently being used in many centers due to the limited access to molecular genetic tests.

**Methods:** 5ART2D patients with homozygous or compound heterozygous mutations in the *SRD5A2* gene were included in

the study. Consanguinity, family history; age, complaint, gender and pubertal status at presentation; gender of rearing and the results of the hormonal tests and molecular genetic analyzes were recorded from the national database.

**Results:** A total of 89 cases were included in the study. The median age at presentation was 2.4 years. Consanguinity between the parents was 75.3%. In 41.1% of the cases there was at least one individual in the family with similar clinical phenotype. 93.3% of the cases presented with the complaint of genital abnormality. At admission, 51.7% of the patients were female, 44.9% were male and 3.4% were ambiguous. After diagnosis, the final sex decision was male in 59.5% and female in 27%, while 13.5% of the patients have not decided yet. Homozygous mutation was found in 79 of the cases and 10 were compound heterozygous. The most frequently identified mutations were p.Ala65Pr; p.Leu55Gln; p.Gly196Ser; and p.Met157del homozygous mutations in 29.2%, 15.7%, 15.7%, and 5.6% of the patients, respectively. While the male phenotype was dominant in the cases with the p.Gly196Ser mutation, p.Ala65Pro and p.Leu55Gln mutations indicated a more undervirilized and female dominant phenotype. Basal and HCG stimulated T/DHT ratio cut-off values were demonstrated in Table 1.

**Conclusions:** This study suggests that a cut-off value >10 for T/DHT ratio can be used for the diagnosis of 5ART2D in centers, where genetic analysis is not available. Clinical findings are heterogeneous due to the severity of the mutation causing enzyme deficiency. In this study, the most frequent mutations observed in Turkish population were p.Ala65Pro, p.Leu55Gln and p.Gly196Ser, respectively. It was found that the virilization defects in the p.Ala65Pro and p.Leu55Gln mutations were more severe than p.Gly196Ser mutation.

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**Table 1.** Sensitivity of basal and stimulated T / DHT ratios in the diagnosis of 5-Alpha Reductase Type 2 Deficiency according to pubertal status:

	Mini-puberty (<6 months) (n=12)	Prepubertal (n=2)	Pubertal (n=14)	Total (n=28)
Basal T/DHT (n=28)				
>8,5	9 (%75)	0 (%0)	12 (%85,7)	21 (%75)
Basal T/DHT (n=28)				
>10	9 (%75)	0 (%0)	12 (%85,7)	21 (%75)
Basal T/DHT (n=28)				
>20	6 (%50)	0 (%0)	9 (%64,3)	15 (%53,6)
Basal T/DHT (n=28)				
>30	3 (%25)	0 (%0)	9 (%64,3)	12 (%42,9)
	Mini-puberty (<6 months) (n=15)	Prepubertal (n=43)	Pubertal (n=4)	Total (n=62)
Stimulated T/DHT (n=62)				
>8,5	14 (%93,3)	39 (%90,7)	4 (%100)	57 (%91,9)
Stimulated T/DHT (n=62)				
>10	13 (%86,7)	38 (%88,4)	4 (%100)	56 (%88,7)
Stimulated T/DHT (n=62)				
>20	9 (%60)	30 (%69,8)	3 (%75)	42 (%67,7)
Stimulated T/DHT (n=62)				
>30	5 (%33,3)	24 (%55,8)	3 (%75)	32 (%51,6)

Values in the round brackets are sensitivity

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P3-1501

**FOG2 (ZFPM2) IS A CANDIDATE DISEASE GENE FOR PRIMARY OVARIAN INSUFFICIENCY**

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**Objectives:** Primary ovarian insufficiency (POI) is a major cause of female infertility affecting approximately 1% of women under the age of 40. POI can be the consequence of either follicle dysfunction or depletion and numerous causes are known, ranging from chemo- and radiotherapy to

autoimmune disorders. For a subgroup of patients POI is related to genetic defects. Based on the identification of a heterozygous *Friend of GATA2 (FOG2, ZFPM2)* deletion in a boy with 46,XY disorder of sex development (DSD) and in his 27 years old mother, who had a low serum AMH, suggestive of decreased follicular reserve, we reasoned that mutations in the *FOG2* gene might contribute to POI pathogenesis. To corroborate this hypothesis, we sequenced the *FOG2* gene in a large cohort (n=381) of women with POI.

**Methods:** Copy number analysis of *FOG2* was performed in the index case with array-CGH followed by qPCR validation. Targeted resequencing of *FOG2* was conducted in 24 Belgian and 357 French women with POI. Functional validation of the identified variants was performed by luciferase assays in HEK293T cells.

**Results:** We identified four novel heterozygous *FOG2* variants in the POI cohort: one out-of-frame duplication and three missense variants. Prediction algorithms suggest a deleterious effect for all variants, and all are either absent in publicly available databases like ExAC and gnomAD or occur at a population frequency <1%. Luciferase assays showed significantly lowered transcriptional activation of the mutated *FOG2/GATA4* complex for three of the identified variants.

**Conclusions:** We demonstrate that *FOG2* haploinsufficiency is associated with POI, suggesting a role for *FOG2* in human ovarian maintenance. The phenotypic spectrum of *FOG2* mutations is herewith expanded to include not only cardiac anomalies, congenital diaphragmatic hernia and 46,XY DSD, but also 46,XX POI.

P3-1502

#### **45,X/46,XY MOSAICISMS IN MALE: LONG-TERM OUTCOMES. A MULTICENTER ITALIAN-DSD STUDY GROUP SURVEY.**

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**Objectives:** To describe the long-term outcomes (i.e. gonadal function, adult height and co-morbidities) in a group of 24 males with 45,X/46,XY mosaicism and variants, recruited by the Italian "It-DSD Study Group" ([www.gruppodistudio-it-dsd.org/](http://www.gruppodistudio-it-dsd.org/)).

**Methods:** Multicenter retrospective study by specific developed electronic data-sheet. Only patients who reached adult or near adult (1 case) height were included.

**Results:** In total, 24 males from 9 Italian Centers were enrolled [mean age at the last evaluation 23.3 years (range 13.5–70 years)]. 37.5%(9/24) of the patients presented a "classical" 45,X/46,XY karyotype in blood (7/24) or gonadal tissue (2/24); 63% showed an abnormal structure or duplication of the Y chromosome. External masculinization score (EMS) at time of diagnosis was 8.0 (r 2–12). 19 patients (79.1%) entered puberty spontaneously; 7 (29.1%) had received testosterone treatment; 8 out of 17 untreated patients (47.0%) presented increased FSH and low testosterone levels at the end of puberty. 13 patients (54.1%) had received growth hormone (GH) treatment, started at a mean age of 10.9 (r 6–13.9 years), for a mean period of 5.6 years (r 1.9 - 9 years) at a dose of 20–40 mcg/kg/d. Whole final height was 155.8 cm (r 140.0–167.9; mean Delta FH-TH -2.7 SDS), with no difference between GH treated (158.3 cm) vs. GH not treated (152.9 cm) cases (p=0.0951). 5 patients (20.8%) had renal abnormalities and 1 (4.1%) had congenital cardiac malformations. 1 patient (4.1%) had a gonadal tumor and apparently no one had precursor lesions.

**Conclusions:** Most of 45,X/46,XY children raised as boys entered puberty spontaneously, but they showed an altered pubertal course. All of them, independently from genital phenotype, have adult short stature and did not benefit significantly from GH therapy, at least at the used doses. The prevalence of gonadal neoplasia *in situ* or tumors appears to be low in this series, although the histology was available in a limited number of cases. The multidisciplinary-multicentre structure of the It.DSD Study Group may represent a national base for collaborative studies in the field of sexual development and an opportunity - in collaboration with official Societies - for the European Reference Network for rare endocrine conditions (ENDO-ERN).

P3-1503

#### **THE EVALUATION OF CASES WITH GONADAL DYSGENESIS: CLINICAL EXPERIENCE FOR 18 YEARS**

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**Objectives:** Gonadal dysgenesis (GD) is a rare subgroup of disorders of sexual development (DSD) which results from underdeveloped gonads, which may consist heterogenous symptoms. They are described as, partial and complet GD, phenotypically, and 46,XY GD, 46,XX GD, 45X/46,XY mixed GD, karyotypically. We aimed to evaluate the characteristics

of the cases with GD and provide some information to help with the diagnosis and treatment of them.

**Methods:** Fiftyone cases with gonadal developmental disorders were followed-up between 1998 and 2016. Within them, 42 cases were diagnosed with GD and 9 cases had ovotesticular syndrome. The age of admission of cases with GD were 0 to 22 years. Clinical and laboratory findings as well as follow-up characteristics of cases were evaluated. Patients with Turner and Klinefelter syndrome were excluded from the study.

**Results:** There were 25 cases (4 complete, 21 partial) in the 46,XY GD, 12 cases (4 complete, 8 partial) were mixed 45X/46,XY GD and 5 cases were 46,XX GD. The mean ages on the admission were; 7.2 years for all cases, 6.72 years for the 46,XY GD, 5.14 years for the mixed 45X/46,XY GD and 15.26 years for the 46,XX GD. Patients with complete GD in the mixed GD group were diagnosed earlier than the patients with complete GD in the 46,XY group.

Additional clinical findings, mainly short stature, were detected in 75% of the patients in the mixed GD and 32% of the patients in the 46,XY GD. Two patients within 46,XX GD group were diagnosed with Perrault syndrome. There was no additional findings in 54% of all patients.

All patients with complete GD in 46,XX and 4 patients with mixed 45X/46,XY GD (13%) were raised as females. There was no gender dysphoria in patients that were raised as females, except one. Gonadectomy was applied to the patients with a mean age of 8.75 years and gonadal pathology results were normal in all cases with no malignity.

**Conclusions:** The cases of GD's consist a heterogenous group within DSD. The more frequent occurrence of additional systemic findings in the mixed 45X/46,XY GD group, especially the ones with the complete GD, could lead to an earlier diagnosis than the cases with 46,XY GD and 46,XX GD. Most of the cases successfully adapted to their selected gender. The decision of early gonadectomy before tumoral development is important.

P3-1504

#### GYNECOLOGIC AND OBSTETRICAL OUTCOMES IN MCCUNE-ALBRIGHT SYNDROME

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**Objectives:** McCune-Albright syndrome (MAS) is a rare bone and endocrine disorder arising from somatic  $G_{\alpha_s}$  mutations, resulting in constitutive  $G_s$ -coupled protein receptor activation. A hallmark feature is recurrent estrogen-producing ovarian cysts. While precocious puberty in MAS

has been well-characterized, little is known about long-term ovarian function. The aim of this study is to evaluate gonadal function, gynecologic outcomes, and fertility in women with MAS.

**Methods:** Clinical data from an MAS natural history study.

**Results:** 72 females  $\geq 15$  years of age were evaluated (median age 34, range 15-98). Among 54 pre-menopausal women, 27 (50%) had ovarian cysts  $>2$  cm visualized on pelvic ultrasound. Subjects with cysts had reduced gonadotropins and elevated estradiol levels in comparison to those without cysts [median (IQR): LH 1.2 U/L (3.0) vs 5.0 (2.9),  $p=0.002$ ; FSH 1.7 U/L (4.0) vs 3.4 (5.1),  $p=0.02$ ; estradiol 140 pg/mL (116) vs 57.9 (72.5),  $p=0.001$ ]. GnRH stimulation was performed in 6 women, showing a mean LH

Detailed menstrual and gynecologic data were available for 38 subjects. Abnormal uterine bleeding (AUB) was reported in 30 (79%), and was frequently associated with complications including anemia (41%), need for iron supplementation (31%), and blood transfusions (10%). Medical treatment of AUB included oral contraceptive pills (83%), levonorgestrel intrauterine device (7%), and contraceptive patch (3%). 9 subjects (30%) underwent hysterectomy, 7 of whom were under age 35 (range 27-44 years).

17 women attempted and 14 achieved pregnancy, resulting in 9 live births. There were no skeletal complications from fibrous dysplasia or increased bone pain in women who achieved pregnancy. Infertility, defined as  $>1$  year to conception or inability to conceive, was reported in 7 women (41% of those attempting pregnancy), demonstrating an increase over the 6% U.S. national average.

**Conclusions:** Women with MAS demonstrate autonomous ovarian activation, resulting in long-term abnormal menstruation, a high incidence of early hysterectomy, and an increased prevalence of infertility.

P3-1505

#### LOW RATES OF TART SCREENING AND FERTILITY COUNSELING AMONG MALES WITH CONGENITAL ADRENAL HYPERPLASIA

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**Objectives:** Reduced fertility is a common complication among males with congenital adrenal hyperplasia (CAH), with nearly half experiencing impaired sperm production. The major cause of oligo/azoospermia in CAH is testicular adrenal rest tumors (TARTs). Studies indicate that ultrasound screening for TARTs should begin during childhood, yet it remains unclear whether pediatric endocrinologists routinely screen for TARTs and/or counsel about infertility risk and potential interventions. The purpose of this study was to examine TART screening and fertility counseling practices among males with CAH.

**Methods:** An IRB-approved retrospective chart review was conducted of all males with ICD-9/10 codes for CAH (2007-



2016) at a large pediatric academic center to examine: age and indication for diagnosis; age at first and last documented pediatric endocrinology visit; history of ultrasound examinations; and documentation of fertility counseling.

**Results:** 46 patients were included, of whom 38 had 21-hydroxylase deficiency. Median age at diagnosis was 2 weeks (range 7 days-10 years). Median age at the most recent pediatric endocrinology clinic visit was 14 years (range 2 years to 42 years). 29 patients were >11 years old (63% of the sample) at the time of the study and 14 of these were >18 years old (30% of the sample). Seven patients (15%) had a screening ultrasound at some point in their care, of whom 3 had TARTs. Six of the subjects (13%) had any mention of fertility in their records. None of the patients had biochemical testing or semen analysis to assess gonadal function, and none were offered fertility preservation.

**Conclusions:** Many of these patients were followed by pediatric endocrinologists through adolescence/young adulthood and into their reproductive years, yet very few had TART screening and/or fertility counseling. Our findings demonstrate the need for more awareness and practice guidelines specific to this important aspect of care for patients with CAH. Patients and families should be educated about infertility risk and potential interventions (with regard to both screening and management), with the goal of improving reproductive outcomes in this population.

P3-1506

#### PARENTING STRESS AND PARENT-RATED QUALITY OF LIFE IN CHILDREN WITH DIFFERENCES OF SEX DEVELOPMENT

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**Objectives:** Differences of sex development (DSD) are conditions evident at birth or later in development in which genetic, gonadal, or phenotypic sex is atypical. Affected children and their families are vulnerable to significant psychosocial risks that can threaten quality of life and cause distress. However, few studies have examined outcomes from the perspectives of parents of children across developmental stages, and control groups have rarely been utilized in these studies. This study addressed these gaps by evaluating parenting stress and parent ratings of health-related quality of life for children with DSD and a comparison group of healthy children.

**Methods:** In this cross-sectional study, 23 parents of DSD patients (child mean age:  $6.3 \pm 6.0$  years; 60.9% male) and a

control group of 101 parents of healthy children (child mean age:  $6.0 \pm 5.5$  years; 48.5% male) completed standardized questionnaires including the Pediatric Quality of Life Inventory (PedsQL), which measures overall health-related quality of life and physical and psychosocial functioning; and the Parenting Stress Index-Fourth Edition (PSI), a measure of stress that parents experience from child characteristics, their own characteristics, and life challenges. Linear regression analyses were used to examine differences between groups on the PedsQL and PSI while accounting for differences in parent marital status and education level.

**Results:** Parents of children with DSD reported significantly lower overall health-related quality of life for their children ( $p = 0.02$ ). Physical ( $p = 0.03$ ) and psychosocial functioning ( $p = 0.04$ ) were also rated as significantly lower for children with DSD. There were no significant differences between groups on the PSI subscales, suggesting comparable levels of parenting stress between groups.

**Conclusions:** Parents perceive children with DSD as having impairments in health-related quality of life, specifically related to physical and psychosocial functioning. Children with DSD may benefit from clinical services to improve well-being. These findings demonstrate the need for an interdisciplinary team with both medical and psychosocial providers to support youth with DSD and their families.

P3-1507

#### DELETION UPSTREAM OF SOX9 IN A 46 XY FEMALE WITHOUT CAMPOMELIC DYSPLASIA, AND IDENTIFIED IN HER MOTHER WITH PREMATURE OVARIAN FAILURE

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**Objectives:** *SOX9* acts as a testis-inducing transcription factor downstream of *SRY* essential for the differentiation of bipotential gonads into testes and chondrocytes differentiation. *SOX9* haploinsufficiency due to mutations or genomic deletions in 17q24.3 cause campomelic dysplasia in combination with sex-reversal in 75% of 46,XY individuals. *SOX9* expression is regulated by several long-distance enhancers/cis regulatory elements whose disruption cause bone disease with phenotypic variability and disorders of sex development.

We report a deletion of *SOX9* encompassing the known 32.5kb sex-reversal region presents in a 46,XY female with delayed puberty. The same deletion was found in her 46,XX mother with premature ovarian failure

**Methods:** Case Report: A 14.5 yr-old girl was referred for incomplete pubertal development. Familial background: mother 36 yr-old with polycystic ovaries and amenorrhea since 33 yrs of age, maternal cousin with menopause at 36 yrs, and grandmother with delayed puberty. At clinical examination: height and weight were at 3<sup>rd</sup>-10<sup>th</sup> centiles respectively, pubertal development B I/III, PH II and normal female external genitalia. No skeletal malformations were observed. Lumbar Spine densitometry showed low bone mineral density. Pelvic ultrasound detected a small uterus (29x7x14 mm) and two images corresponding to small gonads (18 and 16 mm).

**Results:** Laboratory results: LH 44 IU/L; FSH 128 IU/L; E2 10pg/mL; T 41ng/dL. High levels of gonadotrophins (repeated one month apart), and low AMH (<1.2 pmol/L) confirmed complete gonadal dysgenesis. Karyotype: 46,XY. Parental karyotypes were normal. Prophylactic gonadectomy was performed, histological analysis showed bilateral streak without germ cells.

*SRY*, *NR5A1* and *AR* did not reveal mutations. Copy-number variation using CYTOSNP 850K (Illumina) and Karyoarray®8x60K (Agilent based CGH) showed a 260kb deletion at 420kb upstream-*SOX9* in the patient and her mother; according to the databases: arr[hg19]17q24.3(69436041-69696519)x1.

**Conclusions:** Our results detected a new case of 46,XY complete gonadal dysgenesis without campomelic dysplasia, and suggest for the first time an association between a deletion in the *SOX9* regulatory sequences and premature ovarian failure in a 46,XX female.

P3-1508

## DSD ONLINE HEALTHCARE CONTENT: A SURVEY OF QUALITY AT U.S. PEDIATRIC WEBSITES

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**Objectives:** The present study systematically evaluated the quality of DSD-related online health care information presented by the 10 pediatric institutions comprising the DSD-TRN (a US National Institutes of Health-sponsored clinical research network) to determine the degree to which health information presented on DSD-TRN institutional websites meets health literacy criteria and to identify areas for improvement.

**Methods:** Websites were searched using an expert-consensus derived list of search terms and all original online DSD-related health content were scored by two coders. *Reading level* was assessed using the Simple Measure of Gobbledygook (SMOG). *Clarity of presentation* was assessed using the Patient Education Materials Assessment Tool (PEMAT), a validated evaluation system developed within the Agency for Healthcare Research and Quality which covers domains including clarity and focus of content, and whether specific actions are identified that users can take. *Accuracy* of information was assessed by comparing the material to the Clinical Guidelines for the Management of Disorders of Sex Development in Childhood and the Consensus Statement on Management of Intersex Disorders. *Comprehensiveness* of treatment options was assessed using the DISCERN tool, which assesses the transparency of the source of material as well as whether a full range of treatment choices are fully presented with both risks and benefits of options (including the possibility of no-treatment).

**Results:** The survey of online content is ongoing and will be available for presentation.

**Conclusions:** Enhanced health literacy of DSD patients and families is foundational for patient-centered care approaches, shared decision-making and informed consent. Analysis of DSD-related online health information highlights areas for improvement in the quality of material provided. Tensions between specialist providers, patient and parent stakeholders, and human rights communities underscore the importance of ensuring comprehensive, accurate and balanced information about DSD and treatment options are accessible on the websites of institutions delivering care

# CLINICAL HORMONAL CHARACTERISTICS OF DELAED PUBERTY IN FEMALE WITH HYPERGONADOTROPIC HYPOGONADISM

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**Objectives:** To study the clinical hormonal characteristics of female hypergonadotropic hypogonadism (HH).

**Methods:** 30 girls,  $14,9 \pm 0,7$  years, with delayed puberty were examined. Entry criteria were the absence of secondary sex characteristics at 13 and/or if the menarche failed to occur by the age of 15.

Puberty stage according to Tanner, anthropomorphic and genitometric parameters, bone age (BA), LH, FSH, testosterone (Ts), estradiol (E) levels and cytogenic assay were evaluated.

**Results:** Depending on the levels of gonadotropic hormones patients were divided into 2 groups: high (46,7%, 14/30; ?? LH 24,3 mIU/ml; ?? FSH 65,85 mIU/ml) and normal/low level (53,3%, 16/30; ?? LH 3,43 mIU/ml; ?? FSH 3,68 mIU/ml). The reasons to visit a doctor were the same in both groups - the absence of secondary sex characteristics: 71,4 % (10/14) in patients of the first and 75 % (12/16,  $\chi^2=0,645$ ) in the second group. Primary amenorrhea was in 28,6% (4/14) and 25% (4/16,  $\chi^2=0,616$ ) of patients respectively. The girls of both groups had the same height (?? SDS -0,21 vs -0,8,  $\chi^2=0,962$ ). Frequency of pathologic growth inhibition in both groups did not differ (35,7% vs 37,5%,  $\chi^2=0,776$ ). In the first group body mass index was higher (?? SDS 0,24 vs -0,89,  $\chi^2=0,035$ ). BA in the first group was higher (?? SDS of BA (-2,22 vs -3,95,  $\chi^2=0,05$ ), pathologic delayed BA occurred with the same frequency (43,75% vs 57,14%,  $\chi^2=0,916$ ).

The girls with HH had more obvious delayed puberty (?? Tanner breast development stage 1,0 vs 3,0,  $\chi^2=0,012$ ). In the group of girls with HH ovaries of 57,14% (8/14,  $\chi^2=0,021$ ) of patients were not visualized. Uterus size (?? of uterus size 2,28 vs 5,38  $\chi^2=0,027$ ) and sex hormones levels (?? of E 13,75 pmol/l vs 55,15 pmol/l,  $\chi^2=0,005$  and ?? of Ts 0,52 nmol/l vs 0,97 nmol/l,  $\chi^2=0,041$ ) were lower. Turner syndrome was identified in 46,2% (6/13) of patients, 30,8% (4/13) had karyotype 46, XY and 23% (3/13) 46, XX, allowing to diagnose pure gonadal dysgenesis in 53,8 % (7/13) of patients.

**Conclusions:** HH in the structure of delayed puberty in girls is seen in 2 variants of sexual dysgenesis disorder: Turner

syndrome and pure gonadal dysgenesis (46,2% vs 53,8%). Their visits to a doctor were mostly due to the absence of any secondary sexual characteristics.

# APPLICATION OF TARGETED NEXT-GENERATION SEQUENCING FOR MOLECULAR DIAGNOSIS IN PATIENTS WITH 46,XY DSD

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**Objectives:** The identification of the genetic cause of disorders of sex development (DSD) is very important for choosing right decision for the treatment of patients with DSD. Here, we describe our preliminary results of utilization of NGS for the determination of causative mutations among patients with 46,XY DSD.

**Methods:** To investigate the molecular basis of 46,XY DSD using targeted NGS approach 168 subjects with 46,XY DSD were included in the study. A custom Ion AmpliSeq™ panel was designed to sequence 44 candidate genes implicated in 46,XY DSD. Secondary bioinformatics analysis was carried out using ANNOVAR software.

**Results:** 92 of 168 patients (55%) were shown to have a sequence variant in one of the candidate genes. 62 variants were defined as pathogenic (67%), 18 as likely pathogenic (20%), and 12 as variants of unknown significance (13%). We were able to define a genetic diagnosis in 36% of those with suspected disorder of gonadal (testicular) development and in 70% of those with disorder of androgen synthesis or action. The distribution of mutations in targeted genes was as follows: *NR5A1* (n=15), *ZFPM2* (n=5), *SRY* (n=4), *PTGDS* (n=1), *MID1* (n=1), *DMRT1* (n=1), *LHX1* (n=1), *DHH* (n=1), *ESR2* (n=2), *ICK* (n=2), *MAP3K* (n=4), *FKBP4* (n=2), *HSD17B3* (n=6), *HSD3B2* (n=3), *STAR* (n=2), *CYP11A1* (n=2), *CYP5A* (n=1), *POR* (n=4), *LHCGR* (n=3), *ACR1C2* (n=1), *ACR1C4* (n=1), *DHCR7* (n=1), *AMH* (n=6), *AMHR2* (n=2), *AR* (n=21). We have not identified any mutation in 77 patients with DSD.

**Conclusions:** In the present cohort of 46,XY DSD, mutations in *AR* and *NR5A1* were the most common. Targeting NGS sequencing was proven to be an efficient tool to improve the diagnostic yield of DSD.

# THE PREVALENCE OF ADULTS WITH DSD CONDITIONS AT RISK OF HYPOGONADISM IN THE INTERNATIONAL DISORDERS OF SEX DEVELOPMENT REGISTRY

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**Objectives:** Disorders of Sex Development (DSD) can be associated with impaired sex hormone synthesis or action. To date however knowledge regarding the prevalence and outcomes of affected adults is unclear.

**Methods:** The I-DSD Registry was interrogated for anonymised information regarding the diagnosis, karyotype and sex of rearing of all individuals of any karyotype who were over the age of 16 years at the time of search and who had one of the following disorders that may lead to long-term hypogonadism: androgen action, androgen synthesis; gonadal

dysgenesis; Leydig cell hypoplasia; persistent Müllerian duct syndrome or a non-specific disorder of undermasculinisation.

**Results:** At the time of search in January 2017, of a total of 2,141 cases were accessible on the I-DSD Registry. A total of 1,068 (50%) of these cases were currently over the age of 16 years (median 27 (range 16, 90) years). Of these, 614 (57%) had one of the conditions described in the methods. The frequency of conditions reported is summarised in the table. The cases were registered from 34 different centres in 21 different countries, over 4 continents. 207 (34%) (median age 25 years, range 17-75 years) of these individuals were currently registered male. 407 (66%) individuals were currently registered as females (median age 28 years, range 16-90 years). Gonadectomy had been reported on the Registry in 145 cases (24% of total); 16 men (8% of total men) and 77 women (19% of total women). The cases of gonadectomy included CAIS (23, 16%), complete gonadal dysgenesis (21, 14%), partial gonadal dysgenesis (14, 10%) PAIS (11, 8%) non-specific disorders of undermasculinisation (8, 6%), 5 alpha reductase deficiency (4, 3%), 17b-HSD deficiency (3, 2%), Leydig cell hypoplasia (2, 3%) and other (5, 3%).

**Conclusions:** The I-DSD Registry contains a large number of young adults who are at risk of hypogonadism and provides an opportunity to study the effectiveness of current therapeutic interventions and explore novel methods of treating hypogonadism.

Condition	Male	Female
Complete androgen insensitivity syndrome	N/A	167 (41%)
Non specific disorder of undermasculinisation	53 (26%)	6 (1%)
Partial gonadal dysgenesis	56 (27%)	28 (7%)
Partial androgen insensitivity syndrome	48 (23%)	28 (7%)
Complete gonadal dysgenesis	10 (5%)	84 (21%)
17 beta HSD deficiency	1 (0.4%)	35 (9%)
5 alpha reductase deficiency	7 (3%)	15 (4%)
Persistent Müllerian duct syndrome	6 (3%)	N/A
Leydig cell hypoplasia	4 (2%)	7 (2%)
Other	21 (10%)	33 (8%)

P3-1512

#### 46,XX SRY NEGATIVE TESTICULAR AND OVOTESTICULAR DISORDERS OF SEX DEVELOPMENT: CLINICAL ASPECTS, MOLECULAR STUDIES AND MANAGEMENT IN 13 CASES

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**Objectives:** 46,XX testicular and ovotesticular disorders of sex development (TSD and OTSD) represent a very rare and unique cause of DSD where testicular tissue develops in absence of a Y chromosome. The most frequent underlying mechanism identified is a translocation of the *SRY* gene (~20% of the cases), but several new genes and pathways involved in the development of testicular tissue have recently been identified. To date, very few studies have described the phenotype, the clinical and surgical management and investigated the genetic aspects of 46,XX *SRY* negative TSD and OTSD patients.

**Methods:** The records of all 46,XX *SRY* negative TSD and OTSD patients, followed between 1994 and 2015 in the Endocrine Clinics of two French centers were retrospectively reviewed and completed by a prospective genetic evaluation using SNP-array and whole exome sequencing.

**Results:** Among the eleven patients with 46,XX OTSD and two patients with 46,XX TSD included, most (9/13) were seen in the neonatal period. Sex of rearing was male for six patients and female for seven, while the clinical presentation varied, with an external masculinization score from 1 to 10. Ovotestes/testes were found bilateral for 55% of the patients and unilateral (on the left side) for the others (with a contralateral ovary). Two girls were successfully treated with GnRH analog therapy to avoid virilisation during minipuberty. Genital surgery preserved appropriate gonadal tissue in the majority of cases. Spontaneous puberty occurred in two girls and one boy, while two boys required hormonal induction of puberty. One of the girls conceived spontaneously and had an uneventful pregnancy. All patients were *SRY* negative. The DNA of twelve patients was analyzed by SNP-array and a whole-exome sequencing was performed on five patients. Genetic analyses did not find any pathological variation in previously identified genes or candidate genes.

**Conclusions:** This study presents a well-characterized population of patients with 46,XX, *SRY* negative TSD and OTSD. Molecular diagnosis for these patients is currently missing which suggests the existence of defects in other genes or DNA regulatory sequences involved in gonadal determination.

P3-1513

#### GENETIC DIAGNOSIS OF EGYPTIAN PATIENTS WITH DSD USING NEXT GENERATION SEQUENCING

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**Objectives:** this study provides as much information about the underlying genetic anomaly in DSD cases using next generation sequencing approaches

**Methods:** clinical, cytogenetic, hormonal studies were done for all patients with DSD, while exome sequencing was performed for idiopathic cases

**Results:** presented in the uploaded file

**Conclusions:** this study enlarges the scope of both cytogenetic, monogenic mutations and emphasizes the application of new technique for accurate diagnosis and treatment for better genetic counseling

P3-1514

#### SOCIAL SUPPORT AND FINANCIAL CHANGES FOR PARENTS OF CHILDREN BORN WITH AMBIGUOUS GENITALIA

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**Objectives:** Little is known about how parents' financial resources and social support are affected when they have a child born with ambiguous genitalia due to a disorder of sex development (DSD). This investigation sought to evaluate impacted areas of daily living within this population, across one year's time.

**Methods:** As part of an ongoing, prospective, longitudinal study of children born with ambiguous genitalia and their parents, 98 parents (57 mothers, 41 fathers) of 61 children from 11 DSD specialty clinics completed questionnaires within 6-months of DSD diagnosis and at 6 and 12-months post-genitoplasty. Descriptive statistics were used to evaluate parent report of financial and social support changes.

**Results:** Most parents reported some financial concerns (52-61%), with notable expense increases including: medications (79%), travel (73%), home nursing (59%), and mental health services (56%). Most parents have caregiving support from the other parent in the home (86-89% mothers, 95-98% fathers). Parents reported emotional support increasing from baseline to 12-month follow up (13% to 84% mothers, 10% to 74% fathers), and an increase in help with childcare (11% to 56% mothers, 12% to 74% fathers). The modal family income was high at baseline with 34% reporting \$100,000 or more, and 16% reporting less than \$20,000. Of the lower income families, 0% completed 12-month follow-up measures. Additionally, 4% of mothers (7% fathers) reported less than high school education at baseline and 0% at 12-month follow up.

**Conclusions:** Parents reported increased financial expenditures due to their child's condition. Importantly, a large portion of parents reported increased costs in mental health care, suggesting parents are utilizing mental health services. Notably, parents reported an increase over time in emotional support and assistance with childcare. Furthermore, those with higher income were more likely to participate at baseline and to complete follow-up measures, with lower income families not being captured at follow-up. The initial high proportion of high income families and the attrition of lower income families suggests higher earning families are likely to seek and more likely able to maintain care at DSD specialty clinics.

P3-1515

#### **CLINICIAN PERSPECTIVES ON MANAGEMENT OF DISORDERS OF SEX DEVELOPMENT (DSD) IN AOTEAROA/NEW ZEALAND: A QUALITATIVE STUDY**

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**Objectives:** In most societies gender is seen as a binary construct based on biology. This is challenging for young people born with a Disorder of Sex Development (DSD) where gender identity and physical appearance may be ambiguous, and for their parents. Clinical management includes complex and controversial decision-making, often ethically challenging, involving navigation of multiple decision points with divergent and sometimes uncertain consequences. This paper discusses the influences on decision making reported by clinicians in Aotearoa/New Zealand.

**Methods:** This paper reports on one component of a larger qualitative study that examined the perspectives of young adults with DSD, parents and clinicians working within this

complex area. In-depth interviews were conducted with 22 clinicians with subsequent analysis for key themes relating to their experiences, with a focus on identifying factors that influenced decision making.

**Results:** The overall consensus was that decision making was generally shared; participants saw their responsibility being to provide clear clinical information and guidance, with parents ultimately responsible for the final decision(s). However, their own expectations, along with the perceived expectations of colleagues, parents and those affected, had an enormous impact on decision making. Discomfort and/or avoidance of discussing complex issues around gender, body autonomy, sexuality and diversity were also identified. Participants reported varying degrees of confidence in their ability to communicate effectively, especially about potential issues throughout the life span, providing adequate information about treatment options, and psychosocial impact. Participants showed limited awareness of unintended biases, reflecting predominantly culturally mainstream points of view.

**Conclusions:** Whilst clinicians are clearly motivated to facilitate genuinely informed, shared decision making, this is difficult to achieve in practice. Targeted guidance and education is needed to develop awareness and a more reflective, diverse world view, and to enhance professional skills for discussing the sensitive and complex topics that characterise this clinical area.

P3-1516

#### **NATIONWIDE STUDY OF TURNER SYNDROME IN UKRAINE: ANALYSIS OF PHENOTYPIC FEATURES AND MALFORMATIONS**

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**Objectives:** The variability of clinical manifestations of the Turner syndrome (TS) makes it difficult its timely diagnosis. The frequency of main TS complications varies widely in different countries: e.g. heart diseases are observed in 35-56%, defects of the urinary tract – in 30-40%, pathology of eyes and hearing – in 25-30% of patients. We investigated the frequency of phenotypic features and malformations in TS girls in Ukraine.

**Methods:** A retrospective analysis of the database of 538 TS girls and detailed examination of 150 patients, aged 0.11-18.2 y.o. during 2005-2015 years was done.

**Results:** In Ukraine the prevalence of TS is 77,5 in 100 000 live births girls.

The growth delay was a constant feature (98.82% of TS girls). Another most frequent signs were shortening of IV and V metacarpal bones (74.62% patients), abnormal nails (73.31%), broad chest (60.67%), short neck (58.63%) and hypertelorism of nipples (51.37%).

Major congenital abnormalities were malformations of the cardiovascular system (19.62% of TS girls) and urinary system

(13.82%). Cardiovascular abnormalities more often were found in case of mosaicism (26.18%) and structural abnormalities of chromosome X (21.62%) compared to the karyotype 45,X (15.85%), ( $p < 0.05$ ). Urinary system abnormalities were observed mainly in TS girls with karyotype 45,X (14.76%) and less often - in case of karyotype 45,X/46,XX (8.28%) and structural abnormalities of chromosome X (2.75%), ( $p < 0.05$ ). The pathology of vision was found in 20.08% of TS patients and pathology of hearing – in 22.01%. Studies on frequency of autoimmune thyroid disease in TS girls have shown elevated levels of thyroid peroxidase antibodies (ATPO) in 48.45% patients regardless of karyotype ( $p > 0.05$ ). Among TS girls which had increased ATPO level, more often we found subclinical (48.76%) and clinical hypothyroidism (29.14%), ( $p < 0.05$ ). Only 11.87% patients were euthyroid and 10.23% had subclinical hyperthyroidism.

**Conclusions:** In Ukrainian population TS was accompanied by a lower frequency of malformations of internal organs compared to other countries, but hypothyroidism was found more often (in 77.9% of patients with positive ATPO).

P3-1517

# **GENOTYPE - PHENOTYPE CORRELATION IN PATIENTS WITH ABNORMALITIES OF SEXUAL DIFFERENTIATION TYPE TURNER SYNDROME AND THEIR MOSAICS**

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**Objectives:** To characterized our patients with abnormalities of sexual differentiation type classic and mosaic Turner Syndrome

**Methods:** We performed a Genotpe -phenotype analysis in 32 patients with abnormalities of sexual differentiation type classic and mosaic Turner Syndrome between june 2000 and december 2016

**Results:** Hundred percent the cases had short neck,81% had shorth fourth metacarpal bone and 93% had cubitus valgus.They had associated pathologies type :aortic heart disease in the 44%,25% abnormalities renals and 94% pelvics .The differents karyotypes are expressed in the following table

Karyotype	Number	%
45XO..	17	55
46XY45XO..	2	6,4
46XXlq/45XO...	3	9.6
46Xi..	2	6.4
45,X/46XDELXQ...	1	3.2
45,X0/46,XX..	4	13.0
45,X/46XDERY...	1	3.2
45Xo/46XDELX(Q21,2-QTER)	1	3.2

**Conclusions:** Fifty five per cent of our patients with Turner syndrome had a 45X chromosome and the remaining 45% had a variety of mosaic patterns which are diagnosed late despite the presence of clinical manifestations. There were no statistical differences between the clinical manifestations of classic patients and mosaics . Ovarian failure ,cardiac and renal abnormalities that we found are similar to those reported in the literature .

P3-1518

# **FREQUENCY OF METABOLIC SYNDROME IN PATIENTS WITH TURNER SYNDROME FROM THE DSD-LIFE COHORT**

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**Objectives:** to determine the frequency of Metabolic Syndrome in patients with Turner Syndrome from DSD Life cohort

**Methods:** This study was part of the DSD life study ([www.dsd-life.eu](http://www.dsd-life.eu)). After completion of paperwork , signed consent, biometric screenings (height, weight, body mass index (BMI), waist circumference (WC) and blood pressure were completed. Given the small height , we chose to retain the waist to height ratio . Fasting laboratory values were measured, Triglycerides (TG), total cholesterol, HDL cholesterol, glucose levels were performed. Drug list was also requested. The American heart Association (AHA)/National Heart, lung and blood institute (NHLBI) definition requires three of the following five risk factors be present for diagnosis of MS: WC to height ratio  $> 0.5$ ,  $TG \geq 150$  mg/dl,  $HDLc < 50$  mg/dl or taking medication, diastolic blood pressure  $\geq 130$  mmhg and systolic  $\geq 85$  mmhg or taking medication, fasting glucose  $\geq 100$  mg/dl or taking antidiabetic medication.

**Results:** 301 patients with TS (median 28 (15-73) years) were included, median of height was 153 m (132-172 cm) ,BMI was 24.2 kg/m2 (16-45). Overweight and obesity were respectively in 24.9% and 15.6 % of cases. Their karyotype was a monosomy 45X (47%), mosaicism 45X/46XX (10%), karyotype with isochromosome (19%) or other karyotype (25%). Physical activity was less then 2hours in 48.5% , 2 hours in 13% and more than 2 hours in 20.6% of cases. About smoking behavior we noted only 6% of current smoker and former smoker in 3%.. We noted missing data in 63 files (20.9 %). Among patients with complete data : 51 patients had 3 criteria of MBS or more (17%), 14% had two criteria (n=44), 26% had one criteria (n=79)



	WC/H ratio N (%)	High Syst or treated N (%)	HighDiastolic or treated N (%)
Missing data	117 (39)	72 (24)	75 (25)
No	86 (28.5)	147 (48.8)	163 ( 54)
Yes	98 (27.2)	82 (27.2)	63 (21)

**Conclusions:** The most common risk factors are the WC and high systolic blood pressure in more than a quarter of cases. Complete MBS is present in 17%.

It is imperative that the metabolic syndrome be recognized and treated to preserve the health and well-being.

P3-1519

#### PERCEPTIONS OF PERI-PUBERTAL FEMALES WITH XY DSD REGARDING UNDERLYING CONDITION, PUBERTY AND FEMALE HORMONE REPLACEMENT THERAPY

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**Objectives:** To describe awareness and perceptions of peri-pubertal girls with 46 XY DSD and their parents, regarding disclosure of underlying condition, puberty and female hormone replacement therapy (HRT).

**Methods:** A preliminary descriptive study using a semi-structured interviewer administered questionnaire in 46 XY females aged 9-14 years followed up at a specialized Paediatric Clinic in Sri Lanka and their parents.

**Results:** Six children with 46 XY DSD, reared as girls from birth participated. Underlying diagnoses: CAIS (3), NRFA1 mutation(1), penile agenesis(1), no specific diagnosis(1). Five girls were aware about lack of natural hormone production, need for HRT for breast development (undergone gonadectomy), absence of uterus and lack of menstruation. They had commenced HRT between 10-13 years of age, and were happy that HRT would make their body habitus like their female peers. Two were aware of their inability to bear children (disclosed by parents/with parental consent), and were not unduly worried about this. None of the girls were aware of their male genotype. Four were aware about possible need for future surgery. Sexual functioning was not discussed yet.

Age of first disclosure varied from 5-12 years, and was influenced by parental perceptions (child's ability to handle sensitive information/fear of disclosure to others). All were happy about disclosure and information received, and four with its timing. The oldest at disclosure (12y) felt earlier disclosure would have helped allay concerns on lack of breast development. None wanted to share information with peers. Four girls experienced initial breast discomfort with HRT, which improved after few months (Tanner stage 2-3). One child did not have breast development after 13 months of HRT, but said she was not distressed by this.

The youngest (pre-pubertal) girl had been lost to follow up for years, had not undergone gonadectomy and was not yet aware of her condition.

**Conclusions:** Girls with XY DSD appreciated early disclosure ( $\leq 12$  y), and had positive perceptions on commencement of female HRT. However, there were more challenging aspects to be yet discussed including sexual functioning, fertility and gender identity.

P3-1520

#### EVALUATING AND MANAGING 69 CHINESE CHILDREN BORN WITH DISORDERS OF SEXUAL DEVELOPMENT

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**Objectives:** Disorders of sex development are due to congenital defects in chromosomal, gonadal, or anatomical sex development. The objective of this study was to determine the aetiology of these disorders in the Shandong pediatric patients and attempt to find some suggestion in diagnosis and treatment of DSD.

**Methods:** Patients of suspected DSD visiting pediatric departments during 2007-2017 were enrolled in the study. Clinical and laboratory investigations including abdominopelvic imaging, laparoscopy examination as well as basal and stimulated hormone and genetic measurements were collected. And then the definite diagnoses in each subgroup were established and the following treatments were recorded.

**Results:** Overall, 69 patients were recruited for the study. Their age at presentation ranged from 14 day to 12.5 years, with a mean of  $3.9 \pm 0.4$  years. The most frequent complaints at presentation were unknown genitals, isolated perineum hypospadias and clitoral hypertrophy. Several showed vomiting and failure to gain any weight after birth. Treatment time was partly delayed by living in the rural or disease type as simple virilizing CAH, which has the possibility of adrenal tumors and mixed precocious puberty. Out of a total of patients, 40 had 46,XX DSD, 16 had 46,XY DSD, and 7 had abnormal sex chromosome DSD (such as 47,XXY[59]/46,XX[7]; 46,X(28)/46XY(12); 46,X,delY(q)12[18]/45,X[32]; 45X/46r(Y); 45,X,-X,+del(X)(q21)(38)/45X(12); 47XXY; 46XX,14ps+). The most common cause of 46,XX DSDs was congenital adrenal hyperplasia (CAH) and most cause of 46,XY was androgen insensitivity syndrome (AIS). Others had confirmed diseases including cholesterol side-chain cleavage enzyme deficiency, absence of testis and DENYS-DRASH syndrome. Among these patients, deletion in chr15q11.2 and mutations in CYP21A2, CYP17A1, AR, WT-1, MAP3K1 were identified.

**Conclusions:** Further studies using molecular genetic analyses are needed to give a more precise distribution of etiologies of DSDs, especially in 46,XY patients. The most common causes of DSD remain unchanged as CAH and AIS. It is discussed about the delay the operation time, for consideration of sex hormone levels and / or sexual and psychological effects.

# INCREASED GENE DOSAGE: SEX REVERSAL IN TWO PATIENTS WITH DUPLICATIONS OF EITHER DAX1 (46,XY GONADAL DYSGENESIS) OR THE SOX9-REGULATORY REGION (46,XX-TESTICULAR DSD)

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**Objectives:** Duplications of „Dosage sensitive sex reversal adrenal hypoplasia congenita critical region“ (*DAX1*; Xp21) constitute a rare cause of 46,XY-DSD due to suppression of the genetic testicular pathway by increased *DAX1* gene dosage. Analogously, duplications of a regulatory element upstream of *SOX9* (17q24) have been identified in 46,XX SRY-negative individuals with testicular DSD. We observed two such patients.

**Methods:** Clinical data collection, biochemical investigations and genetics testing (Karyotyping, CGH- Array, MLPA) were performed using routine techniques/procedures.

**Results:** 19-year-old patient 1 (188cm/88kg, phenotypically female) was referred to our department because of secondary amenorrhea. She was mentally retarded and received antipsychotic treatment due to a severe behavioural disorder. In addition, she had dyslipidemia, hepatic steatosis and mild type 2 diabetes (HbA1c 7.1%). Karyotype was 46,XY. Hormone tests showed primary gonadal insufficiency, AMH <0,08ng/mL. Pelvic MRI revealed a hypoplastic uterus and irregular gonadal structures with a right-sided cyst. CGH-array analysis showed a 9.5 Mbp duplication in Xp [Xp22.11p21.1(23,917,544-33,382,057)x2], including *DAX1*. 9-year-old patient 2 was referred to our surgical department for right undescended testis (inguinal). He had had surgery for hypospadias in early childhood (Syria). Karyotype was 46,XX. On MRI no Mullerian structures could be visualized, AMH lying in the male range. HCG test (5000 IU/sqm) showed a diminished testosterone rise (0.3ng/mL). MLPA revealed a 1 Mbp duplication upstream of *SOX9* that contains *SOX9*-regulatory elements [17q24.3(68,694,434-69,773,309)x3].

**Conclusions:** Increased *DAX1* or *SOX9* gene dosage may lead to suppression of predetermined gonadal differentiation resulting in 46,XY-DSD with gonadal dysgenesis or 46,XX testicular DSD, respectively. Associated psychomental symptoms in our *DAX1*-duplication patient are attributable to additionally duplicated genes whereas metabolic syndrome was probably drug-induced (atypical antipsychotics).

P3-1522

# 46,XY DISORDERS OF SEX DEVELOPMENT IN 6 VIETNAMESE PATIENTS DUE TO CHROMOSOME REARRANGEMENT

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**Objectives:** Causative mutations have not been identified in more than 50% 46,XY DSD cases. Recently, submicroscopic chromosome rearrangements have been identified as a novel genetic causes of 46,XY DSD.

Our aim is to identify chromosomal rearrangement in the development of 46,XY DSD in Vietnamese patients.

**Methods:** This is a case series report including clinical presentations and data from array-based comparative genomic hybridization analysis for 6 genetic males with genital abnormalities combines with mental disability and other congenital anomalies.

**Results:** Heterozygous submicroscopic deletions and/or duplications were identified in six cases. A ~ 7.2Mb terminal deletion at chromosome 9 including deletion of *DMRT1* gene and a ~ 2.7Mb terminal duplication at chromosome 17 were detected in case 1 that presented with prematurity, dysmorphism and ambiguous genitalia; a terminal deletion affects *DMRT1-3* at 9p22-23 was identified in case 2 with ambiguous genitalia, mental disability and dysmorphism; a ~ 18Mb terminal duplication at chromosome 5 was detected in case 3 with DSD, growth retardation, microcephaly and dysmorphism, ptosis, ventricular septal defect and craniosynostosis; an interstitial deletion including deletions of *WT1*, *PAX6*, and *PRRG4* genes at chromosome 11 was detected in case 4 with WAGR syndrome: mental disability, Wilms' tumor removed at 6 years of age, hypospadias, micropenis, right cryptorchidism, bilateral aniridia was confirmed by ophthalmologist from 3 months of age; a terminal duplication at chromosome 7 was detected in case 5 with DSD: severe hypospadias, phallus size was 1 cm at 3 years of age, no testis found clinically, right testis was found at inguinal canal by ultrasound; a ~ 5Mb terminal deletion at chromosome 4 and a ~ 6 Mb terminal duplication of chromosome 16 were detected in case 6 with severe motor mental retardation, microcephaly (head circumference -3.5 SD), micrognathia, and DSD (hypospadias, micropennis, bilateral cryptorchidism).

**Conclusions:** The results indicate that chromosomal rearrangements constitute an important part of the molecular bases of 46,XY DSD and that submicroscopic deletions and/or duplication can lead to various types of 46,XY DSD combined with other congenital anomalies and/or mental disability.

P3-1523

# A NEWBORN DELIVERED WITH AMBIGUOUS GENITALIA INDUCED BY MOSAIC DEFECTS IN SEX CHROMOSOME

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**Objectives:** Sex chromosome anomalies are classified as a rare category of 46, XY disorders of sex development (DSD).

Chromosomal aberrations of sex chromosomes, both X and Y, are commonly associated with ambiguous genitalia. So that karyotyping is one of the initial work-up in any case with ambiguous genitalia. Mosaic defects in sex chromosome had a wide range of clinical presentation. The combination of mosaic 45, X/46, Xq12 with presenting 2 copies of SRY gene is very unusual cytogenetic finding.

**Methods:** Here, we are discussing a case of a newborn delivered with ambiguous genitalia in the form of bilateral undescended testes, chordee and hypospadias.

Unexpectedly, Ultrasound pelvis revealed persistent müllerian structure (uterus). Magnetic Resonant Imaging (MRI) of the pelvis showed both testicles were located in the inguinal canal with average size, the uterus was seen in the same anatomical position and measures about 13x5mm. Testosterone response post human chorionic gonadotropin (HCG) stimulation test came to be normal.

**Results:** Based on the clinical picture, fluorescent in-situ hybridization (FISH)-metaphase technique analysis of various Y regions (Yp11.3, Xp22.3, Yp-arm, Yq-arm) has been requested, which revealed unusual Mosaic 45, X/46, X, idic(Yq12) with presenting 2 copies of SRY gene; which is to our knowledge; only few cases have been published in the literatures.

**Conclusions:** Hence, the disturbance in sex chromosome may lead to defects in both testicular cell lines that may manifest with internal and external genital ambiguity.

P3-1524

#### TEN YEARS REMISSION IN A 46,XY DSD PATIENT AFTER A STAGE IV TUMOR DISEASE DEVELOPED FROM A MIXED CHORIOCARCINOMA AND GONADOBLASTOMA

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**Objectives:** Patients with 46,XY partial gonadal dysgenesis are at high risk for the development of gonadal tumors. Although the most common tumor of the dysgenetic gonad is the gonadoblastoma with good prognosis, the more rare nonpregnancy related choriocarcinoma is highly aggressive.

**Methods:** We present a female raised patient who underwent an emergency abdominal surgery at the age of 13 years. After the exploration an enlarged 8x7x6 cm sized bleeding tissue mass of the right gonad was removed. Pathological examination established gonadoblastoma combined with choriocarcinoma. Based on the clinical findings, the hormone results (HCG: 1738 mIU/l, Testosterone: 40 ng/dl) and the 46,XY karyotype a partial gonadal dysgenesis was diagnosed. According to the germ cell study classification the oncologist established stage IV disease.

**Results:** The patient responded very well to the chemotherapy MAKEI 96 protocol and showed a complete regression of the residual abdominal tumor and distance

metastasis. The patient has been in a remission for over ten years.

**Conclusions:** We present the first case report when the stage IV tumor disease was cured successfully with chemotherapy and surgical intervention in a patient whose disease developed from a dysgenetic gonad which contained gonadoblastoma and choriocarcinoma together.

P3-1525

#### 46,XX OVOTESTICULAR DISORDER OF SEX DEVELOPMENT (DSD):- DUPLICATION OF THE XX SR REGION UPSTREAM OF THE CRITICAL TESTICULAR GENE SOX9.

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**Objectives:** A term baby had a 2cm phallus (mild chordee), perineal urogenital opening, bifid fusion of labioscrotal folds containing palpable gonads and no other dysmorphic features. Karyotype was 46,XX (no Y chromosome). FISH was negative for SRY and Y centromere probes. Sinugram indicated a large prostatic utricle. Surgical assessment on day 11: no fallopian tubes/uterus; vas deferens, vessels entered the inguinal rings; gonads macroscopically were bipolar ovotestes, histologically ovarian/testicular tissue in upper/lower poles. A male gender of rearing was decided. A 2-stage penile reconstruction and urethroplasty was performed.

Gender confusion, rather than dysphoria, was apparent from 4 years, amidst complex psychosocial circumstances. Breast tissue developed prior to 8 years with Tanner stage 1 pubic hair/genitalia. Leuporelin testing was pubertal. Ultrasound indicated symmetrical, prepubertal sized gonads.  $\alpha$ -FP and  $\beta$ -HCG were low. At 9 years (height 8<sup>th</sup> percentile, bone age advanced for a male), puberty is suppressed with depo leuporelin. Gender identity will continue to be assessed.

**Objective:-**Genetic analysis of this patient with SRY-negative 46,XX ovotesticular DSD.

**Methods:** Genomic DNA analysed (i) Targeted Massively Parallel Sequencing (MPS) DSD panel (64 diagnostic genes including *SOX9*) (ii) Single-nucleotide polymorphism (SNP) array analysis (iii) Multiplex Ligation-dependent Probe Amplification (MLPA) - known DSD genes, including *SOX9* and upstream regulatory regions.

**Results:** No causative variations were identified by the MPS DSD panel. SNP array detected a heterozygous interstitial duplication at 17q24.3, 519-623Kb upstream of *SOX9*.

MLPA confirmed (i) *SRY*-negative 46,XX DSD (ii) a duplication upstream of *SOX9*. This covers the *XX SR/RevSex* (XX sex reversal) region, but does not extend to *XY SR* at the 5' end, nor the *TESCO* (testis-specific enhancer of *SOX9* core), or the *SOX9* gene at the 3' end.

**Conclusions:** The *SOX9* enhancer duplication likely led to high levels of *SOX9* in the developing ovary, causing ovotestes. An increased risk of germ cell cancer is not expected. The testicular/ovarian components may be hormonally active. Ongoing assessment of gender identity will be crucial to guide management.

P3-1526

#### THE CHALLENGES IN GENDER ASSIGNMENT IN A NEWBORN WITH MIXED GONADAL DYSGENESIS DUE TO MOSAICISM AND ISO-DICENTRIC Y CHROMOSOMES. SEVEN-YEAR FOLLOW-UP

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**Objectives:** Background. Isodicentric chromosomes can result in male infertility, disordered sex development (DSD) and Turner Syndrome (TS) phenotypes. Sex hormones during development affect gender identity (GI), and sex chromosome genes contribute to some aspects Of GI. Gender dysphoria (GD) occurs more frequently in individuals with DSD

**Methods:** We report a 7.7 yo Hispanic child born at 33 wks GA, with clitorimegaly, a perineal urethral meatus and labio-scrotal folds with no palpable gonads, normally configured uterus and cervix, and a vagina with a normally located introitus. Peripheral blood karyotype: 45,X/46,X,idic(Y)(p11.3)/47,X,idic(Y)(p11.3)+idic(Y)(p.11.3, and FISH positive for *SRY*. At 3 wks of age, the testosterone level was normal for a male (279 ng/dL), but anti-Mullerian hormone was low. LH and FSH were normal (14 and 14 mIU/mL, ICMA). Right gonad had descended, and clitoral structure had increased in size. Parents expressed strong desire to raise the child as a female, and after consultation with her care team female gender was assigned. Growth failure was noted at 2 y age, and the child was monitored, and treated according to TS Guidelines. She enjoyed normal psychomotor development, and responded to growth hormone therapy. Previously, parents had not reported any signs of gender dysphoria in the child, or difficulty interacting with peers. Most recently the mother has noticed "worrisome" changes in her behavior. Considering the high risk for potential problems in her GI development, related to

pre-and post-natal androgen exposure, and chromosomal aberrations, we used Parent-report Gender Identity Questionnaire for Children, developed by Elizabeth and Green (1984) to screen her for gender identity disorder.

**Results:** Results placed the child in the subthreshold group for DSM criteria for gender identity disorder, but differed slightly from control population scores. The patient was referred to Psychology for further evaluation.

**Conclusions:** Gender assignment in DSD continues to be a challenge. Full disclosure, close observation, and appropriate psychometric tools may help with early identification of children at risk for GID.

P3-1527

#### A CASE WITH ATYPICAL GENITALIA CAUSED BY CHROMOSOME 9Q DELETION

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**Objectives:** Steroidogenic factor 1 gene (*SF1*) plays essential role for sex development and steroidogenesis. *SF1* mutation can be the cause for 46,XY DSD with wide spectrum of clinical presentation. *SF1* locates on long arm of chromosome 9 (9q33). Here we report a patient with atypical genitalia who has a deletion of 9q31-qter and an added segment of unknown origin.

**Methods:** A baby was born from a 38-year-old mother at 33 weeks of gestation after complicated pregnancy with pregnancy-induced hypertension. Amniocentesis was performed and chromosome analysis showed 46, XY, add(9)(q31). The baby showed atypical genitalia at birth BW of 1634 g with severe edema, complicated with ventricular septal defect, cheilognathopalatoschisis, and single umbilical cord artery. He had no pigmentation. His penile length and diameter was 10 mm and 8 mm with perineal hypospadias. No vaginal orifice was observed. The right testis was palpable in inguinal area, while left testis was not palpable.

**Results:** Abdominal ultrasound showed inguinal and intra-abdominal testes-like structure. Uterus nor ovary was detected. Blood test at day 2 showed LH 0.41 mIU/ml, FSH 4.15 mIU/ml, AMH 7.05 ng/ml, testosterone 0.11 ng/ml (ECLIA) and 0.0499 ng/ml (LC-MS/MS), respectively. HCG loading test was performed from day 14 for 3 days. Peak testosterone level was low at 0.08 ng/ml (ECLIA), 0.211 ng/ml (LC-MS/MS), and 5- $\alpha$ DHT.

**Conclusions:** Chromosome analysis reconfirmed the deletion of 9q31-qter. The atypical genitalia, presumed adrenal insufficiency, and other abnormalities may be due to lack of the genes on 9q31-qter including haploinsufficiency of *SF-1*.

### A RARE CAUSE OF CONGENITAL ADRENAL HYPERPLASIA: CONGENITAL LIPOID ADRENAL HYPERPLASIA

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**Objectives:** Lipoid congenital adrenal hyperplasia (CLAH) is a rare autosomal recessive disorder caused by mutations in steroidogenic acute regulatory protein (STAR gene), which is required for the movement of cholesterol from the outer to the inner mitochondrial membranes to synthesize pregnenolone. CLAH is characterized by early-onset adrenal crisis, 46,XY sex reversal and wide hyperpigmentation. Herein we described an infant with adrenal crisis due to CLAH because of novel STAR mutation.

**Methods: Case:** A twenty-day patient was hospitalized for an adrenal crisis with hypoglycemia (plasma glucose: 35 mg/dl), hyponatremia (Sodium: 108 mmol/L) and hyperpotassemia (Potassium: 9.9 mmol/L). Parents were first degree cousin married. On physical examination, the patient had intense pigmentation throughout his body. The genital examination was consistent with the girl appearance (Prader stage 1) and the gonads were in the bilateral inguinal region. In laboratory: ACTH: >1250, Kortizol: 3.4 µg/dl, 17-OH Progesterone: 1.6 mg/ml, Progesterone: 0.68 ng/ml, FSH: 3.88 mIU/ml, LH: 8.91 mIU/ml, Total Testosterone 0.29 ng/ml, Renin: >500 pg/ml, Aldosterone: 1 pg/ml, Triglyceride: 188 mg/dl, Total Cholesterol: 147 mg/dl. Pelvic ultrasonography showed no echogenicity of the uterus and ovaries, but echogenicity consistent with the testis was observed bilaterally in the inguinal canal. Glucocorticoid and mineralocorticoid treatment was started for adrenal insufficiency.

**Results:** Molecular analysis revealed a novel homozygous IVS3+1G>C (c.306+1G>C) mutation in the *StAR* gene. In silico analysis, according to Mutation Taster and Human Splicing Finder analyzes, this mutation was considered to be the most likely cause of adrenal insufficiency because it affected the splice site region and was compatible with the clinic.

**Conclusions:** In patients with adrenal insufficiency, hyperpigmentation, girl genitalia appearance but 46,XY, CLAH should always be considered and molecular analysis should be performed to confirm the diagnosis of star gene mutation.

P3-1529

### LATE DIAGNOSIS OF P450 OXIDOREDUCTASE DEFICIENCY IN A PATIENT WITH ARGININOSUCCINATE LYASE DEFICIENCY.

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**Objectives:** P450 Oxidoreductase (POR) Deficiency is the most complex form of congenital adrenal hyperplasia. It usually causes genital ambiguity in both sexes, and eventually peculiar skeletal malformations resembling Antley-Bixler syndrome. Co-occurrence of POR deficiency and Argininosuccinate Lyase Deficiency (ALD) in the same patient born to unrelated parents has never been reported.

**Methods:** Gas chromatography/mass spectrometry has been used for determination of urinary metabolites.

**Results:** The patient, a boy, was born at term to unrelated parents, with a weight of 3.35kg. He was diagnosed with ALD (homozygous p.V178M mutation) at the age of 3 years, following diagnosis in his older brother. Despite good compliance to diet, during follow-up the child developed absences (7 years of age), keratoconus (7.5 years of age), optic and auditory nerve atrophy (8 and 11 years, respectively), the latter being not typical of ALD. He was referred at the age of 17.4 years because of short stature (Height -2.02 SDS; target height 0.46 SDS), delayed puberty (P2, testicular volume 10 ml bilaterally; penile length 7.2cm) and bone age of 13 years. No skeletal malformations were detected. Laboratory work-up revealed LH 14.3mU/ml; FSH 16.1mU/ml; ACTH 222pg/ml; DHEA-S 41ug/dl (80-560); Androstenedione <0.3ng/ml (1.1-3.5); 17-OHP 28.75ng/ml (0.5-2.1); Testosterone 100 ng/dl; Progesterone 21.1 ng/ml; Cortisol 90ng/ml; normal electrolytes; Renin 36.4pg/ml (0.9-20). Urinary steroid profile confirmed combined signs of 21-hydroxylase and 17-hydroxylase deficiency, typical of POR deficiency. Synacthen test showed suboptimal cortisol response (peak Cortisol 69 ng/ml), so that the patient was started on Hydrocortisone. Given the lack of progression into puberty, the boy has been started on testosterone. Genetic analysis of the POR gene is pending.

**Conclusions:** Our case highlights the phenotypic heterogeneity of POR deficiency. In fact this defect can rarely be associated with late and mild signs, such as delayed, slow-progressive puberty and/or infertility. We report for the first time co-occurrence of two rare autosomal recessive diseases, POR Deficiency and ALD in a patient born to unrelated parents. Characterization of POR genotype and enzyme activity will clarify the relationship between these two rare conditions.

P3-1530

### MALE 46,XX/45,X: TURNER SYNDROME MOSAICISM IN A BOY?

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#### Objectives:

Turner Syndrome in male phenotypic patients has rarely been described in the literature so far, and its association with Disorders of Sexual Development (DSDs) can be considered an interesting subject for pediatric endocrinologists.

Objective: Describe a curious case of DSD with male phenotype and a Turner syndrome mosaicism

Methods: Retrospective review of medical records

Results: A.L.M, 10 months old, sent to Pediatric Endocrinology service by the Pediatric Surgery unit due to ambiguous genitalia. At the age of 5 months, the child had had clinical suspicion of Down’s syndrome and revealed karyotype 46,XX, despite presenting male phenotype and being raised as a boy. In our service were observed labioescrotal fusion, 3cm falus, 0,5ml and 1,0ml gonads, almond-shaped eyes, round face, ogival palatus and nipple hypertelorism. Pelvic ultrasound showed no uterus, research for the SRY gene was positive while other Y gene markers were negative and a new G band karyotype evidenced 46,XX/45,X [30]. Abdominal video laparoscopy did not show müllerian structures and gonad biopsy revealed bilateral testicles. Testosterone level after stimulation with hCG was 422ng/dL and others androgenic markers were in the reference range. In the following years, a short neck became evident. The diagnostic hypothesis was then made for DSD and Turner syndrome variant in a male phenotype. No positivity of thyroid or antiendomysium antibodies were found, neither kidney or heart malformations, ALT and AST were normal. The child has received growth hormone for six months, due to short stature, that was suspended due to no response. At age 4, received 3 doses of testosterone due to penis size shorter than 2SD. Currently, the patient is 8 years old, eutrophic, penis size normalized (4.8cm), and shows learning difficulties.

Conclusions: Turner syndrome in female patients has been widely discribed, including several cromosome mosaicisms and gonadal dysgenesis. However, this patient showed clinical features and cromosomic findings that differ from what is usually seen in 46,XX testicular DSD. The hypotesis of a Turner variant in a 46,XX/45,X boy is discussed.

P3-1531

TURNER SYNDROME (45,X) WITH CLITOROMEGALY AND LEIDYD CELL HYPERPLASIA

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Background: Turner syndrome (TS) is one of the most common chromosomal abnormalities seen in girls. Chromosome monosomy (45,X) is present in 50-60% of the cases. Abnormalities include short stature and gonadal dysgenesis. The risk of developing any kind of gonadal lesion, whether tumoral or not, justifies investigation of Y-chromosome sequences. We report a patient with TS and clitoromegaly who despite undetectable Y mosaicism in

peripheral blood, presents with hystological Leydig cell hyperplasia.  
Case Report :  
A 9 year old girl with TS, underwent cytogenetic analysis showing a pure 45,X karyotype. At the age of 11, clitoromegaly was assessed. She had an according bone age; adrenal and tumoral pathology were excluded. Peripheral blood, oral mucose and urine material were studied by means of FISH and PCR in order to determine Y-chromosome-specific sequences (SRY and AZF), which turned out negative. Bilateral gonadectomy was performed. Hystopathologic report showed the presence of hyperplasic Leydig cells, confirmed by immunohistochemistry assay (calicrein and melan A). See Table 1.

Methods: N/A

Results: N/A

Conclusions: Our case represents a rare association of clitoromegaly in a girl with TS and 45,X karyotype. Reviewing the literature we found that Leydig cells hyperplasia is not a frequent finding in children and whenever found, it is more frequent in 46 XY mosaicism, typically presenting as precocious puberty with high testosterone levels. Our patient showed no evidence of Y sequences and despite having low testosterone levels, she developed clitoromegaly. It is difficult to differentiate this type of hyperplasia clinically from a Leydig cell tumor. Only one similar case of TS with clitoromegaly and ovarian hillus cell hyperplasia was found, but no TS associated to Leydig cell hyperplasia has been reported.

ACTH	CORTISOL	17-OH-PROGESTERONE	TESTOSTERONE	ANDROSTENEDIONE
14.1pg/ml (0.1-45 pg/ml)	7.3ug/dl (5-25 ug/dl)	1ng/ml (0.5-2.0 ng/ml)	<20 ng/dl (<20 ng/dl)	0.35 ng/ml (0.5-3.0 ng/ml)

P3-1532

46,XY DSD CAUSED BY A DE NOVO MISSENSE MUTATION IN THE TALE HOMEDOMAIN OF PBX1

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Objectives: The development of the mammalian gonad is regulated by a double repressive system where equilibrium of mutually antagonistic pathways must be attained for normal development of either the testis or ovaries. In human, any perturbations of the tight balance existing between these two antagonistic genetic and physiological sequences can lead to inappropriate gonad differentiation and function. DSD is defined as ‘congenital conditions in which the development of chromosomal, gonadal, or anatomical sex is atypical’.

46,XY DSD includes errors of testis-determination such as 46,XY gonadal dysgenesis. Mutations in genes like *SRY*, *NR5A1*, *MAP3K1* may explain about 40% of 46,XY DSD, although most cases remain unexplained. Here, we identified a new cause of DSD in a syndromic form of 46,XY gonadal dysgenesis.

**Methods:** A 46,XY girl presented with female external genitalia, elevated serum FSH and LH levels and no testosterone. The girl had a subtle fusion of the radius and ulna (radio-ulnar synostosis). Further examination revealed 46,XY complete gonadal dysgenesis with normal adrenal and kidney function. A candidate gene approach, together with whole exome sequencing of DNA from the girl and her parents was performed. Protein-DNA and protein-protein assays were performed to evaluate the effect of the mutation on the biological activity of the protein.

**Results:** Sanger sequencing revealed a *de novo* heterozygous missense mutation (p.R235Q) in the evolutionary conserved TALE homeodomain of the PBX homeobox 1 (PBX1) gene. Exome sequencing indicated no other mutations in genes known to cause DSD. This mutation is absent from the public databases and it was not observed in 300 healthy ancestry-matched control individuals. Mice lacking Pbx1 die *in utero* at E15-16 with multiple organ hypoplasia and they exhibit impaired testes development. We observed that the p.R235Q mutation did not affect the DNA-binding properties of the protein but abolished specific protein-protein interactions with factors known to be necessary for gonad development.

**Conclusions:** Combined genetic and functional assays indicate that a mutation involving the highly conserved transcription factor PBX1 is a new cause of 46,XY complete gonadal dysgenesis.

P3-1533

#### A JAPANESE PEDIGREE OF ATR-X SYNDROME IN WHICH EACH INDIVIDUAL SHOWED VARIOUS DEGREES OF MANIFESTATIONS

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**Objectives:** ATR-X syndrome is a condition associated with 46,XY disorder of sexual development (DSD), X-linked intellectual disability, characteristic facial appearance, and alpha-thalassemia. We report the pedigree of ATR-X syndrome in Japanese patients with a novel mutation in the *ATR-X* gene, in which each patient showed different degrees of manifestations.

**Methods:** Written informed consent was obtained for genetic analysis.

**Results:** The proband was an 8-year-old boy born with ambiguous genitalia, which was close to female type. Although he was first assigned female, genital virilisation and an elevated level of testosterone occurred at the age of 6

months. Because he had testes in the inguinal region, no uterus, and 46,XY chromosomal karyotype, his gender was changed to male. There were no mutations in the *NR5A1*, *AR*, or *SRD5A2* genes. He had severe intellectual handicap, a characteristic dysmorphic face, and alpha-thalassemia; interestingly, central precocious puberty developed after the age of 5 years. His maternal male cousin also had intellectual disability and cryptorchidism, and there were two male relatives manifesting intellectual disability and cerebral palsy, respectively, on his mother's side, leading to genetic analysis of the *ATR-X* gene. A novel c.7192 C>T mutation (p.Gln2398X) was found in exon 34, and ATR-X syndrome was diagnosed.

**Conclusions:** Although the pathophysiology of ATR-X syndrome remains to be completely elucidated, ATRX protein is somehow involved in the expression of multiple genes. Therefore, various manifestations and various degrees of abnormalities are seen even among affected individuals with the same genetic backgrounds. Although the C-terminal domain of this gene has been reported to be responsible for urogenital manifestations, individuals in this pedigree did not have urogenital abnormalities to the same extent. Even in the C-terminal domain, there appear to be no obvious genotype-phenotype correlations. ATR-X syndrome should be included in the differential diagnosis for patients with 46,XY DSD who belong to families with X-linked intellectual disability. The genital virilisation in infancy and central precocious puberty seen in our patient are unusual and interesting phenomena in this syndrome, which should be further investigated.

P3-1534

#### DYSGERMINOMA AND BILATERAL GONADOBLASTOMA AT 6 YEARS OLD IN A PATIENT WITH A 46,XY GONADAL DYSGENESIS AND DMRT1 DELETION

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**Background:** Partial monosomy of 9p causes a syndrome characterized by mental retardation, cranio-facial abnormalities and genital anomalies. In 46,XY patients, partial or complete gonadal dysgenesis has been reported, with a variable phenotype including cryptorchidism, hypospadias, ambiguous genitalia or completely female phenotype. The region responsible for the gonadal dysgenesis is precisely localized to 9p24.3, which includes the *DMRT1* gene. *DMRT1* is expressed in the embryonic gonads of both sexes, and is required for fetal testicular development and maintenance of adult testis. Loss of *DMRT1* in mice results in a high incidence of teratomas



suggesting that *DMRT1* is a dose-sensitive tumor suppressor gene.

#### **Methods:**

Case presentation.

**Results:** A 17-month-old phenotypic female child was referred to our Endocrinology Department because of complete sex reversal. She had severe developmental delay, dysmorphic features (bulbous nose, hypertelorism), hip dislocation, scoliosis. External genitalia were female. Array CGH analysis showed a 46,XY karyotype, with deletion in 9p24.3 24.2 and 9p24.2p13.3 duplication. Endocrine evaluation showed low AMH (0.21 ng/mL), inhibin B (<3 pg/mL), LH (2.1U/L) and  $\beta$ hCG (<1.2 ng/mL) and high FSH (45U/L) levels. Pelvic ultrasound showed a normal uterus, with no visible gonads. Given the increased risk of gonadal malignancy, a gonadectomy was proposed at 6 years of age. Surgery exploration showed right dysgenetic gonad with some cells of gonadoblastoma and a voluminous gonadal tumour (measuring 12.5 cm), histological diagnosis was dysgerminoma, and left dysgenetic gonad with gonadoblastoma. Serum AMH (3.9 ng/mL), inhibin B (15 pg/mL) and  $\beta$ hCG (72 ng/mL) levels were high and normalized after tumor resection. No additional treatment was necessary.

**Conclusions:** Based on the high frequency (30%) of gonadoblastoma reported by authors in patients with gonadal dysgenesis and partial 9p monosomy (8/27 at histological analysis) at an early age (since 12 months of age), and occurrence of a malign tumour at the age of 6 years in this patient, we suggest that bilateral gonadectomy is performed at an early age in 46,XY patients with no or low differentiated dysgenic gonads caused by *DMRT1* deletion.

P3-1535

#### **LOOKING FOR THE MISSING MENSES.**

*Shannon Reakes, RN; Cecilia Garcia Rudaz, MD, ACT Health, Canberra, Australia*

**Objectives:** To highlight two rare cases of primary amenorrhea due to anatomical defects.

**Methods:** Amenorrhea is the absence of menstrual blood flow. Primary amenorrhea should be investigated in any girl with secondary sexual characteristics who has not had menstruation by the age of 15 years or 5 years post breast development. Primary amenorrhea is usually a result of genetic or anatomical abnormalities, therefore, all girls with fully developed secondary sexual characteristics presenting with primary amenorrhea should be investigated for an anatomical abnormality

**Results:** Both girls were referred at the age of 16 years for investigation of primary amenorrhea. Neither girls had a particular phenotype, the onset of thelarche was age appropriate. At presentation both had completed puberty with breast Tanner stage V, pubic hair stage V, and no family hx of late puberty. Case One has a background of type 1 DM, diagnosed 1 year prior with excellent control. Further clinical investigations were taken including a pelvic U/S, with a

finding of uterine didelphys with two separate endometrial cavities, two cervical canals, both distended due to haematocolpos, associated unilateral kidney hypoplasia. Case Two presented to her general practitioner with PCOS like symptoms, i.e acne and was commenced on the contraceptive pill. Due to the absence of bleeding, she was referred to our clinic. Clinical investigations were taken including a pelvic U/S, with a finding the absence of the uterus and a rudimentary cervix, no introitus could be visualised, but had normal ovaries.

**Conclusions:** These cases highlight the need for investigations in girls with primary amenorrhoea independent of their primary diagnosis or presentation. Even though amenorrhoea can occur more frequently associated with type 1 DM, these cases highlight an extremely rare situations and enabled early diagnosis that prevented physical and psychological complications and in case One, potentially prevented a serious life threatening event.

P3-1536

#### **MISMATCH BETWEEN FETAL SEXING AND BIRTH PHENOTYPE: A CASE OF COMPLETE ANDROGEN INSENSITIVITY SYNDROME**

*Keisuke Yoshii, PhD; Yasuhiro Naiki, PhD; Reiko Horikawa, PhD, National Center for Child Health and Development, Tokyo, Japan*

**Objectives:** Complete androgen insensitivity syndrome (CAIS) is X-linked recessive disorder in which affected individuals present female external genitalia and normal breast development at puberty but lack of menstruation. The disease is caused by androgen receptor (AR) dysfunction leading to hormone resistance. Most patients with CAIS are diagnosed in adolescence with primary amenorrhea or in childhood with inguinal hernia. In the present report, we describe a patient with CAIS diagnosed extremely early after birth due to the mismatch between karyotype detected by amniocentesis and external genitalia phenotype at birth.

**Methods:** Case presentation

**Results:** Amniotic fluid check was performed at 16 weeks of pregnancy because of advanced maternal age, and showed 46,XY. Fetal echography didn't any abnormalities except being unable to identify the scrotum. The patient was born after uncomplicated pregnancy at the gestational age of 40 weeks. Female external genitalia and bilateral inguinal mass were observed. There were no other external malformations. The patient had normal balance of electrolytes and normal glucose levels. ACTH, 17-hydroxyprogesterone and cortisol levels were within normal range. Testosterone level at the first day of life was elevated to 2.1 ng/mL (7.28 nmol/L), and LH and FSH levels were suppressed below 0.1mIU/mL. Testosterone level was decreased to 0.29 ng/mL on day 11. Imagings revealed bilateral testis at inguinal regions, and no uterus nor ovaries. HCG test showed markedly elevated testosterone and normal ratio of T/androstenedione and T/DHT. The presence of SRY gene was detected by fluorescent in situ hybridization. Genetic analysis identified a

known nonsense mutation in *AR* gene. There was no mutation in *SRD5A2* gene. The parents made a decision of female gender assignment after full disclosure of the diagnosis and implications by our multidisciplinary team.

**Conclusions:** Amniotic fluid check is a very reliable test for prenatal diagnosis of fetal chromosomal abnormalities. Fetal chromosomal sex is found out by amniocentesis, although it is different from originally intended purposes. The increasing number of amniocentesis leads to the early diagnosis of CAIS and other disorders of sex development.

P3-1537

#### TESTOSTERONE LEVELS IN NEWBORNS WITH CLITOROMEGALY IN CENTRAL BROOKLYN

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**Objectives:** Clitoromegaly in newborns is defined as clitoral length (CL) of  $\geq 10$ mm and/or clitoral width (CW) of  $\geq 7$ mm. Recent studies suggest that clitoral size varies among ethnic groups, however, normative data is lacking. Through the years, we noticed high number of referrals for evaluation of clitoromegaly. Here in, we describe our experience with clitoromegaly in the newborn period in our predominantly African American population.

**Methods:** An IRB-approved, retrospective chart review was conducted. Charts from 2006-2017 were analyzed. Data regarding gestational age (GA), birth weight (BW), CL, CW, race, baseline testosterone ( $T_b$ ) and repeat testosterone ( $T_r$ ) level were obtained. Patients with adrenal disease and disorder of sex development were excluded. Pearson correlation and t-test were used for statistical analysis.

**Results:** From 45 charts reviewed, 36 newborns have true clitoromegaly. None had known maternal history of hyperandrogenism. Overall, the mean CL was  $10.4 \pm 2$ mm and mean CW was  $5.4 \pm 1.6$ mm. Mean  $T_b$  ( $n=44$ ) was  $143 \pm 102$ ng/dl (normal: 20-64 ng/dl) and mean  $T_r$  ( $n=26$ ) was  $29 \pm 27$ ng/dl among all subjects. There were no statistical differences in regards to the  $T_b$  between those with  $CL \geq 10$  mm and  $\leq 9$ mm, and those with  $CW \geq 7$ mm and  $\leq 6$ mm.  $T_b$  was elevated irrespective of CL and CW. There were no correlation between testosterone levels (either  $T_b$  or  $T_r$ ) and BW, GA, CL and CW. There was significant positive correlation between CL and CW ( $r=0.35$ ,  $p<0.03$ ). Neither GA nor BW correlated with CL or CW.  $T_b$  levels were statistically higher than  $T_r$  ( $p<0.01$ ).

**Conclusions:** In our experience, most of the newborns evaluated for clitoromegaly had elevated  $T_b$  that normalized

within one month of life without any intervention. Nevertheless, workup for clitoromegaly is still recommended. Increased  $T_b$  was seen in those with true clitoromegaly as well as those with normal clitoral size. Our study suggests that testosterone level may differ among ethnic groups. Further studies are needed to assess the etiology of elevated  $T_b$  in our population.

P3-1538

#### MIXED GONADAL DYSGENESIS, REGARDING A CASE

Karen Eve Ramos, MS/MA; Kelly Cin Franco, MS/MA, Child Health National Institute San Borja, Lima, Peru

**Objectives:** Describe clinical, biochemical, cytogenetic and pathological characteristics of mixed gonadal dysgenesis.

**Methods:** Review the clinical archive and the following of the patient with mixed gonadal dysgenesis.

**Results:** A one year and two month old patient presented at ambulatory clinic with no contributory history besides of presence of hypospadias and bilateral cryptorchidism since birth. At physical examination: Weight: 7 kilograms, Length: 89 centimeters. Genitourinary system: Presence of slight curvature of phallus (length: 1.5 cm) penoescrotal hypospadias, undescended testicles, not palpable in scrotal sacs. In the auxiliary exams we found: Karyotype: 45 X [7] /46 XY [43], laboratory exams: total testosterone: 0.025 ng/mL, antimüllerian hormone: 135.9 ng/mL (60-80), alfafetoprotein: 2.78 ng/mL, carcino embryonic antigen: 4.24 ng/mL. We did test with human chorionic gonadotropin (HCG) result testosterone value after HCG in 0.11 ng/mL (Bad response). Testicular ultrasound showed: Right testicle in the inguinal canal, homogeneous, volume: 0.5 cubic centimeters, no calcifications. No left testicle defined. Urology did left orchiectomy and right orchidopexy, they found a right testicle of 1.5x1 cm and a fibrous and hypotrophic left testicle (0.5x0.88 cm); in the microscopy: presence of oviducts and nodular formation with 25% of seminiferous tubules and 75% of tumoral cells with PLAP (placental alkaline phosphatase), cytokeratin and calretinin positives concluded germinal cells intratubular tumor. Finally urology did also left orchidopexy.

**Conclusions:** We present this case because of the importance of early discovery of disorder of sex development and timely refer to the specialist in order to do an adequate diagnosis, management and prevention of gonadal cancer. In our patient we detected a bad testicular response which later correlate with the presence of germinal cells intratubular tumor which finally permitted orchidopexy bilateral. After that this patient will require a multidisciplinary team composed by endocrinologist, urologist, geneticist and psychologist.

P3-1539

#### OVOTESTICULAR DSD: PATIENTS FROM THE CHILDREN'S INSTITUTE OF SÃO PAULO/BRAZIL (HCFMUSP)

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**Objectives:** Ovotesticular DSD is a rare condition responsible for disorder of sexual differentiation, coursing with an ample clinical spectrum and none of these clinical features is capable of distinguishing from other etiologies of atypical genitalia. The diagnosis must be histopathological, containing testicular (seminiferous tubules and / or spermatozoa) and ovarian (follicles) tissues in the same individual.

**Objective:** An overview of the OT DSD cases followed at a referral center.

**Methods:** Retrospective analysis of medical records.

**Results:** Thirty-six individuals were studied, seventeen of these were raised as boys, six were gendered as girls and ten were undetermined. Atypical genitalia was seen in 97% of the patients, except one patient. The mean age of the first visit was 2.7 years. After the biopsy, three patients had their sex altered from masculine to feminine. In the feminine sex group there were no changes. All patients that were initially characterized as undetermined sex were raised as girls. The distribution of the karyotypes was 55.5% (20) of 46,XX; 30.5% (11) of mosaics and approximately 14% (5) of 46,XY.

**Conclusions:** The diagnosis of ovotesticular DSD should always be considered in cases that present atypical genitalia, but it must be remembered that it may also be present in patients with normal genitalia. Most of the cases are 46,XX karyotype, mosaicism is frequent and the 46,XY karyotype is least common.

## POSTER SESSION 3

Saturday, September 16, 2017, 12:00-1:00pm

### P3 - Syndromes

#### P3-1600 – P3-1619

P3-1600

#### ENDOCRINE DYSFUNCTION IN CHILDREN WITH KABUKI SYNDROME IN A KOREAN POPULATION

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**Objectives:** Kabuki syndrome (KS) is a rare syndrome characterized by distinct dysmorphic facial features, postnatal growth retardation, intellectual disabilities, and skeletal abnormalities. This study was undertaken to investigate frequencies and clinical course of endocrine abnormalities in patients with KS in Korea.

**Methods:** Twenty nine unrelated patients (15 males, 14 females) diagnosed with KS by clinical diagnostic criteria and direct sequencing of *KMT2D* and *KDM6A* genes were included in this study. To elucidate further the endocrine disorders of KS patients, we screened clinical parameters such as age at growth hormone (GH) treatment, growth pattern, thyroid function, and pubertal status in a cohort of 29 individuals with KS.

**Results:** The age at diagnosis and last follow-up were  $50.8 \pm 48.4$  months and  $81.8 \pm 51.6$  months, respectively. Eleven (37.9%) patients of 29 patients demonstrated vitamin D deficiency. Short stature (height < -2 SDS) was observed in 8 (27.5%) patients. Five (17.2%) patients presented with primary hypothyroidism. Early puberty was shown in 5 (17.2%) patients, premature thelarche in one patient (3.4%), and central precocious puberty in one female patient (3.4%). Four (26.6%) male patients of 15 male patients had cryptorchidism and one patient presented with recurrent hypoglycemia. Obesity and overweight were observed in two (6.8%) patients, respectively. Four (13.7%) patients were treated with GH due to profound short stature. The mean age at the start of GH treatment was  $8.7 \pm 3.4$  years (66–142 months). The mean treatment duration was 2.1 years (6.5–3.6 years). After two years of GH treatment, height SDS increased from  $-2.66 \pm 0.57$  to  $-1.64 \pm 0.78$  ( $P=0.07$ ). IGF-I SDS and IGF binding protein-3 (IGFBP-3) SDS increased from  $-0.92 \pm 2.45$  to  $1.72 \pm 1.85$  and  $-0.14 \pm 1.0$  to  $0.09 \pm 0.34$  ( $P>0.1$ ,  $P=0.07$ ), respectively.

**Conclusions:** Short stature was the most common endocrine dysfunction in KS but seems to respond well to GH treatment during the first two years. Vitamin D deficiency was also common so that Vitamin D levels should be followed and supplementation given if needed. Regular check-up for endocrine function are required due to high incidence of endocrine dysfunction in patients with KS.

P3-1601

#### PRENATAL DIAGNOSIS OF 47,XXY IS ASSOCIATED WITH BETTER COGNITIVE AND BEHAVIORAL, BUT NOT PHYSICAL PHENOTYPES IN CHILDHOOD

Shanlee M Davis, MD, MS, University of Colorado / Children's Hospital Colorado, Aurora, CO, United States; Karen Kowal, Physician's Assistant; Judith Ross, MD, Nemours DuPont Hospital for Children / Thomas Jefferson University, Philadelphia, PA, United States

**Objectives:** 47,XXY/Klinefelter syndrome (KS) affects 1/600 males, and due to non-invasive prenatal screening, prenatal diagnosis is exponentially increasing. Little data are available about phenotypes in prenatally vs. postnatally diagnosed KS, particularly in childhood. Our objective was to compare

cognitive, behavioral, and physical phenotypes in pre- vs postnatally diagnosed childhood KS cohorts.

**Methods:** 80 boys with KS (non-mosaic 47,XXY), ages 4.0-12.9 years, no intellectual disability (IQ >70), underwent a cognitive evaluation (Differential Ability Scales II (DAS)), physical examination, bone age, fasting labs (lipids, glucose, and testicular function biomarkers), and parent-report Child Behavior Checklist (CBCL). Outcomes in pre- vs. postnatally diagnosed groups were compared using analysis of covariance adjusting for age, socioeconomic status (SES), and prior testosterone treatment.

**Results:** 52/80 (65%) had a prenatal diagnosis. Mean age of the cohorts was similar ( $7.4 \pm 2.5$  years), however the prenatal group had higher mean SES. The prenatal group had higher DAS General Ability IQ standard scores  $97.6 \pm 11.5$  vs  $91.1 \pm 11.7$  ( $p=0.02$ , effect size 0.5), with the greatest difference in non-verbal IQ ( $101.2 \pm 1.7$  vs  $92.3 \pm 2.3$ ,  $p=0.003$ ). The prenatal group had better standard scores on the CBCL Total Problem Behavior scale ( $p=0.002$ ), with the greatest difference in the internalizing behavior domains. The two groups had similar standard deviation scores for height, weight, body mass index, body fat percentage, stretched penile length, and testicular volume. Lipid profiles, blood glucose, gonadotropins, total testosterone, inhibin B, anti-müllerian hormone, and bone age delay were also similar. Several cognitive and behavior scores were higher in boys who had previously received testosterone in infancy, however after adjusting for age, SES, and prenatal diagnosis, these differences did not persist.

**Conclusions:** Cognitive and behavior profiles may be better in children with KS who are diagnosed prenatally vs postnatally, however, physical phenotype and testicular function were similar in both groups. These findings have implications for prenatal counseling and also highlight the need to study the natural history of prenatally diagnosed cohorts longitudinally.

P3-1602

#### METABOLIC SYNDROME DURING TRANSITION PHASE IN PRADER-WILLI SYNDROME

*Graziano Grugni, MD; Alessandro Sartorio, MD, Italian Auxological Institute, Verbania, Italy; Danilo Fintini, MD; Antonino Crinò, MD, Bambino Gesù Hospital, Palidoro (Rome), Italy*

**Objectives:** Prader-Willi syndrome (PWS) is the most frequent cause of syndromic obesity. PWS patients are prone to premature death due to the complications related to obesity, including cardiovascular problems (CVD) and disorders associated with type 2 diabetes mellitus (DMT2). The metabolic syndrome (MS) is a strong risk factor for atherosclerotic CVD and DMT2, and it is not possible to rule out the hypothesis that MS may be one of the mechanisms responsible for excessive mortality in PWS. Because T2DM and hypertension frequently develop during the transition phase of these individuals, this study is aimed to estimate the prevalence of MS in a group of transition subjects with PWS,

in comparison to what observed in patients with simple obesity.

**Methods:** Fifty-five PWS subjects [BMI  $40.1 \pm 1.7$  (mean $\pm$ SE)], 29 females, aged  $21 \pm 0.3$  yr], were studied. As control group, a sample of 24 patients, 15 females, matched to PWS for BMI ( $42.1 \pm 0.9$ ) and age ( $21.5 \pm 0.4$  yr), was considered. Height, weight, waist circumference and blood pressure (BP) were measured by using standardized equipment. Biochemical testing included measurements of fasting glucose, triglycerides (TG) and HDL cholesterol levels. According to the literature (Circulation 2009;120:1640) MS was defined as having central obesity plus any two of the following: high systolic or diastolic BP, high TG, low HDL and impaired fasting glucose (IFG).

**Results:** In our sample of PWS, the distribution of each element of the MS was the following: visceral obesity 83.6%, elevated BP 23.6%, high TG 16.3%, low HDL 41.8% and IFG 16.3%. The PWS group showed a similar MS prevalence than obese controls (21.8% vs 20.8%). Likewise, no difference between PWS and the control group was observed as regards TG ( $104.1 \pm 8.0$  vs  $106.7 \pm 10.0$  mg/dl), HDL ( $50.0 \pm 1.9$  vs  $44.6 \pm 1.8$  mg/dl), systolic BP ( $119.5 \pm 1.5$  vs  $118.8 \pm 2.2$  mmHg), diastolic BP ( $75.8 \pm 1.1$  vs  $74.8 \pm 1.5$  mmHg) and glycemia ( $88.1 \pm 7.9$  vs  $77.6 \pm 1.8$  mg/dl).

**Conclusions:** This study demonstrates that frequency of MS in transition patients with PWS is very close to those of obese controls, confirming the crucial role of obesity status in the development of metabolic abnormalities in these subjects. In this context, screening for associated MS should be a routine element of care and treatment for patients with PWS during the transition period.

P3-1603

#### ABDOMINAL ADIPOSITY ASSESSED BY WAIST CIRCUMFERENCE DOES NOT PREDICT ANDROGEN EXCESS IN OBESE ADOLESCENT GIRLS

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**Objectives:** To test the hypothesis that waist circumference (WC) is a better predictor of hyperandrogenism (HA) and insulin resistance (IR) than BMI in girls with and without known HA.

**Methods:** BMI, WC and WC/BMI were correlated with free testosterone, fasting insulin (FI) and fasting glucose (FG) levels in postmenarchal adolescent girls with (HA group) and without (non-HA group) known HA. Exclusion criteria: oral contraceptives or metformin at initial visit.

**Results:** Fifty-two subjects in the HA group (mean age 15.8 yrs) and 31 in the non-HA group (mean age 14.3 yrs) met inclusion criteria. There were no significant differences in BMI-z-score, WC, or laboratory values between the groups, except free testosterone was higher in the HA group (Table

1). BMI z-score, but not WC, correlated with free testosterone in both groups, with a stronger predictive value for those without HA (Table 2). WC predicted FG and FI in the HA group but not in the non-HA group (Table 3). BMI z-score correlated with FI in the HA group but only a trend was noted in the non-HA group.

**Conclusions:** The positive correlation between abdominal adiposity measured by WC and HA reported in adult women was not seen in this study. In contrast, BMI was a better predictor of androgen levels than WC in this study’s overall group and was an even stronger predictor of free testosterone in those without known HA. In further contrast to adult studies, WC was only predictive of markers of IR in subjects with HA and not in all obese subjects. These data suggest that WC measurement does not improved detection of HA in obese adolescent females. If these findings are corroborated by further studies, early intervention to avoid metabolic sequelae of androgen excess should be prompted by elevated BMI in these subjects. Future longitudinal studies are needed to illuminate the changes in the relationship between WC and HA that occur between adolescence and adulthood.

This research is supported by a T32 grant DK077586.

Table 1. Demographics and Laboratory Values Between Hyperandrogenism and Non-Hyperandrogenism Groups

	HA Group (N=52)		Non-HA Group (N=31)		p-value
	Mean	SD	Mean	SD	
WC(cm)	103.91	15.20	99.58	13.87	0.1984
BMI	34.20	6.48	31.14	5.56	0.0320
%BMI	93.18	18.49	95.97	3.17	0.4093
BMI-z	1.87	0.86	1.85	0.35	0.8909
Fasting Glucose(mg/dl)	89.17	12.56	85.00	7.09	0.0978
Fasting Insulin(mg/dl)	36.82	47.71	27.97	14.56	0.3215
Free Testosterone (pg/ml)	8.54	3.89	5.21	3.16	0.0002
Total Testosterone(ng/dl)	49.43	20.68	35.32	20.77	0.0049

Table 2. Correlation between WC, BMI z-score vs. Free/Total Testosterone between HA and non-HA groups.

		Hyperandrogenism Group (N=52)				Non-Hyperandrogenism Group (N=31)			
		Correlation	195% CI	95% CI	p-value	Correlation	195% CI	95% CI	p-value
WC	vs. Free Testosterone	0.15	-0.14	0.41	0.31	0.34	-0.03	0.62	0.069
BMI-z	vs. Free Testosterone	0.28	0.00	0.52	<0.05	0.44	0.08	0.68	<0.02
%BMI	vs. Free Testosterone	0.28	0.00	0.52	<0.05	0.44	0.08	0.68	<0.02

P3-1604

**MICRO-NUTRIENT INTAKES IN CALORIE RESTRICTED DIETS OF CHILDREN WITH PRADER-WILLI SYNDROME**  
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**Objectives:** Worldwide consensus is that Prader-Willi Syndrome (PWS) children require fewer calories (only 60%) to promote optimal growth as compared to non PWS children. There is no published UK data about adequacy of vitamin & mineral intakes or prevalence of micronutrient deficiencies in these significantly calorie restricted diets. This study assesses if calorie restricted diets in PWS children results in

micronutrient intakes below Reference Nutrient Intakes (RNI) and more specifically and clinically relevant, below Lower Reference Nutrient Intakes (LRNI).

**Methods:** PWS children attending a specialist clinic led by a multi-disciplinary team, completed 3-day food diaries (weighed or portion size) as part of their regular assessments. Food diaries were analysed using specialist software (DietPlan); data input and analysis was done by 1 of 2 trained dietitians. The results were expressed as % of RNI and LRNI adjusted for age and sex. Longitudinal data was retrospectively collated from food diaries submitted and analysed from 2002 to 2015.

**Results:** 45 food diaries from 16 PWS children (aged 1.1-16 years; 7 males and 9 females) collected from 2002 to 2015 were reviewed. At least 1 micronutrient was below 100% RNI in 43 of the 45 analyses. The relevant micro-nutrients and proportion of food diaries where the RNI was <100% were Zinc, Selenium, Iron, Niacin and B12 in 76%, 57%, 45%, 32% and 9% respectively.

At least 1 micronutrient was below 100% LRNI in 14 of the 45 analyses. The relevant micro-nutrients and proportion of food diaries where the LRNI was <100% were Zinc, Selenium, Iron, B12 and Niacin in 19.5%, 13.3%, 10.6%, 8.5% and 6.4% respectively. The relevant micro-nutrients <100% LRNI by number of children were Zinc, Iron, Selenium, Niacin and B12 in 5, 4, 4, 3 and 2 children respectively.

**Conclusions:** This study describes the diets of PWS children in UK and likely micronutrient deficiencies in them. Nutrient intakes below RNI are common, but may not always be clinically significant. Although less common, intakes below LRNI are a clinically relevant concern. Particular attention should be paid to zinc, selenium and iron when monitoring calorie restricted diets in PWS children.

P3-1605

**AORTIC DIAMETER IN ADOLESCENT PATIENTS WITH TURNER SYNDROME EVALUATED BY HEART MRI**  
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**Objectives:** Aaortic dissection are the major cause of death in patients with Turner syndrome (TS), even in a young woman and the monitoring of aortic diameter in TS patient is really important. However, the study of detailed aortic diameter in adolescent with TS is a few. In addition, there is still no proper adjust method of aortic diameter in adolescent patients in TS. This study aimed to measure the detailed aortic diameter in adolescent patients with TS by cardiovascular magnetic resonance imaging (CMRI) and evaluate the risk factors of aortic dilation. In addition, we tried to propose a suitable adjust method of aortic diameter in adolescent patients with TS.

**Methods:** Forty-seven patients with TS were enrolled in this study. The aortic diameter in nine positions of aorta was measured in patient with TS, used CMRI. Aortic diameters were adjusted by body surface area (BSA) and root BSA. Aortic dilation was defined by two criteria: First, the aortic size index (ASI, adjusted by BSA) was greater than 2 cm/m<sup>2</sup>; second, a ratio of the ascending to descending aortic diameters was above 1.5. By dividing into two groups based on age 19, we compared aortic diameters.

**Results:** By first criteria, 22 patients (46.8%) had aortic dilation, while there were 15 patients (31.9%) with aortic dilation by second criteria. Aortic diameter was increased according to height, weight, body mass index and BSA. Especially, aortic diameter was increased according to age, while, ASI was decreased as to the increasing age in adolescent patients and increased in accordance with increasing age in young adult patients. Whereas, aortic diameter which was adjusted by root BSA was increased according to age in adolescent patients as well as young adult patients.

**Conclusions:** Even in young patients with TS, nearly half of patients had aortic dilation, thus, the monitoring of detailed aortic diameter should be started in adolescent. However, aortic diameter adjusted by BSA was decreased according to age in adolescent patients, therefore it suggested that absolute aortic diameter should be also considered when cardiovascular monitoring is performed. In addition, adjusted by root BSA could be an alternative method.

P3-1606

#### VON HIPPEL LINDAU (VHL) SYNDROME: AN INTERNATIONAL DATA-SHARING CONSORTIUM FOR GENETIC AND PHENOTYPIC CHARACTERIZATION

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**Objectives:** von Hippel-Lindau (VHL) disease is an inherited cancer predisposition condition with diverse clinical manifestations spanning multiple organ systems, making it one of the most complex hereditary endocrine cancer disorders. Manifestations include pheochromocytomas, retinal and central nervous system hemangioblastomas, renal cell carcinomas and several

others. Germline variants in the *VHL* tumour suppressor gene identify the majority of vHL families. Certain VHL pathogenic variants have been shown to predispose individuals to distinct manifestations of the disease. To collate the genetic impact of variants among of VHL families across the world, we have initiated a data-sharing consortium to develop a standardized genomic and pheotypic data capturing protocol.

**Methods:** Our initial data set comprises 2251 cases derived from existing cohorts in the Netherlands and Toronto, as well as published literature and publicly-accessible databases. We have developed a standardized data collection protocol that captures all aspects of the complex VHL phenotype. We will use this data collection protocol to input phenotype and genotype data on an additional 100 VHL patients collected in Toronto and other collaborating sites. We have worked closely with the National Institutes of Health Clinical Genome Resource in order to define a platform with which to share our data. We will contribute this in-depth phenotype-genotype data into ClinGen, a freely-available public data-sharing resource that facilitates collaboration with other scientists in the VHL field.

**Results:** N/A

**Conclusions:** By collating the Dutch, Canadian and other published VHL patients and mutations, we plan to create the most comprehensive and well-curated VHL data-sharing mechanism to best understand this complex disorder. We invite other collaborators with extant vHL databases or clinical cohorts to contribute additional cases to improve the predictive power and characterization of genotype-phenotype relationships in this complex disorder, and will make the data collection tools freely available to interested investigators.

P3-1607

#### CLINICAL AND ENDOCRINE CHARACTERISTICS AND GENETIC ANALYSIS OF KOREAN CHILDREN WITH MCCUNE–ALBRIGHT SYNDROME: A RETROSPECTIVE COHORT STUDY

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**Objectives:** McCune–Albright syndrome (MAS) is a rare disease defined by the triad of fibrous dysplasia (FD), café au lait spots, and peripheral precocious puberty (PP). Because of the rarity of this disease, only a few individuals with MAS have been reported in Korea. We describe the various clinical and endocrine manifestations and genetic analysis of 14 patients with MAS in Korea.

**Methods:** Patients' clinical data—including peripheral PP, FD, and other endocrine problems—were reviewed

retrospectively. In addition, treatment experiences of letrozole in five patients with peripheral PP were described. Mutant enrichment with 3'-modified oligonucleotides - polymerase chain reaction (MEMO-PCR) was performed on eight patients to detect mutation in GNAS using blood. MEMO-PCR is a simple and practical method that enables the nondestructive selection and enrichment of minor mutant alleles in blood.

**Results:** The median age at diagnosis was 5 years 2 months (range: 18 months to 16 years). Eleven patients were female, and three were male. Thirteen patients showed FD. All female patients showed peripheral PP at onset, and three patients

subsequently developed central PP. There was a significant decrease in estradiol levels after two years of letrozole treatment. However, bone age was advanced in four patients. Two patients had clinical hyperthyroidism, and two patients had growth hormone (GH) excess with pituitary microadenoma. c.602G > A (p.Arg201His) in GNAS was detected

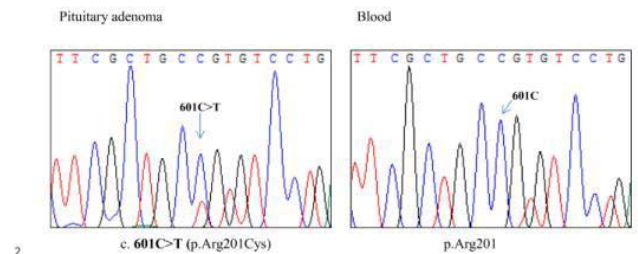
in two patients in blood, and c.601C > T (p.Arg201Cys) in GNAS was detected in one patient in pituitary adenoma.

**Conclusions:** This study described the various clinical manifestations of 14 patients with MAS in a single center in Korea.

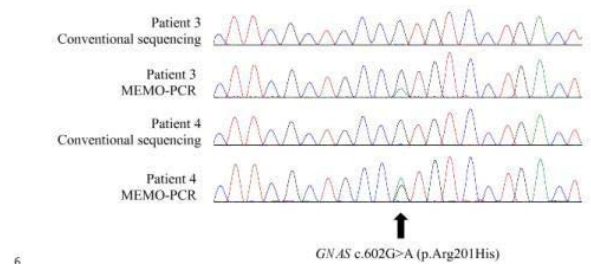
This study first applied MEMO-PCR on MAS patients to detect GNAS mutation. Because a broad spectrum of endocrine manifestations could be found in MAS, multiple endocrinopathies should be monitored in MAS patients. Better treatment options for peripheral PP with MAS are needed.

PLEASE SEE TABLE IN NEXT COLUMN

# FIGURE LEGENDS



**Figure 1.** DNA sequencing of the GNAS gene from patient 12: the Arg201Cys mutation was only detected in pituitary adenoma tissue and not detected in peripheral blood leukocytes.



**Figure 2.** Conventional Sanger sequencing and MEMO-PCR of GNAS gene from patients 3

P3-1608

## COEXISTENCE OF SILVER-RUSSELL SYNDROME AND TURNER SYNDROME

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**Objectives:** Silver-Russell syndrome (SRS) is a rare, clinically and genetically heterogeneous condition, which affects one in 100,000 births. Turner syndrome (TS) is a chromosomal disorder, with an incidence of one in 2,500 live-born females. Both genetic disorders have characteristic features. Patients with SRS and mosaic 45, X/46,X,del(X) karyotypes have a wide range of phenotypic manifestations. Two rare genetic syndromes are not mutually exclusive, especially when characteristic features are shared for both of them.

**Our aim** is to present a case report of a patient in whom Silver-Russell and Turner syndromes have been confirmed.

**Methods:** Genetic examination, clinical observation, recombinant growth hormone treatment

**Results:** The patient is a 4-year old girl who had a karyotype of 45,X on prenatal amniocytes analysis. After delivery she was small for gestational age and her phenotype was quite consistent with Russell-Silver syndrome. She had a characteristic dimorphic facial skeleton with a triangular face with prominent forehead, thin nose, hypotonia and hemihypertrophy. She was admitted to hospital with short stature and body weight deep deficiency. Skin fibroblast and DNA analysis showed mosaic karyotype 45,X[14]/46,X,del(X)(p21.2) and hypomethylation of a gene



H19 located on chromosome 11p15. At present the patient is being treated with growth hormone in our clinic with good therapeutic results.

#### Conclusions:

The diagnosis of a rare genetic disorder does not exclude simultaneous presence of the other rare genetic diseases. Early diagnosis of the coexistence of two different rare genetic syndromes, although very difficult, is crucial to start rapid and appropriate therapy for patients and prevent them from developing serious complications.

P3-1609

#### ACGH ARRAY ANALYSIS OF A PATIENT WITH UNEXPLAINED SHORT STATURE

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**Objectives:** To analyze a patient with unexplained short stature by using aCGH and correlation between genotype and phenotype.

**Methods:** Peripheral blood sample was taken from the patient for the extraction of DNA. aCGH was used to determine the copy number variation in patient and her parents.

**Results:** Proband was clinical diagnosed as short stature, mental retardation, diabetes, corneal dystrophy, and has special face feature. aCGH array analysis has identified a 1.6 Mb deletion, arr[hg19]17q12(34,822,465-36,410,559)X1 in patient, but her parents were normal.

**Conclusions:** Unexplained short stature, mental retardation, diabetes, corneal dystrophy consider use aCGH for diagnose 17q12 microdeletion.



Fig 1 Facial phenotypes of patients with 17q12 microdeletion: forehead, chubby cheeks.

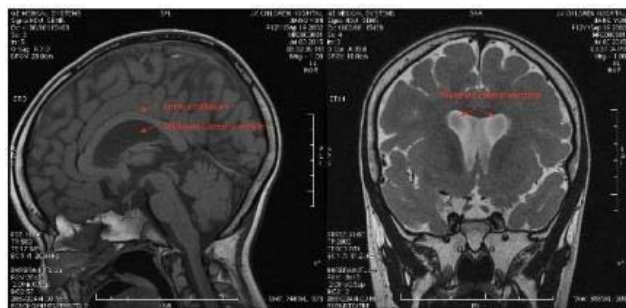


Fig 2 Neuroanatomical features revealed by MRI in patients with corpus callosum abnormalities and widened lateral ventricle.

P3-1610

#### CLINICAL MANIFESTATIONS & MOLECULAR ANALYSIS OF ELEVEN PALESTINIAN FAMILIES WITH SANJAD SAKATTI SYNDROME REVEALING A COMMON DELETION FOUNDER EFFECT AND ANOTHER TWO NOVEL MUTATIONS

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**Objectives:** Sanjad-Sakatti syndrome or hypoparathyroidism-retardation-dysmorphism syndrome (HDRs) is a rare autosomal recessive multisystem disorder characterized by intrauterine and postnatal growth retardation, infantile-onset hypoparathyroidism that can result in severe hypocalcemic seizures, dysmorphic facial features, and developmental delay.

**Methods:** Eleven unrelated Palestinian infants to a consanguineous Palestinian families presented in early infancy with hypoparathyroidism, hypocalcemic seizures, dysmorphic features, growth retardation and developmental delay, assessed to have Sanjad-Sakatti syndrome and were managed accordingly. Clinical manifestations of all presenting patients and their molecular analysis has been checked to correlate clinical presentation with the specific genotype.

**Results:** Sequencing of the TBCE gene showed that nine patients of our series of Eleven patients are homozygous for the mutation (c.155-166del12;p.del52-55) in exon 3 of this gene, the common deletion founder effect of the TBCE gene in Arab patients, while the other two patients had novel mutations: c.355\_356delAT in exon 4 of TBCE gene and c.354\_355del, p.S118fs of the TBCE gene (which has been detected by whole exome sequencing).

**Conclusions:** To our knowledge, this is the first description of a series of Eleven families of Palestinian origin of this disease with molecular confirmation, showing the common deletion founder effect, allowing accurate genetic counseling, early diagnosis of affected kindreds, early therapeutic interventions and avoiding complications. Checking novel mutations for this disease, allowing to check if the clinical presentation does correlate well with the specific genotype in Palestinian patients.

P3-1611

#### SCHAAF-YANG SYNDROME WITH MULTIPLE PITUITARY HORMONE DEFICIENCY: A CASE REPORT

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**Objectives:** N/A

**Methods:** Case Report: A 2<sup>10/12</sup> years old male patient consults for growth evaluation. He had some dysmorphias associated with delayed psychomotor development and arthrogyrosis. Full exome sequencing was requested. An

heterozygous, *de novo* pathological variant at MAGE-LIKE 2 (MAGEL2; OMIM \* 615547) was found diagnosing Schaaf-Yang syndrome (SHFYNG). History and physical exam revealed neonatal hypotonia, development delay/intellectual disability, feeding problems, cryptorchidism with bilateral orchiopexy, chronic constipation, dysmorphic facial features, strabismus, vices of refraction, hypotonia at time of exam, small hands, small feet and short stature with deceleration of growth rate (5 cm/year). Laboratory exams showed repeated low IGF-1 (31.9 and 39 ng/ml); ACTH stimulating test: basal cortisol 10.4 ug/dl and 60 min 10.2 ug/dl; TSH 2.87 uIU/ml, prolactin 145.9 ng/ml (91% recovery). Magnetic resonance of the Sellar Region informed hypoplastic pituitary. Multiple pituitary hormone deficiency was diagnosed with adrenal insufficiency, growth hormone deficiency and hyperprolactinemia.

**Results:** Review of Literature: Schaaf-Yang syndrome is a rare illness due to truncating mutations in the maternally imprinted, paternally expressed gene MAGEL2, which is located in the Prader-Willi critical region 15q11–13. It is characterized by developmental delay/intellectual disability, hypotonia, feeding difficulties, contractures of the small finger joints and autism spectrum disorder. Also sleep apnea, gastroesophageal reflux, and decreased fetal movement are frequently reported. Endocrinological pathologies associated are low stature and hypogonadism. Nevertheless a systematic endocrinological assessment of individuals with SHFYNG has not been reported to date.

**Conclusions:** It seems important that patients with Schaaf-Yang syndrome needs to be evaluated by endocrinologist. Panhypopituitarism has not been described in previously published cases. A complete study of pituitary hormones should be performed in cases already described to see if multiple pituitary hormone deficiency is part of the syndrome.

P3-1612

#### METRELEPTIN USE IN CHILDREN WITH CONGENITAL GENERALIZED LIPODYSTROPHY

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**Objectives:** Congenital generalized lipodystrophy (CGL), is an inherited disorder characterized by loss of adipose tissue and a predisposition to developing insulin resistance and its associated complications, such as diabetes mellitus, hypertriglyceridemia, hepatic steatosis, polycystic ovarian syndrome, and hypertension. Affected individuals have acanthosis nigricans, muscular appearance, umbilical hernia, and, in women, clitoromegaly, hirsutism, and PCOS. We describe the youngest subjects treated with metreleptin reported in the literature.

**Methods:** Our subjects are treated with recombinant metreleptin (Myalept, Aegerion Pharmaceuticals, Inc.) at a starting dose of 0.08 mg/kg/d. We monitor our patients every 3-6 months and perform laboratory evaluation including liver enzymes, urinalysis, glucose, lipid panel, hemoglobin A1c.

**Results:** Patient 1 was evaluated for a sacral dimple and was noted to have a muscular appearance and hyperphagia. At 2 years 2 months, height was at the 25-50th percentile, weight at 10-25th percentile, testosterone total <20 ng/dL, glucose 79 mg/dl, insulin level 1.7 (2.6-24.9 mcU/mL), c-peptide 0.8 (1.1-5.0 ng/mL), hemoglobin A1C 5.3 (4.0-6.0 %), cholesterol 142 (0-169 mg/dL), HDL 38 mg/dL, LDL Cholesterol 89 mg/dL, triglycerides 75 mg/dL, ALT 27 U/L, AST 46 U/L. Since the start of treatment, her appetite has decreased and her liver enzymes have normalized.

Patient 2 is her sister product of a twin pregnancy (twin sister unaffected) born at 35 weeks, birth weight 1789 grams. At 11 months of age, testosterone total was <20.0 ng/dL, insulin level 47.4 mcU/ml, c-peptide 6.7 ng/ml, glucose 84 mg/dl, hemoglobin A1C 5.4 %, cholesterol 214 mg/dl, HDL 23 mg/dl, triglycerides 422 mg/dl, Alkaline Phosphatase. 281U/L, ALT 35 U/L, AST 36 U/L. she has failure to thrive which is currently under investigation.

**Conclusions:** Myalept® (metreleptin) has been approved by the FDA for the treatment of congenital or acquired generalized lipodystrophy. Within 4 months of treatment, the requirement or need for lipid lowering agents and insulin decreases in patients with diabetes and dyslipidemia. The hope in our subjects is that early intervention with metreleptin will prevent complications such as diabetes mellitus, hypertension, fatty liver and pancreatitis.

P3-1613

#### MILD PHENOTYPE OF IPEX SYNDROME CAUSED BY A NOVEL MUTATION OF EXON 12 OF THE FOXP3 GENE

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**Objectives:** To present a case with early onset diabetes due to a novel mutation in *FOXP3*, but without all the features of IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome.

**Methods:** Genetic testing was done using a commercially available next-generation sequencing panel (<http://dnatesting.uchicago.edu>) for the 12 most common causes of congenital diabetes. Upon enrolling in our research studies of monogenic diabetes, we were also able to interrogate over 100 genes implicated in diabetes.

**Results:** The patient presented at the age of 5 months with new-onset neonatal diabetes (serum glucose 1161 mg/dl) in severe DKA (pH 6.9). His past medical history was significant for prematurity, maternal chorioamnionitis, paralysis of the right diaphragm, and several severe respiratory infections requiring additional hospitalizations, one of which was associated with cardiorespiratory failure, all occurring prior to

the diagnosis of diabetes. Next generation sequencing revealed a novel missense variant in exon 12 of *FOXP3* (c.1178A>T) resulting in an amino acid change from lysine to methionine at position 393. The variant has not been reported in ExAC and is predicted to be possibly damaging (polyphen score: 0.63).

**Conclusions:** Mutations in *FOXP3* cause IPEX syndrome or may cause an IPEX-like condition with a variable clinical phenotype. Our patient did not demonstrate evidence of severe dermatitis or diarrhea, although he developed diabetes as an infant. In addition, he did have a history of several severe respiratory infections. Without more complete genetic testing, we would have been unaware of his diagnosis, which could have implications for treatment as well as familial recurrence risk.

P3-1614

#### **NOVEL COMPOUND HETEROZYGOUS ASXL3 MUTATION CAUSING BAINBRIDGE-ROPER'S LIKE SYNDROME AND PRIMARY IGF1 DEFICIENCY**

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**Objectives:** De novo truncating and splicing mutations in the additional sex combs-like 3 (*ASXL3*) are implicated in Bainbridge-Ropers syndrome (BRPS) characterised by severe developmental delay, short stature and characteristic facial features. We describe, for the first time, a patient with severe short stature secondary to IGF1 deficiency, learning difficulties, feeding difficulties and dysmorphic features with a novel compound heterozygous mutation in *ASXL3*.

**Methods:** A 7-year-old boy had severe short stature (-3.5 SDS), dysmorphic features [downward slanting of eyes, low set ears, short neck, hypoplastic toe nails, shortening of metacarpals and ring finger], severe learning difficulties, and speech delay. Peak growth hormone (GH) was 11.7 µg/l to arginine stimulation and bone age was delayed by 3 years. The rest of the pituitary function was normal. IGF1 was persistently low at 4.9 nmol/l (-3.1 SDS) with no increase on IGF1 generation test. A trial of high dose GH (50 µg/kg/day) was ineffective and recombinant IGF1 therapy was commenced. CGH microarray did not reveal any copy number changes.

**Results:** Whole exome sequencing revealed two novel heterozygous *ASXL3* mutations [p.(Arg989Gly), p.(Lys1026Asn)] in the patient, inherited from his unaffected mother and his unaffected father respectively. The missense mutations affect highly conserved amino acid residues across several species and in silico analysis predict the changes to be deleterious (SIFT), disease causing and probably damaging (MutationTaster, PolyPhen and SIFT) on protein

function. Detailed bioinformatic analysis showed that the molecular defects caused by the mutations affect phosphorylation and interaction of *ASXL3* with proteins regulating cell cycle, thus synergistically impacting on two points of the molecular interaction network of *ASXL3*.

**Conclusions:** *ASXL3* is a putative Polycomb group (PcG) protein that is required to maintain the transcriptionally repressive state of homeotic genes throughout development. We hypothesise that *ASXL3* potentially has a role in transcriptional activation of *IGF1* in signalling pathways that regulate cell proliferation, which could potentially be contributing to short stature encountered in these patients.

P3-1615

#### **ANTIBODY NEGATIVE HYPOTHYROIDISM ASSOCIATED WITH GAIN-OF-FUNCTION STAT1 MUTATION**

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**Objectives:** Gain of function mutations in *STAT1* are associated with T-cell deficiencies, specifically decreased numbers of Th17 cells. The vast majority of affected children present with chronic mucocutaneous candidiasis (CMC) and then develop frequent bacterial and fungal respiratory tract and skin infections. Autoimmunity is also a feature of the condition with a high incidence of autoimmune thyroid disease, type 1 diabetes mellitus, and lupus.

**Methods:** N/A

**Results:** We present the case of a Hispanic female with history of CMC, bronchiectasis, and frequent pneumonias. At the age of two years she discovered to have a T385M mutation within the DNA binding domain of *STAT1* which has been previously described. Subsequently at age five she developed acute weight gain, constipation and cold intolerance. She was found to be profoundly hypothyroid with TSH 732.81 mIU/L (normal 0.5-4.3) and free T4 <0.4 (normal 0.71-1.85). Thyroid peroxidase antibody and thyroglobulin antibodies were undetectable. Ultrasound of the thyroid showed small and hypovascular thyroid gland. She achieved euthyroid state on levothyroxine 4.5 mcg/kg/day. Her current dose is 3.3 mcg/kg/day. BMI improved from 90<sup>th</sup> percentile at time of diagnosis to 21<sup>st</sup> percentile within 6 months. To date, at the age of seven years, she is normoglycemic and has not developed any cytopenias. Monthly IVIG infusions and long term antibiotic and antifungal agents have reduced her frequency of pulmonary infections.

**Conclusions:** Gain-of-function *STAT1* mutations are associated with autoimmune thyroid disease in addition to the features described above. Our patient developed profound hypothyroidism without laboratory evidence of autoimmunity. It is possible that the lack of antibodies could

be related to the atrophy of the gland. However, this may also suggest that there are additional mechanisms that can cause or contribute to the hypothyroidism associated with this condition.

P3-1616

#### UNUSUAL ASSOCIATION OF TURNER SYNDROME AND HYPOPIUITARISM IN A TUNISIAN FAMILY

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**Objectives:** Familial occurrence of either Turner syndrome or hypopituitarism is very rare. Particularly, their association is an uncommon finding. In this context, we describe for the first time 4 sisters with Turner syndrome, hypopituitarism was reported in three among them.

**Methods:** Our cohort consists of four Tunisian adult sisters belonging to a consanguineous family. Biochemical analysis, resonance magnetic imaging and cytogenetic analyses were performed.

**Results:** Turner syndrome was diagnosed at the ages of 14, 17, 31 and 43 years in cases 1, 2, 3 and 4 respectively. They suffered from short stature, dysmorphic syndrome and/or delayed puberty. Interestingly, 3 among them showed also hypopituitarism, hypogonadotrophic hypogonadism and central hypothyroidism. Somatotrophic insufficiency was proven in one case. Pituitary MRI has shown an empty sella turcica with hypoplastic pituitary gland in three cases. Their karyotypes were compatible with 45X in one case, 45X/46XX in the second and 45X/46XX/47XXY with x label in two cases.

**Conclusions:** Hence, the presence of these familial cases of TS must evoke new etiopathogenetic arguments. Coincidence of hypopituitarism in this family, might suggest common genetic background for the two diseases. This particular family would be a precious tool for an extensive molecular analysis. More attention should be given to other family's members mainly in the presence of delayed puberty and sterility in other members.

P3-1617

#### COFFIN-SIRIS SYNDROME DIAGNOSED DURING EVALUATION FOR SHORT STATURE- CASE REPORT

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**Objectives:** First described in 1970 by Coffin and Siris this syndrome is a rare congenital genetic disorder characterized by aplasia or hypoplasia of the distal phalanx, short stature,

cognitive delay, specific facial features and other variable clinical manifestations.

**Methods:** We present the case of a 4 years old girl admitted in our Department for short stature and cognitive delay. Her weight was 10 kg and height 91 cm (-3,81 SD). The clinical examination revealed: microcephaly, coarse face, bushy eyebrows, bulbous nose, flat nasal bridge, dental anomalies, thick lips, scoliosis, hypoplastic nails on the 5<sup>th</sup> digits.

**Results:** Hormonal profile showed normal thyroid function, IGF1=50,4ng/mL (normal range 49-289) and GH level failed to increase over 7 ng/mL during the arginine stimulation test. X-Ray of the hand showed hypoplastic distal phalanx of the fifth digit and delayed bone age (2 years and 6 months). Clinical and hormonal picture required MRI which revealed: agenesis of the corpus callosum and pituitary hypoplasia. The karyotype was normal and the molecular diagnosis of possible loss of function mutation in ARID1B was not performed.

**Conclusions:** Taking into account that the diagnosis of this condition is based on the most frequent clinical features and the role of genetic evaluation is complementary, we used the clinical criteria of Schrier et al. to conclude that this is a case of Coffin-Siris syndrome. Our patient meet the criteria of major findings (facial features, cognitive delay and hypoplastic nails on the 5<sup>th</sup> digits with hypoplastic distal phalanx) and minor findings: ectodermal (dental anomalies), constitutional (microcephaly, short stature) and organ related (brain/cranial malformations).

P3-1618

#### CLINICAL FEATURES OF PRADER-WILLI SYNDROME IN A PATIENT WITH MOLECULAR DIAGNOSIS OF ANGELMAN SYNDROME

*Elena Bogova, PhD; Natalya Volevodz, MD, Endocrine Research Centre, Moscow, Russian Federation; Valentina Peterkova, MD-PhD, Institute of Pediatric Endocrinology, Moscow, Russian Federation*

**Objectives:** Angelman syndrome (AS) and Prader-Willi syndrome (PWS) are distinct genetic disorders caused by a deficiency of imprinted gene expression from the maternal or paternal chromosome 15. AS is characterized by early onset of seizures, severe mental retardation, microcephaly, lack of speech, prognathia, ataxia, and a happy disposition. PWS is characterised by muscular hypotonia, feeding problems in newborns, obesity, short stature, acromicria, hypogonadism and behavioural abnormalities.

**Methods:** We report on 13 years old girl, who was referred to an endocrinologist due to overweight. Physical examination revealed: height 133 cm (SDS=-1,52), weight 47,9 kg, BMI=27,75 kg/?2 (SDS=+2,56), acromicria (short hands and feet), prognathia and Tanner stage 3. She had obsessive-compulsive symptoms.

**Results:** Due to clinical signs of PWS the methylation test of 15q11-13 chromosome was done. However the genetic results showed the absence of methylation of SNRPN (15q11.2), typical for AS. The girl didn't have major features

of AS. Laboratory data didn't show hormonal imbalance. OGTT test showed basal (45,3 mlu/l) and posprandial hyperinsulinemia (max. 228,2 mlu/l) with normal glucose levels. Basal insulin resistance index HOMA was high 9,46 (<3,2) and Matsuda index was low 1,25 (>2,5). The girl was placed on metformin therapy.

**Conclusions:** We report a case on a patient, who has genetically confirmed AS, but presented with obesity, acromicria and obsessive-compulsive disorder, typical for Prader-Willi syndrome. Since methylation analysis detects PWS and AS in the same test, a molecular diagnosis of AS was made, although initially PWS was suspected. The mild phenotype of AS may be due to an incomplete imprinting defect or to cellular mosaicism. At present, it is not possible to distinguish between these possibilities. Further studies are needed to improve our knowledge about the genes involved in AS and PWS.

P3-1619

#### **CHRONIC LIVER DISEASE IN TURNER SYNDROME: 103 SUBJECTS FOLLOWED FROM PEDIATRIC TO YOUNG ADULT AGE**

*Laura Mazzanti, MD, S.Orsola-Malpighi University Hospital, Bologna, Italy; Federica Tamburrino, MD; Annamaria Perri, MD; Margherita Costa, MD; Teresa Ciccarelli, MD; Antonio Colecchia, MD; Emanuela Scarano, MD, S.Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy*

**Objectives:** Liver involvement is a frequent finding of TS patients and the prevalence increases with age, from adolescence to the adult age. The cause of liver test abnormalities in TS patients is still debated.

We report liver function, laboratory and imaging data from a large cohort of **103 TS subjects** followed up from childhood to the young adult age, for  $14 \pm 6$  years (range 2-25), evaluating the influence of anthropometry, karyotype, metabolic, hormonal and autoimmune status and GH and estro-progestinic therapy.

**Methods:** An annual follow-up was performed for height, weight, BMI, hepatic enzymes, serum lipids, autoantibodies, insulin sensitivity and B-cell function with fasting measurements (HOMA, glucose 0'/insulin 0') and OGTT every two year. Chronic liver involvement was defined when abnormal liver enzymes were detected for 3 times consecutively and abdominal US was performed.

**Results:** 22 of 103 pts (21.4%) showed a chronic liver involvement at a mean age of  $13 \pm 5$  years (3.3-24) with an increase of the prevalence with age. 3 patients showed a chronic liver involvement before 7 years of age. 7 subjects were submitted to liver biopsy. Chronic liver involvement correlated with hepatic steatosis (68% of subjects with high liver enzymes), high BMI, HOMA-IR and negatively with spontaneous menarche and X-mosaicism. Multiple regression analysis confirmed that liver enzymes alterations correlated positively with high BMI and hepatic steatosis. In pediatric age obesity and steatosis are the main risk factors for hepatic

chronic disease. Fibrosis was found in 23% of subjects with chronic liver involvement.

**Conclusions:** In TS the study follow-up of liver involvement from childhood to young adulthood has shown that the process is progressive and the main pathogenic factor seems an early metabolic dysregulation. The estrogen deficiency appears to play an important role together with genetic mechanisms. In fact, individuals with TS spontaneous menarche and / or X-mosaicism appeared to risk less hepatic involvement. We hypothesize that in TS subjects early estrogen replacement therapy and a healthy lifestyle may help to prevent the progression of hepatic involvement.

#### **POSTER SESSION 3**

**Saturday, September 16, 2017, 12:00-1:00pm**

#### **P3 - Thyroid**

#### **P3-1700 – P3-1741**

P3-1700

#### **HIGH INCIDENCE OF TRANSIENT CONGENITAL HYPOTHYROIDISM AND HYPERTHYROTROPINEMIA IN PRETERM INFANTS**

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**Objectives:** There is an increasing evidence of thyroid dysfunction in preterm infants, but little data on the long-term follow-up. Our aim was to determine the evolution of congenital hypothyroidism (CH) in preterm infants after a follow-up of 7-9 years.

**Methods:** The study was conducted on 21 preterm infants (gestational age 24-35 weeks), all positive to neonatal CH screening, diagnosed with CH with eutopic thyroid, and treated with Levo-thyroxine (L-T4) (started between 4 and 109 days of life). The sample included 11 twins, 4 of which were born after assisted reproduction techniques and 5 newborns were small for gestational age.

At the age of 2-3 years, all patients underwent a first clinical re-evaluation including thyroid function testing (TFT) after L-T4 therapy withdrawal. According to the result of the TFT after the withdrawal of therapy, patients were divided into 3 groups: permanent CH (TSH persistently >10 mU/L), persistent hyperthyrotropinemia (HT) (TSH 5-10 mU/L) and transient CH (TSH <5 mU/L). In all cases FT4 values were normal. In

patients affected by permanent CH, a second clinical re-evaluation between the ages of 4- 7 years was performed.

**Results:** After the first clinical re-evaluation, 5 patients resulted affected by permanent CH and resumed L-T4 therapy, 5 patients had HT, and 11 patients had transient CH. Patients affected by HT and transient CH did not require the reintroduction of therapy. At the second clinical re-evaluation performed in the 5 permanent cases, 2/5 patients showed permanent CH, and 3/5 patients had HT. Two patients diagnosed with HT at 3 years, became euthyroid during the follow-up. At the age of 7-9 years only 2 patients were on treatment (permanent CH), while the other 19 patients did not require therapy (6 cases of HT and 13 cases of transient CH). The two patients affected by permanent CH presented with malformations.

**Conclusions:** Our data highlights the high incidence of transient CH and HT in preterm infants, and the importance of diagnostic re-evaluation to determine the definitive diagnosis. Although the majority of preterm infants have transient CH or HT, they might require L-T4 therapy in the neonatal period and in the first year of life.

P3-1701

#### PROGNOSTIC FACTORS FOR AGGRESSIVE BEHAVIOUR IN DIFFERENTIATED THYROID CARCINOMA IN CHILDREN AND ADOLESCENTS

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**Objectives:** The MACIS scoring system (metastases, age at diagnosis, completeness of resection, invasion, size of the tumor) is used to identify aggressive behaviour in differentiated thyroid carcinoma (DTC) in adults, with a cut-off score of 6. Our study aims to identify the clinical, biochemical and therapeutic factors associated with unfavourable course of DTC and to propose a cut-off value of MACIS score in children.

**Methods:** The medical records of 54 children and adolescents admitted in a tertiary centre of endocrinology (2011-2017) were reviewed retrospectively. "Aggressive behaviour" of DTC was defined: local invasion, extensive lateral cervical lymph node/distant metastasis, recurrent/persistent disease. Receiver operating characteristic (ROC) analysis was performed to determine the MACIS scoring cut-off for predicting poor prognosis.

**Results:** Extrathyroidal invasion was noted in 25.9% cases, extensive regional lymph node metastasis in 27.7%, distant metastases in 9.2% cases. Total thyroidectomy was performed in 63% cases, total thyroidectomy and lymph node dissection in 35.2% cases. Postoperative adjuvant RAI treatment was used in 35 patients (77%).

After a follow-up period of 30.4 months, local recurrence and persistent biochemical/structural disease were noted in 5.5% cases and 20.4 % cases respectively. Smaller age at diagnosis, multifocal carcinoma, histological type (the diffuse sclerosing papillary thyroid carcinoma and cribriform papillary carcinoma) and invasive forms of DTC were significant predictor factors for poor prognosis. A MACIS score  $\geq 3.8$  had 95% sensitivity and 65% specificity for aggressive behaviour.

**Conclusions:** Clinical and pathological factors, as well as MACIS scoring system have good ability in predicting aggressive behaviour in DTC in children.

P3-1702

#### EPIDEMIOLOGY OF THYROID CANCER IN PEDIATRIC POPULATION IN SLOVENIA

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**Objectives:** Thyroid cancer is a rare disease in pediatric population. Estimated prevalence of thyroid nodules is 0,2-5%. Malignant component is present in approximately 25% of children with thyroid nodules. We aimed to evaluate the epidemiology of thyroid cancer in children and adolescents on a national level.

**Methods:** The thyroid cancer incidence rate was obtained from the Cancer Registry of Slovenia. The data on 119 patients diagnosed with thyroid cancer before 21 years of age between 1990 and 2016 nationwide were collected from the archives of the Institute of Oncology Ljubljana, University Medical Centre Ljubljana and ascertained in the Cancer Registry of Slovenia and analysed.

**Results:** Average yearly incidence rate of thyroid cancer from the year 1971 to 1991 was 0,22 cases per 100.000 (0 to 0,5), and from 1992 to 2012 0,78 cases per 100.000 children and adolescents up to 19 years old (0,2 to 2,4). Among 119 patients diagnosed since 1990 80,7% had papillary cancer (86,5% females), 6,7% follicular cancer (100% females), 5,9% medullary cancer (100% males), 3,3% oxyphilic cancer (50% females) and 3,4% other types (malignant thymoma and PNET) or undefined cancer. 36% of patients had regional metastases and 2,5% systemic metastases at the time of diagnosis, and in 11,7% cancer was multifocal. Average age at diagnoses was 16,2 years (2-20 years), only 3 patients were younger than 10 years, 32% were 10-15 years old. All patients underwent surgical therapy, a subset had subsequent radioiodine therapy. Only 4,5% of children had post-operative

complications, the majority being transitory hypocalcemia.

Of all patients, 2 patients with medullary cancer died from disease progression 5 and 10 years after the diagnosis at ages 22 and 26, respectively, and 1 patient died 19 years after the diagnosis of papillary cancer from pancreatic cancer.

**Conclusions:** A significant rise in thyroid cancer incidence is noted in the last 20 years. Similarly as in adult populations there is a strong female preponderance and papillary cancer predominance. Though the disease is often in advanced stage when diagnosed, the long term survival rate in differentiated thyroid cancer in our population is so far 100%.

P3-1703

#### **TREATMENT OF OBESITY ASSOCIATED CENTRAL HYPOTHYROIDISM IN CHILDREN IS ASSOCIATED WITH PARADOXICAL WEIGHT GAIN**

*Sachin Bendre, MD, West Virginia University-Charleston Division, Charleston, WV, United States; Richard Gau, BS/BA, University of Charleston, Charleston, WV, United States*

**Objectives:** To investigate changes in thyroid function and weight after thyroid-hormone replacement therapy (THRT) in obese/overweight children with tertiary or hypothalamic hypothyroidism.

**Methods:** A retrospective chart review of 1167 obese children screened for thyroid abnormalities in our Pediatric Endocrinology clinic. Patients found to have isolated low fT4 with low or normal TSH with no other pituitary hormone deficiencies, with a normal pituitary MRI were diagnosed with tertiary/hypothalamic hypothyroidism and were included in the analysis. All patients received THRT with either L-thyroxine or desiccated thyroid. Clinical exam and weight along with serum levels of fT4 (equilibrium dialysis), fT3 (immuno-extraction), reverse T3 (RIA), and TSH (ICMA), were recorded both before THRT was started and 3 to 6 months after THRT. Statistical analysis of thyroid lab values and weight change was done using SPSS software.

**Results:** All 51 patients were at pubertal age (girls > 10 years and boys > 12 years). Before THRT, fT4 levels in all patients were below normal (<0.8ng/dL), and TSH was either normal or low normal. THRT led to only short-lasting improvement in hypothyroid symptoms in 46(90%) of treated children while fT4 normalized only in 38(75%) of treated patients. Out of 51 patients on THRT, 45 (88%) had significant weight gain over the next 3-6 months even though their fT4 and fT3 levels were higher than before THRT was started. Weight gain was associated with an increase in both fT3 and reverse T3 levels, but only reverse T3 levels were statistically significant. Values for fT3/fT4 ratio were higher ( $p<0.05$ ) and fT3/reverse T3 were lower ( $p<0.05$ ) after THRT. Discontinuation of THRT after 3 to 6 months led to rapid weight loss in all 45 patients that had gained excess weight on THRT.

**Conclusions:** This study shows that overweight/obese adolescents may have an altered hypothalamic/pituitary-thyroid-axis response in the form of normal or low TSH production despite low fT4 levels, possibly due to sustained normal fT3 levels. THRT to correct low fT4 in these

patients may disrupt this central metabolic adaptation leading to further weight gain. Whether THRT leads to increased deiodinase activity and in turn to higher reverse T3 activity further impeding thyroid hormone action, needs further studies.

P3-1704

#### **SERUM fT4 IN ADOLESCENTS WITH KLINEFELTER SYNDROME: ASSOCIATION WITH ADIPOSITY AND INSULIN RESISTANCE.**

*Jean A De Schepper, PhD, Vrije Universiteit Brussel UZ Brussel, Brussels, Belgium; Jesse Vanbesien, MD; Ellen Anckaert, PhD; Inge Gies, PhD, UZ Brussel, Brussels, Belgium*

**Objectives:** The objective of the study was to evaluate thyroid function in adolescents with Klinefelter syndrome (KS) and its correlation with metabolic parameters. In adult KS men serum fT4 concentrations were reported to be in the lower part or just below the reference range and found to be unrelated to testosterone concentrations and not to be associated with a compensatory increase in TSH, suggesting a hypothalamic pituitary dysfunction (Bjorn AM, J. Clin. Endocrinol. Metab 2009). However, up to now, the association of fT4 with increased adiposity and insulin resistance, known to be present already in childhood in KS, has not been studied.

**Methods:** Twenty-five (4 prepubertal) non-mosaic KS teenagers, aged between 10.1 and 18.1 years (median age: 14.5 years), without testosterone supplementation were studied retrospectively. Serum fT4, TSH and anti-TPO antibodies were measured by the Cobas 6000 Roche Diagnostics system. Fasting glucose, insulin, SHBG, FSH, LH, testosterone, cholesterol, HDL cholesterol, LDL cholesterol and triglycerides were measured by standard laboratory methods. Body weight and height were measured and BMI z-score was calculated using national references.

**Results:** The BMI z-score of the studied patients ranged between -2.67 and 2.76 (2 patients had a score > 2). Fasting insulin conc. ranged between 31 and 250 pmol/L (9 patients had a conc. > 91 pmol/L). Four patients had elevated triglycerides (> 150 mg/dl) and 15 had elevated FSH values (> 15 IU/L). fT4 were within normal limits, ranging between 8.6 and 13.7 ng/L (reference values: 8.6 -18.6). Sixteen patients had a fT4 value < 12 ng/L. TSH concentrations were between 0.84 and 3.44 mIU/L (reference values: 0.27 -4.2). No anti-TPO antibodies were present. Serum fT4 conc. correlated significantly with BMI z-score ( $r = -0.61$ ;  $p < 0.005$ ), triglycerides ( $r = -0.46$ ;  $p < 0.05$ ), insulin ( $r = -0.55$ ;  $p < 0.005$ ) and SHBG conc. ( $r = 0.57$ ;  $p < 0.005$ ), but not with the other studied metabolic and hormonal parameters.

**Conclusions:** In adolescents with Klinefelter syndrome, serum fT4 concentrations are in the lower part of the reference range, especially in the more obese and insulin resistant patients. Further studies are needed to assess the link between thyroid function and adiposity in KS patients, favoring both a worse metabolic profile.



### SHOULD THYROID FUNCTION STUDIES BE MONITORED MORE FREQUENTLY IN INFANTS WITH DOWN SYNDROME?

*Penny M. Feldman, MD; Mary M. Lee, MD, University of Massachusetts Medical School, Worcester, MA, United States*

**Objectives:** Current recommendations may delay diagnosis of hypothyroidism in infants with Down syndrome (DS). This study examines the optimal screening intervals for early identification of thyroid dysfunction and evaluates whether there is an autoimmune etiology.

**Methods:** Consent to participate in this study was obtained from the families of infants with a confirmed diagnosis of DS who are <6 months of age and born at  $\geq 30$  week gestation. Thyroid function studies were measured with a capillary blood sample collected on a newborn filter paper screening card at birth, 2 and 4 weeks of age and then monthly thereafter until age 12 months. Samples were analyzed at the New England Newborn Screening (NBS) Program, Jamaica Plain, Massachusetts. Study subjects with abnormal TSH and T4 had a confirmatory venous sample for TSH and free T4. Infants with confirmed hypothyroidism (TSH>than the normal for age and/or free T4<normal value for age) promptly started treatment and were managed per the standard of care. Thyroid antibodies were measured at 12 months of age in study subjects diagnosed with hypothyroidism.

**Results:** 15 of the 55 enrolled study subjects were diagnosed with hypothyroidism (5 by abnormal NBS; 2 at 3-4 wks of age; 4 at 3 mo; 1 at 5 mo; and the remaining 3 at 7, 9 and 12 mo) and started on treatment. One study subject diagnosed by NBS tested positive for the TSH receptor antibody, another (diagnosed on DOL 21) had a lingual thyroid, and one (diagnosed at 3mo) had thyroid dysgenesis. The etiology of the hypothyroidism in the remaining subjects is unknown. The incidence of hypothyroidism in this study is 27.3%. 1 study subject was diagnosed with hyperthyroidism at age 8 mo.

**Conclusions:** We identified 10 infants with DS and hypothyroidism not detected by the NBS. Of these 10 infants, 7 were detected before the recommended screening time of 6 months and 3 were identified between 6 and 12 months of age. Preliminary data from this study indicates that thyroid function studies may need to be repeated more frequently than the current recommendations in infants with Down syndrome for early detection and prompt institution of treatment to optimize neurodevelopmental outcomes.

P3-1706

### HIGHER INCIDENCE OF CONGENITAL HYPOTHYROIDISM WITH LATE TSH ELEVATION IN PRETERM INFANTS.

*Francisca Grob, MD; Monserrat Gutierrez, MD; Liliana Leguizamón, MD; Jorge Fabres, MD, Pontificia Universidad Católica de Chile, Santiago, Chile*

**Objectives:** Congenital hypothyroidism (CH) is diagnosed the first days of life in term newborns with the determination of

thyroid stimulating hormone (TSH). The initial screening may be insufficient in preterm children, and additional screening is required a few weeks later to reveal a late rise of TSH. In Chile, the screening program does not obtain TSH concentrations after the first 15 days of life and may be failing to identify children with the disease, leading to irreversible neurological damage in this at-risk population. The aim of this study is to determine the incidence of late CH in preterm infants.

**Methods:** A prospective study was conducted on preterm infants under 34 weeks and/or less than 1500 gr born in a university hospital in Santiago de Chile, between June and October 2016. TSH was obtained at 48 hours, 15, 30 and 60 days of life. CH was diagnosed at first screening (48 hours and 15 days) with TSH cutoff >15 mU/L, at second screening with TSH cutoff >10 mU/L and at third screening with TSH cutoff >5 mU/L. Serum TSH was obtained to confirm diagnosis. All diagnosed patients underwent thyroid ultrasound.

**Results:** We included 27 patients with median gestational age of 32. The first screening did not identified patients with CH, and the second screening identified 100% of patients (n=4). The cumulative incidence was 14.8% (1:7). In infants under 1000 gr it was 1:27. The incidence of CH between 28 to 32 weeks and between 32 to 34 weeks of gestational age was 1:27 and 1:9 respectively. There were no cases of CH in infants under 28 weeks. Among patients with CH, one was twin, 2 presented Down syndrome, 2 congenital heart disease. All were adequate for gestational age. None received corticosteroids, dopamine or blood transfusions prior to sampling. All the patients had normal thyroid ultrasound.

**Conclusions:** We report a very high incidence of late CH in preterm children. All of the patients had eutopic thyroid gland and did not present significant comorbidities at the time of diagnosis of CH.

P3-1707

### CHILDREN WITH PERMANENT CONGENITAL HYPOTHYROIDISM AND CELIAC DISEASE REQUIRE ELEVATED DOSES OF LEVOTHYROXINE

*Maria J Korpai- Szczyrka, PhD; Malgorzata Mysliwiec, PhD, Medical University of Gdansk, Gdansk, Poland*

**Objectives:** Adequate oral administration of levothyroxine in children with permanent congenital hypothyroidism (CH) is essential to maintain an euthyroid state that provides their proper physical and intellectual outcome. Some patients treated for CH require doses of levothyroxine above standard daily dosage to maintain an euthyroid state. The accurate evaluation of potential causes of that state is important. Among factors that should be analyzed is intestinal absorption of levothyroxine. Especially celiac disease (CD) with the prevalence of 1% in general population should be taken into account. Objective was to evaluate the presence of CD in the group of children with permanent CH and to analyze treatment control in them.

**Methods:** In 41 children (9 boys, 32 girls) aged 3,5 -17,8 yrs. with permanent CH serum anti-transglutaminase, anti-

endomysial antibodies and IgA were evaluated. Diagnosis of CD was confirmed by performing duodenal biopsies (villous blunting-Marsh 3) in children with elevated specific antibodies. Diagnosis of CH was based on elevated TSH values in newborn screening blood test confirmed by subsequent determination of TSH and freeT4 (fT4) in venous blood and ultrasound evaluation. In all patients levothyroxine doses, auxological parameters, TSH and fT4 serum levels were analyzed.

**Results:** In 3/41 patients(2 girls, 1 boy) elevated serum anti-transglutaminase and anti-endomysial antibodies were stated. Diagnosis of CD was confirmed in 2/41(5%) of them. One girl had slightly elevated anti-transglutaminase antibodies but normal duodenal biopsies. CD was diagnosed at the age of 6(girl) and 10 yrs(boy), both with thyroid agenesis. No typical clinical symptoms of CD were noted, but in both poor thyroid control was observed despite of good compliance. Both required levothyroxine dose over 5mcg/kg/day while a mean dose in non-CD group was 3,4±1,1mcg/kg/day. Strict adherence to a gluten-free diet resulted in normalization of specific antibodies after 6 months but not in levothyroxine dose reduction. Height and BMI expressed in standard deviation scores in children with CD did not differ from non-CD group.

**Conclusions:** Levothyroxine is likely malabsorbed in patients with CH and CD. Children with CH who require higher doses of levothyroxine to maintain a euthyroid state should be screened for CD.

P3-1708

**LONG-TERM TREATMENT ADHERENCE AND LEVOTHYROXINE DOSE REQUIREMENTS IN CHILDREN WITH ACQUIRED HYPOTHYROIDISM: A SINGLE-CENTER STUDY**

Rashmi Jain, MD, St. Christopher's Hospital for Children, Drexel University College of Medicine, Philadelphia, PA, United States; Kelly Cann, Medical Student, Drexel University College of Medicine, Philadelphia, PA, United States; Filippina F Dimitriadi, MD, "Aghia Sophia" Children's Hospital, National and Kapodistrian University of Athens- Faculty of Medicine, Athens, Greece; Francesco Deluca, MD; Rita Ann Kubicky, MD, St. Christopher's Hospital for Children, Drexel University College of Medicine, Philadelphia, PA, United States

**Objectives:** In children treated for hypothyroidism, a consistent euthyroid state prevents impaired cognition, growth, and puberty. Yet, it is often difficult to maintain an adequate treatment in children with chronic disorders. Our study aimed to analyze the biochemical status and the levothyroxine (LT4) dose requirements in children with long-standing acquired hypothyroidism.

**Methods:** We reviewed charts of patients diagnosed with acquired hypothyroidism at St. Christopher's Hospital for Children between 1997 and 2017. Inclusion criteria were: age at diagnosis of ≥ 1yr; being followed for ≥ 3 yrs. Mean TSH values and mean LT4 doses were calculated for each year of the following follow-up periods: 0-3 yrs, 3-6 yrs and 6-15 yrs. Mean TSH value of ≥ 5 mIU/L was considered high. Mean

annual LT4 doses were compared to the age-matched doses (mcg/kg/day) currently recommended in the literature (1-3 yrs: 4-6, 3-10 yrs: 3-4, 10-15 yrs: 2-4, ≥ 15 yrs: 2). Prescribed doses smaller than those recommended were defined as "low".

**Results:** 80 patients were included. Mean age at diagnosis: 9.5±3.7 yrs, mean follow-up duration: 6.0±3.0 yrs. 85% of patients had either positive thyroid peroxidase or thyroglobulin antibody. 60 of the 80 patients had at least one high annual TSH value during follow-up. Refer to the table for the results.

**Conclusions:** In our patient population, the majority of children with acquired hypothyroidism were unable to consistently maintain a euthyroid state during a long-term follow-up. The intermittently hypothyroid state was due approximately half of the time to poor treatment adherence (high TSH associated with adequate LT4 doses). However, frequency of the hypothyroid state and poor treatment adherence did not worsen with longer disease duration, but rather, may have improved. Lastly, the LT4 doses currently recommended in the literature may exceed the actual LT4 requirements in children with acquired hypothyroidism.

Follow-up duration (yrs)	0-3	3-6	6-15
Number of patients (% of total patients)	60 (100%)	58 (97%)	34 (57%)
Mean TSH (mIU/L)	10.16 ± 23.01	7.80 ± 10.24	5.23 ± 5.91
% of patients with high TSH at least once	76.7	72.4	50.0
% of adequate LT4 doses associated with high TSH	52.0	50.0	41.4
% of low LT4 doses associated with normal TSH	58.2	60.8	78.6

P3-1709

**FREQUENCY AND ABNORMALITIES OF THYROID FUNCTION TESTS WITH AMIODARONE USE AFTER CARDIAC SURGERY**

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**Objectives:** Amiodarone, an anti-arrhythmic medication used postoperatively in pediatric cardiac surgery, has been associated with thyroid dysfunction. Adequate guidelines for screening of thyroid dysfunction in this population are lacking. We hypothesize that postoperative abnormalities in the thyroid function of pediatric cardiac patients receiving amiodarone are common.

**Methods:** Patients 0-18 years, who underwent cardiac surgery and received oral amiodarone postoperatively between January 2010 and June 2016 were retrospectively identified from the electronic medical records. Data including demographic characteristics, cardiac defect and surgery, thyroid function testing and amiodarone dosing were

recorded. Patients with a pre-existing diagnosis of thyroid disease were excluded.

**Results:** 50 patients (out of total 1168 patients undergoing cardiac surgery in the study period) received oral amiodarone (with or without intravenous amiodarone). See Table 1 for details. Oral amiodarone was administered for a median 6 days during hospital stay while 29% (n=15) patients were prescribed it at discharge. 6% patients had thyroid function testing (TFT) only prior to their surgery, 56 % underwent TFTs within 30 days and 22 % received TFTs between 31 days and 6 months post-operatively. Of those tested post-operatively, 75% had some abnormality in TSH, T4 and/or T3 (see table). Hypothyroidism was diagnosed in 2 patients; they were started on levothyroxine.

**Conclusions:** Nearly 3/4<sup>th</sup> of patients exposed to amiodarone and tested had some abnormality in their TFT's with two patients diagnosed with hypothyroidism. Only 1 in 5 patients had testing done beyond 30 days from the date of surgery. TFT's were not assessed in 34% patients treated with oral amiodarone. Thyroid function testing in the immediate preoperative, postoperative and post amiodarone periods is needed to understand frequency of thyroid dysfunction in amiodarone exposed children undergoing cardiac surgery. Timely treatment can prevent significant morbidity.

Table 1: Characteristics of patients receiving oral amiodarone after cardiac surgery

Characteristic	Data (mentioned as Median (IQR) or as percentage of total patients, n=50)
Age	5.3 months (IQR 2 days to 15.4 years)
Females	50%
Race	54% Black, 32% White, 16% Multiple/other race
Duration of ICU stay	0.8 days (IQR= 4.3-34.4 days).
Thyroid function test	Not done: 34%, Pre-op only: 6%, Post-op: 60%
Follow-up TFT	22%
Abnormalities in TFT	Congenital hypothyroidism, n=2 Sick Euthyroid syndrome, n=5 Sick Euthyroid syndrome versus Central hypothyroidism, n=5 Hyperthyrotropinemia with/without T4/ T3 abnormality, n=5 Other abnormalities of TSH, T4 and/or T3, n=6

P3-1710

**PREDICTORS OF TRANSIENT CONGENITAL HYPOTHYROIDISM IN CHILDREN WITH EUTOPIC THYROID GLANDS**

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**Objectives:** Congenital hypothyroidism (CH) is the most common cause of preventable mental retardation. Recently, the detection of CH cases with eutopic thyroid glands has increased due to neonatal screening programs. In this study, we aimed to identify and evaluate predictive factors that could distinguish between permanent and transient CH in patients with a eutopic thyroid gland.

**Methods:** We retrospectively reviewed 100 children diagnosed with CH and with a eutopic thyroid gland. All subjects were treated with levothyroxine and underwent re-evaluation after 3 years of age.

**Results:** Of the 100 CH patients, 35 (35.0%) were diagnosed with permanent CH (PCH) and 65 (65.0%) were diagnosed with transient CH (TCH). The initial thyroid stimulating hormone levels were significantly higher in the TCH subjects

than in PCH subjects. In addition, the mean doses of levothyroxine (µg/kg/day) at the 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> year of treatment were significantly lower in subjects with TCH than in PCH subjects with a eutopic thyroid gland. Based on the receiver operating characteristic (ROC) curve, the optimal cut-off dose of levothyroxine at 3 years of 2.76 µg/kg/day could predict TCH, and was associated with 87.3% sensitivity and 67.6% specificity, with an area under the ROC curve of 0.769.

**Conclusions:** The levothyroxine dose requirement during treatment period has a predictive role in differentiating TCH from PCH in CH patients with eutopic thyroid glands.

P3-1711

**CONGENITAL HYPOTHYROIDISM IN PATIENTS WITH DOWN SYNDROME DIAGNOSED ON NEWBORN SCREENING IN THE REPUBLIC OF IRELAND**

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**Objectives:** To assess the incidence and management of congenital hypothyroidism in Down Syndrome patients detected by the national newborn bloodspot screening programme in the Republic of Ireland.

**Methods:** The national newborn screening records of all infants diagnosed with congenital hypothyroidism from July 1979 to December 2016 were reviewed. Screen positive infants had a bloodspot TSH value of >15mU/L on day 3-5 of life; values of 8-15mU/L required a repeat screening card and where the repeat screening card TSH was >8mU/L TFTs were requested. Screen positive infants with a diagnosis of Down Syndrome were identified. Data on gender, gestation, birth weight, day of life screened, bloodspot TSH result, liquid TFTs result, diagnosis, day of initiation of thyroxine and thyroxine dose was collected.

**Results:** Between July 1979 and December 2016 2,361,281 patients were screened for congenital hypothyroidism in the Republic of Ireland. One thousand and forty-seven patients screened positive and were diagnosed with congenital hypothyroidism. Of the 1047 screen positive infants, 32 had Down syndrome (19 male, 13 female). Median gestational age was 38 weeks ( range 34-41 weeks) and mean birth weight was 3.1kg (range 1.8 to 3.9kg). Twelve infants diagnosed with CHT had an initial borderline TSH value (8-15mu/L). Levothyroxine treatment was initiated later in the DS cohort, median age of 15 days (range 8 to 86 days) compared to cohort average (10 days) reflecting the milder elevation in TSH. Mean thyroxine dose initiated was 8.7ug/kg/day in the DS group, lower than the mean dose of 11ug/kg in the overall cohort. Twenty DS patients (62%) with CHT had thyroid imaging, of which 19 had a normal thyroid gland in situ and 1 patient had thyroid hypoplasia.

**Conclusions:** Congenital hypothyroidism detected by newborn screening, is common in patients with Down Syndrome. CHT in the DS cohort was milder and thyroxine was

initiated later. Imaging was performed less often in the DS infants compared to overall cohort. Although hypoplasia is described in patients with DS, the majority of patients who had imaging had a normal thyroid gland in situ.

P3-1712

**THYROTOXICOSIS LONGER THAN 5 WEEKS AFTER 22 WEEKS OF GESTATION CAN DEVELOP CENTRAL HYPOTHYROIDISM DUE TO MATERNAL GRAVES' DISEASE.**

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**Objectives:** Central hypothyroidism(CH) in neonates born to mothers with poorly-controlled Graves' disease (GD) was first reported in 1988. For the development of this type of CH (CH-mG), the following factors must be present:(1) passage of maternal thyroid antibodies through the placenta; (2) negative feedback in the fetal pituitary-thyroid axis; (3) requisite duration of thyrotoxicosis in both the mother and the fetus. To elucidate the minimum duration of maternal and fetal GD for the development of this disorder, assuming that conditions (1) and (2) above are established at the gestational age of 22 week.

**Methods:** "Pubmed" was searched for clinical information on 20 cases of CH-mG from 8 papers published between 1988 to 2010. All diagnoses were re-confirmed. The duration of maternal and fetal thyrotoxicosis (from the suspected onset of maternal GD to delivery) was calculated. Our assumption that factors (1) and (2) were established at GW 22 stemmed from the following facts: transplacental passage of TRAb has been reported at GW 21 (Thyroid. 1992) ; fetal GD presenting an undetectable TSH level and markedly elevated thyroxine has been documented at GW 20 ( Clin Endocrinol. 1999) ; intra-amniotic thyroxine therapy for fetal hypothyroidism was effective at GW 22.

**Results:** The timing of the diagnosis of maternal GD during pregnancy ranged from the gestational age of 14 to 31 weeks. In the patient with the latest diagnosis of maternal GD during pregnancy at GW 31, the timing of the delivery was GW 37, suggesting that the duration of thyrotoxicosis for both the mother and fetus was at least 6 weeks. The timing of delivery varied from 27 to 41 weeks. In the most premature case at 27 weeks, the period of maternal and fetal thyrotoxicosis was 5 weeks, as calculated by subtracting 22 weeks from 27 weeks. The minimum period of thyrotoxicosis was thus estimated to be more than 5 weeks.

**Conclusions:** Thyrotoxicosis in both the mother and fetus after GW 22 for a duration of more than 5 weeks was required for the development of CH-mG.

PLEASE SEE TABLE IN NEXT COLUMN

Table 1

case No	GA (wk)	duration	maternal data		neonatal data		
			GA of confirmed thyrotoxicosis (wk)	fT4 (ng/ml)	TSH (μU/ml)	fT4 (ng/ml)	Day of Dx
1	32.5	10.5	28	4.1	4.39	0.6	14
2	27.2	5.2	27	8.1		0.4	14
3	34	12	31	7.65		0.65	28
4	36	14	34	4.7	0.49	0.87	7
5	38	16	38	4.1	0.09	1.05	5
6	30.5	8.5	30	6	<0.05	0.3	29
7	37	15	throughout	1.9~5.4<	3	5.1 (T4)	5
8	36	14	throughout	2.5~4.0	3	7.5 (T4)	4
9	34.6	12.6	33.4	2.5	1.1	0.9	61
10	34.6	12.6	33.4	2.5	1.1	0.8	71
11	37	15	throughout	1.8~4.0	0.7	0.6	50
12	28	6	day 7	5.4<	0.1	0.7	15

Table 2

case No	GA (wk)	duration	maternal data		neonatal data		
			GA of GD Dx (wk)	fT4 (ng/ml)	TSH (μU/ml)	fT4 (ng/ml)	Day of Dx
1	31	8	23	6.4		0.6	425
2	37	6	31	3.92		0.66	2
3	36.2	14.2	22	4.5	0.08	0.5	70
4	33.4	12.4	21	4.8	<0.05	0.27	58
5	38.3	7.2	31.1	5.4<	4.1	0.6	2
6	38	8	30	4.7	7.5	0.8	6
7	36.9	6.2	30.7	5.4<	0.7	0.6	96
8	36.9	6.9	30	3.5	0.9	0.5	40
9	35.4	13.4	14.3	5.4<	0.1	0.8	9

P3-1713

**A NOVEL MUTATION IN THE SODIUM/IODIDE SYMPORTER CARBOXY-TERMINUS UNCOVERS A CRITICAL TRYPTOPHAN-ACID DOMAIN REQUIRED FOR PLASMA MEMBRANE TARGETING**

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**Objectives:** Iodide transport defect (ITD) is an autosomal recessive disorder whose hallmark is the inability of the thyroid to actively accumulate iodide. ITD is an uncommon cause of dyshormonogenetic congenital hypothyroidism that results from inactivating mutations in the *slc5a5* gene—which encodes the sodium iodide symporter (NIS). Clinical manifestations include low to absent thyroid and salivary iodide uptake and, if untreated, variable degrees of hypothyroidism, goiter, and even mental retardation. To determine if a pediatric patient with a clinical phenotype of ITD harbors an inactivating mutation in the *slc5a5* gene, and if so, to ascertain the molecular mechanisms of the effect of the mutation on the biogenesis and activity of NIS.

**Methods:** The genomic DNA encoding NIS was sequenced, and *in silico* computational and *in vitro* functional studies of a newly identified NIS mutation were performed.

**Results:** We report a novel homozygous missense and loss-of-function mutation in the *slc5a5* gene as a cause of ITD in a pediatric patient with dys hormonogenic congenital hypothyroidism. The patient carries a G>A transition at position +1.682 in exon 14 resulting in a Gly to Glu substitution at residue 561 (G561E). We show that G561E markedly reduces iodide uptake when the protein is heterologously expressed in MDCK-II cells, because targeting of G561E NIS to the plasma membrane is severely impaired. Replacing G561 with Gln also resulted in severe intracellular retention, suggesting that a bulky side-chain rather than a negative charge at position 561 interferes with NIS cell surface trafficking. Bioinformatics and biochemical analysis indicates that G561E impair the recognition of an adjacent tryptophan-acid domain by the kinesin light chain 2, thus impairing mutant NIS exit from the endoplasmic reticulum and subsequent plasma membrane targeting.

**Conclusions:** Altogether, our results indicate that a small residue at position 561 is required for NIS maturation and plasma membrane trafficking. Of note, comparison of *slc5a5* gene sequence across different species indicates a high conservation of the kinesin light chain 2-recognized tryptophan-acid domain.

P3-1714

#### GRAVES DISEASE IN EARLY CHILDHOOD BELOW FOUR YEARS OF AGE

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**Objectives:** Hyperthyroidism is uncommon in children, with Graves Disease (GD) being the commonest cause. It is rare below 4 years of age, worldwide incidence being 0.1-3/100,000. It is characterized by atypical presentation running a severe course and failure of remission. GD below 4 years is infrequently reported from India. It is also seen with genetic syndromes like Trisomy 21 (DS).

We aimed to study the clinical and investigative profile of children with GD less than 4 years of age.

**Methods:** 7 children (6F,1M) were seen in last 5 years. At presentation, clinical, ophthalmological and systemic evaluation was done. Thyroid profile (TFT), antibody study and ultrasound were obtained. Follow-up included clinical, growth parameters and laboratory response to treatment with Beta blockers (initial 2-3 months) and Carbimazole (0.5-1mg/kg/day). Complete blood count and liver profile were monitored. Follow-up clinical and TFT profile (at 1, 2, 3, 6, 12 monthly intervals) determined dose titration.

**Results:** Age at onset, F:M=6:1, was between 2-4 years. DS was seen in 3/6F. At presentation, poor weight gain (5F), delayed milestones (4F,3DS), speech impairment (1M,4F), hyperactivity (1M,3F), behavioral problems (1M,2F), diarrhoea (1M,2F), tachycardia (1M,5F), goiter (4F), eye prominence (1M,5F), exophthalmos (2F) were noted. 1DS had T3 toxicosis and Type 1 Diabetes Mellitus. Seizures, craniosynostosis and papilloedema were seen in one infant.

Initial HtSDS and WtSDS were -0.4+/-2.5cm and -1.3+/-2.6kg. Mean T3, T4 and TSH were 573.3+/-170.8ng/dl, 23.6+/-3.8ug/dl and 0.019+/-0.018uIU/ml respectively. All had positive TSH receptor (TRaB) and Antithyroid Peroxidase (Anti-TPO) Antibodies. Initial Carbimazole dose was 0.4+/-0.1mg/kg/day. Follow-up HtSDS and WtSDS upto 2 years were -0.7+/-2.1cm and -0.9+/-1.6kg at mean Carbimazole dose of 0.6+/-0.3mg/kg/day. Thyroxine was added in 2F. No remission noted inspite of good compliance.

**Conclusions:** Unlike other reported series, present study has female predominance with 3DS patients. Behavioral problems were common. High T3, T4 (except 1) and suppressed TSH with TRaB, anti-TPO antibodies were noted in all. No remission or adverse events observed over 2 years but longer follow-up is planned.

P3-1715

#### IMPACT OF LATE TREATMENT INITIATION OF CONGENITAL HYPOTHYROIDISM ON INTELLECTUAL DISABILITY AND QUALITY OF LIFE

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**Objectives:** To describe intellectual outcome and health related quality of life in children and adolescents with primary congenital hypothyroidism (CH), to explore the association between age of treatment initiation and current FT4 level vs. intelligence quotient and quality of life and to evaluate the etiology of CH

**Methods:** All CH patients were included. After informed consent was obtained, medical history was obtained from medical record. Intelligence was measured by psychologist with Wechsler Preschool Primary Scale of Intelligence (WPPSI) for children under seven years of age, the Wechsler Intelligence Scale for Children (WISC) for children above seven years of age and using the Wechsler Bellevue (WB) questionnaire for children between sixteen and eighteen years old. The PedsQL Parent Proxy-report 4.0 was completed by the parents or guardians to measure the Quality of life of the subjects. TSH and FT4 were assayed by ECLIA. Thyroid ultrasonography and scintigraphy were performed to explore the etiology of CH.

**Results:** Among 25 subjects of CH, only 1 subjects who was diagnosed and treated in age less than 1 month, and 19 subjects underwent thyroid ultrasonography and scintigraphy. Full scale IQ and verbal IQ were negatively correlated with the age of treatment initiation, but not significantly. ( $r = -0.261$ ,  $p = 0.071$  and  $r = -0.232$ ,  $p = 0.265$ ). Performance IQ was significantly negatively correlated to the age of treatment initiation. ( $r = -0.325$ ,  $p = 0.025$ ). There was significant correlation found between full scale IQ, performance IQ and current level of FT4. (resp.  $r = 0.314$ ,  $p =$

0.046 and  $r=0.320$ ,  $p=0.043$ ). Quality of life and IQ were significantly correlated as well. ( $r=0.491$ ,  $p=0.017$ ). Hemiagenesis is the most common etiology in CH. All groups of etiology had IQ below normal and the highest IQ score was achieved by hypoplasia group (borderline)

**Conclusions:** Delay of treatment initiation is affecting IQ and verbal IQ negatively, and performance IQ even significantly. Early treatment initiation will significantly improve the prognosis of the CH patients' cognitive development, suggesting that more optimal treatment might be possible

P3-1716

**MILD SUBCLINICAL HYPOTHYROIDISM IN CHILDREN AND ADOLESCENTS: ADAPTIVE INTERRELATIONS BETWEEN THE THYROID PARAMETERS**

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**Objectives:** TSH, as the standard diagnosis parameter in thyroid pathology, has several limitations: adaptive modifications, inter-individual variability and lack of consensus about its reference limits and prognostic heterogeneity. In addition, TSH serum concentration does not always present a normal distribution, nor it represents a precise marker for euthyroidism. Consequently, some authors defend the diagnostic, therapeutic and prognostic importance of adjusted  $ft4 - TSH$ . Our aim was to analyze the  $TSH-ft4$  relationship in children and adolescents with mild subclinical hypothyroidism.

**Methods:** Retrospective and longitudinal study of 40 iodine sufficient paediatric patients (26 males and 14 females) with subclinical hypothyroidism (SCH) defined as TSH serum concentration 5-10 mIU/ml in 2 independent determinations with  $ft4$  and  $ft3$  within normal range, without positive thyroid autoimmunity. We determined: thyroid hormone profile (direct chemiluminescent), urinary iodine concentration (Benotti-Benotti) and thyroid volume and morphology by ultrasound. We analysed: body mass index (BMI), lipid profile, atherogenic indexes, clinical evolution and the  $TSH-ft4$  relationship by the formulae  $\ln TSH = 1.4 + 3.5 / 1 + e^{(7.0 - T4I) / 1.0}$  and  $\ln TSH = -3.7 + 5.3 / 1 + e^{-(20.6 - T4I) / 3}$ , as proposed by Hadlow NC et al (*J Clin Endocrinol Metab* 2013). Statistical analysis was performed using SPSS 24.0. The data are presented as mean  $\pm$  SD. A p value

**Results:** The results are summarized in table 1. The mean follow-up period was  $2.07 \pm 1.6$  years. No significant statistical differences were found between sexes. During the follow up, we identified a cause for SCH in 14 patients: obesity (3), US define US alterations (8) and autoimmune thyroiditis (7; 3 of which received treatment). At the last visit, TSH levels normalized in 8 males and 5 females. In the idiopathic SCH

subgroup ( $n=26$ ; 18 males, 8 females), we found that the proposed  $TSH-ft4$  formulae were not suitable for our population.

**Conclusions:**

1. Mild subclinical hypothyroidism in the paediatric population presents a wide clinical spectrum, including thyroid dysfunction and euthyroidism. 2. The proposed formulae to evaluate the  $TSH-ft4$  relationship do not seem to be applicable to our population.

Table 1. Clinical, ultrasound and biochemical characteristics in the cohort ( $n=40$ ; 26 males and 14 females)

	$\bar{X} \pm SD$	Median	IQR	Range	Reference range
Time of follow-up (years)	$2.07 \pm 1.61$	2.00	—	0.25 – 7.00	—
<b>Clinical characteristics</b>					
Age (years)	$6.03 \pm 3.77$	5.87	2.33 – 8.50	1.00 – 14.25	—
Basal BMI (BMI Z-score)	$-0.24 \pm 1.15$	-0.14	-0.95 – 0.29	-2.88 – 2.48	—
<b>Thyroid Ultrasound</b>					
Thyroid volume (cc) <sup>b</sup>	$2.83 \pm 2.13$	2.13	—	0.51 – 11.19	—
<b>Biochemical characteristics</b>					
TSH ( $\mu$ U/ml)	$6.90 \pm 0.92$	6.76	6.27 – 7.40	5.27 – 9.11	0.35 – 5.00
$ft4$ (ng/dl)	$1.15 \pm 0.14$	1.13	1.04 – 1.24	0.91 – 1.47	0.70 – 1.98
$ft3$ (pg/ml)	$3.86 \pm 0.39$	3.99	3.83 – 4.11	2.60 – 4.19	2.30 – 4.20
<b>Positive autoimmune status<sup>c</sup></b>					
Iodine excretion ( $\mu$ g/L) <sup>d</sup>	$138.75 \pm 71.05$	124.50	83.25 – 176.50	38 – 332	100–199
Total cholesterol (mg/dl)	$160 \pm 36$	159	141 – 177	84 – 270	130 – 200
Triglycerides (mg/dl)	$64 \pm 21$	64	45 – 80	26 – 103	30 – 200
HDL-cholesterol (mg/dl)	$60 \pm 18$	88	47 – 68	33 – 106	45 – 90
LDL-cholesterol (mg/dl)	$89 \pm 27$	88	76 – 99	46 – 177	100 – 129
<b>Idiopathic hyperthyrotropinaemia subgroup (<math>n=26</math>; 18 males and 8 females)</b>					
Time of follow-up (years)	$1.90 \pm 1.53$	2.00	—	0.25 – 6.00	—
<b>Clinical characteristics</b>					
Age (years)	$6.12 \pm 3.92$	5.87	2.25 – 8.54	1.00 – 14.25	—
Basal BMI (BMI Z-score)	$-0.21 \pm 0.94$	-0.09	-0.65 – 0.37	-2.88 – 1.57	—
Annual BMI (BMI Z-score)	$-0.23 \pm 1.45$	-0.07	-1.45 – 0.72	-2.45 – 3.10	—
<b>Thyroid Ultrasound</b>					
Thyroid volume (cc)	$2.27 \pm 1.12$	2.00	—	0.51 – 4.30	—
<b>Biochemical characteristics</b>					
TSH ( $\mu$ U/ml)	$6.46 \pm 0.94$	6.56	5.66 – 7.22	3.93 – 7.90	0.35 – 5.00
$ft4$ (ng/dl)	$1.15 \pm 0.11$	1.13	1.06 – 1.22	1.00 – 1.36	0.70 – 1.98
$ft3$ (pg/ml)	$3.92 \pm 0.44$	3.99	3.72 – 4.21	3.06 – 4.59	2.30 – 4.20

a Thyroid Ultrasound (US) was performed in 35 of 40 patients (87.5%). US alterations were found in 8 individuals (5 males and 3 females).  
b Thyroid volume (WHO proposed formula): Lobule volume (cc) = 0.479 x depth (cm) x wide (cm) x length (cm).  
c  $n=4$  (3 males and 1 female).  
d Iodine excretion was determined in 30 of 40 subjects (75%)

P3-1717

**X CHROMOSOME INACTIVATION PATTERN IN FEMALE CHILDREN AND ADOLESCENTS WITH AUTOIMMUNE THYROID DISEASES: A PRELIMINARY STUDY**

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**Objectives:** X chromosome inactivation (XCI) is the process necessary for balancing gene dosage in females. Either paternally or maternally inherited X chromosome is randomly inactivated in each cell. In some females, this inactivation predominantly occurs to one specific parental X chromosome, so-called skewed XCI. Skewed XCI is age-dependent with increased frequency in older age females. Previous adult studies reported the frequency of skewed XCI in autoimmune thyroid diseases (ATD) at 20-34%. No study of skewed XCI in pediatric ATD is available. Therefore, this study aim to determine the XCI pattern in female children and adolescents with ATD.

**Methods:** Thirteen girls with ATD who have been followed at our Pediatric Endocrine Clinic were enrolled. Clinical and



laboratory data related to their ATD were collected. To determine the XCI pattern, DNA was digested with methylation sensitive *HpaII* and *HhaI*, and was amplified for the polymorphic CAG repeats in androgen receptor gene. Fragment analysis was performed and ratio between methylated and unmethylated amplicons was calculated. Skewed XCI is defined as 80% or greater of a specific parental X chromosome being inactivated.

**Results:** Of the 13 patients, 10 had Graves’ disease (GD) and 3 had Hashimoto thyroiditis. Their mean (SD) ages at diagnosis and enrollment were 11 (3.1) and 14.4 (3.1) years, respectively. Two patients (1 GD and 1 Hashimoto thyroiditis) with CAG repeat homozygote were excluded. Skewed XCI was demonstrated in 6 (4 with GD) of 11 patients (54.5%). All 5 patients with random XCI had GD. The mean ages at the disease onset of skewed and random XCI patients were 11.4 and 12 years, respectively with younger age at enrollment in the skewed XCI group (13.9 and 16.4 years). Considering GD patients, only 1 of 4 patients with skewed XCI had a disease relapse, whereas 3 of 5 GD patients with random XCI had a disease relapse.

**Conclusions:** The frequency of skewed XCI seemed to be greater in pediatric ATD as compared to adults. Early onset skewed XCI may contribute to earlier onset of disease in pediatric ATD patients. The present study is ongoing with recruiting more patients and controls.

P3-1718

**EVALUATION OF DYNAMIC THIOL-DISULPHIDE HOMEOSTASIS IN CHILDREN AND ADOLESCENTS WITH NON-AUTOIMMUNE SUBCLINICAL HYPOTHYROIDISM**

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**Objectives:** It has been shown that thyroid hormones affect the synthesis and degradation of antioxidant proteins, vitamins and enzymes. Oxidant molecules turn thiol groups into reversible disulphide (S-S) bond structures. These disulphide bonds are again reduced to thiol groups (-SH) by antioxidants. Thus thiol/disulphide hemostasis is continued. These disulphide bonds are reversible and constitute an early detection of protein oxidation. We aimed at evaluating the thiol-disulphide homeostasis in children with non-autoimmune subclinical hypothyroidism.

**Methods:** Thiol-disulphide hemostasis was evaluated in 60 children and adolescents negative for thyroid auto-antibodies (anti-thyroid peroxidase, anti-thyroglobulin) and with TSH values higher than 5 mIU/L and in 40 healthy individuals negative for thyroid auto-antibodies and having normal TSH levels for the same gender and age (Table1.).

**Results:** Native thiol (466±32.8 µmol/L vs 462±32.1 µmol/L p=0.59), total thiol (508±34.0 µmol/L vs 506±32.7 µmol/L, p=0.81), disulphide (21±5.5 µmol/Lvs 22±5.8 µmol/L, p=0.41), disulphide/native thiol (4.5±1.2% vs 4.8±1.3%, p=0.36), disulphide/total thiol (4.1±1.0% vs 4.3±1.1%, p=0.36) and native thiol/ total thiol (91±2.1% vs 91±2.1% p=0.31) levels were similar in children with subclinical hypothyroidism and cases in the control group (p>0.05)(Table1.). There was no difference between total cholesterol, triglyceride and LDL levels of the groups (p>0.05). No difference was detected in thiol disulphide and lipid levels among the cases with or without iodine deficiency in the subclinical hypothyroidism group (p>0.05).

**Conclusions:** Dynamic thiol-disulphide hemostasis is not changed in children and adolescents with non-autoimmune subclinical hypothyroidism

Table 1. Clinical and laboratory characteristics of the cases in Subclinical Hypothyroidism and Control Subjects

	Patients (n=60)	Control subjects (n=40)	p
Age(year)	9.7±3.5	10.8±2.5	0.09
Sex (f/m)	27/33	22/18	0.21
BMISDS	0.71±1.03	0.04±0.71	0.89
TSH	6.5±1.1	2.5±1.0	<0.001
sT4	0.9±0.1	0.9±0.0	0.71
Native thiol(SH) (µmol/L)	466±32.8	462±32.1	0.59
Total thiol (SH+SS) (µmol/L)	508±34.0	506±32.7	0.81
Disulphide(SS) (µmol/L)	21±5.5	22±5.8	0.41
Disulphide/Native thiol (%)(SS/SH)	4.5±1.2	4.8±1.3	0.36
Disulphide/Total thiol (%)	4.1±1.0	4.3±1.1	0.36
Native thiol/ Total thiol (%)	91±2.1	91±2.1	0.34

Mean±SD

P3-1719

**GROWTH AND PUBERTY IN CHILDREN WITH CONGENITAL HYPOTHYROIDISM DETECTED BY NEONATAL SCREENING PROGRAM**

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**Objectives:** We evaluated growth and puberty in children with congenital hypothyroidism (CH) detected by a neonatal screening programme. The aim of this study was to describe pubertal onset (PO) and final height (FH) in early treated patients with permanent CH.

**Methods:** We assessed 173 patients (F=130; M=43) born between 1995 and 2002, detected by neonatal screening, were followed up from diagnosis and start of treatment up to the age of FH. The following parameters were assessed: age,



anthropometric measures, levothyroxine dose (LTd), TSH, FT4 and T4 at start of treatment, PO, FH and menarche in the female group. We calculated bone age (BA) -Greulich and Pyle method-, mean FH, total pubertal growth, median predicted FH (PFH) at PO -Bayley-Pinneau method- and mean target height (TH). Statistical analysis: T-test, Mann-Whitney test and Spearman correlation.

**Results:** Chronological age at diagnosis was 17 days (14;26). Initial LTd was 12.81 mcg/kg/day (11.47;14.32). Serum TSH was 146 uIU/ml (65.4;387) and T4 was 3.25 µg/dl (0.80; 5.70). LTd at PO was 2.64 µg/kg/day (2.23;3.08). Other parameters are shown in table 1.

**Table 1.** Pubertal growth parameters in CH children

	Female	Male
<b>Age PO (years)</b>	10,06±1.15	11.34±1.33
<b>BA PO (years)</b>	10.0 (9.5;11.0)	11.3 (10.0;12.5)
<b>H PO (cm)/SDS</b>	137.8±6.92/-0.16 ±1.08*	146.9±7.71/0.23±1.01*
<b>PFH PO (cm)/SDS</b>	158.4 (153;163)/-0.37 (-1.26;0.37)	179.4 (174.6;187.7)/0.97 (0.26;2.19)
<b>Age menarche (years)</b>	12.08±1.04	
<b>BA menarche (years)</b>	12,5 (12;13)	
<b>H menarche (cm)/SDS</b>	152.9±6.08/0,29±1,05	
<b>FH (cm)/ SDS</b>	158.0±6.05/-0.53 ± 0.86	171.8±7.33/-0.09±0.96
<b>Total pubertal growth (cm)</b>	21.29±5.45	26.2±4.02
<b>TH (cm)/SDS</b>	158.6±5.55/-0.71±0.85	172.2±3.8/-0.60±0.52

There were significant differences between genders in height SDS at PO ( $p=0.03$ ). There was high correlation between FH SDS and TH, height PO and PFH SDS ( $\rho=0.88$ ;  $\rho=0.77$ ;  $\rho=0.69$  -  $p<0.0001$ ). We found a negative correlation between menarche age and initial T4.

**Conclusions:** Pubertal onset and menarche occurred within normal limits for age with according BA. Severity of CH at diagnosis could influence menarche age. FH was within normal range and related to TH. Therefore, early diagnosis and adequate follow up allow attaining normal growth and pubertal development.

**Table 1.** Pubertal growth parameters in CH children

	Female	Male
Age PO (years)	10,06±1.15	11.34±1.33
BA PO (years)	10.0 (9.5;11.0)	11.3 (10.0;12.5)
H PO (cm)/ SDS	137.8±6.92 / -0.16 ±1.08*	146.9±7.71 / 0.23±1.01*
PFH PO (cm)/ SDS	158.4 (153;163) / -0.37 (-1.26;0.37)	179.4 (174.6;187.7) / 0.97 (0.26;2.19)
Age menarche (years)	12.08±1.04	
BA menarche (years)	12,5 (12;13)	
H menarche (cm)/ SDS	152.9±6.08 / 0,29±1,05	
FH (cm)/ SDS	158.0±6.05 / -0.53 ± 0.86	171.8±7.33 / -0.09±0.96
Total pubertal growth (cm)	21.29±5.45	26.2±4.02
TH (cm) /SDS	158.6±5.55 / -0.71±0.85	172.2±3.8 / -0.60±0.52

P3-1720

## DIFFERENCES IN LEVOTHYROXINE DOSAGES FOR REPLACEMENT OF CHILDREN WITH PRIMARY AND CENTRAL PERMANENT HYPOTHYROIDISM

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**Objectives:** Replacement of Congenital (CH), Autoimmune (AH) and Central (PH) hypothyroidism is based on Levothyroxine (L-T4) administration. However, the initial L-T4 doses used for the optimal treatment in CH, AH or PH patients are widely different. Several studies evaluated L-T4 maintenance euthyroid doses administered for the appropriate replacement in children with CH and AH, while data concerning PH are scanty.

**Objective and hypotheses:** To compare mean L-T4 doses administered in CH, AH or PH children to maintain optimal hormone replacement.

**Methods:** This is cross-sectional and retrospective study. We enrolled 67 children (Female 37), with overt and permanent hypothyroidism, who were appropriately replaced (on the basis of serum fT4 and TSH levels for CH and AH and fT4 for PH) for almost 3 yrs (mean  $8.2 \pm 5.2$  yr). Our study population consisted of : 22 children affected by CH (14 by thyroid dysgenesis, 8 by dysmorphogenesis), 23 by AH and 22 by PH (13 by idiopathic hypopituitarism, 9 secondary to pituitary tumors). Serum fT4 and TSH levels were measured at mean age of  $14.6 \pm 2.6$  yrs. Serum fT4 and TSH levels were measured by commercial kits, Statistical analysis was performed by ANOVA.

**Results:** In AH children, mean L-T4 maintenance euthyroid doses were significantly lower than in the CH and PH groups ( $1.4 \pm 0.4$  vs  $1.7 \pm 0.4$ ,  $p=0.01$  and  $1.4 \pm 0.4$  vs  $1.9 \pm 0.5$ ,  $p=0.008$  respectively), while no differences were found between CH and PH groups ( $1.9 \pm 0.5$  vs  $1.7 \pm 0.4$ ,  $p=0.2$ ). Mean L-T4 doses to maintain euthyroidism were similar in patients with athyreosis vs dysmorphogenesis ( $1.6 \pm 0.3$  vs  $1.7 \pm 0.6$ ,  $p=0.1$ ) and in those with idiopathic and secondary PH ( $1.8 \pm 0.8$  vs  $1.9 \pm 0.5$ ,  $p=0.3$ ). There is no correlation between LT4 dosage and serum FT4 levels or chronological age in all forms of permanent hypothyroidism in our study population. In all groups mean fT4 levels were not different, and in AH and CH mean TSH values were similar.

**Conclusions:** In our experience PH children need (weight-based daily) L-T4 dosages similar to CH ones, while

significantly lower doses are sufficient to maintain clinical and biochemical euthyroid status in those with AH.

	AH	CH	Thyroid dysgenesis	Dys-hormonogenesis	PH	Idiopathic hypopituitarism	Pituitary tumors
DIAGNOSIS							
Mean age (yr)	10.5±2.2	0.06±0.01	0.06±0.01	0.06±0.01	8.2±5.2	7.1±5.8	9.9±4.8
TSH	98.3±214	326.9±335.6	418.2±355.4	167.1±239.9	-	-	-
FT4	9.5±4.7	7.5±4.9	6±4.3	10.0±5.0	7.8±2.0	7.7±2.0	7.9±2.1
LT4(µg/kg/die)	1.4±0.8	11.8±8.7	10.0±2.3	10.5±1.9	2.5±1.5	3.0±1.7	1.7±0.5
FOLLOW-UP							
Mean age (yr)	15±2.1	13.2±2.8	14±2.5	12.0±2.9	15.6±2.2	16.1±1.8	14.8±2.5
TSH	1.5±1.2	2.2±1.5	2.2±1.4	2.2±1.7	-	-	-
FT4	16.7±4.2	16.9±2.7	17.1±1.9	16.6±3.9	15.0±5.1	16.9±4.5	13.7±4.3
LT4(µg/kg/die)	1.4±0.4	1.7±0.4	1.6±0.3	1.7±0.6	1.8±0.7	1.8±0.8	1.9±0.5
Statistically significant differences:							
♦ LT4 DOSES AT DIAGNOSIS				♦ LT4 DOSES DURING THE FOLLOW UP			
• AH vs PH: p=0.0007				• AH vs PH: p= 0.008			
• AH vs CH: p<0.0001				• AH vs CH: : p= 0.01			
• CH vs PH: p<0.0001							

P3-1721

A NEW THYROID HORMONE RECEPTOR-A (THRA) GENE VARIANT MIMICKING AN ISOLATED CONGENITAL CENTRAL HYPOTHYROIDISM

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**Objectives:** INTRODUCTION: Since the first human case of THRA gene mutation (encoding Thyroid Hormone Receptor TRα1) described in 2012, less than 20 patients have been reported. We report a new THRA gene variant in a patient initially diagnosed with isolated congenital central hypothyroidism.

**Methods:** CASE REPORT: A 2-year-old Guinean girl had psychomotor retardation associated with macrocephaly (HC = +4 SDS) and obesity [weight = 15 kg (+3 SDS), height = 86 cm (+0.5 SDS), BMI = 21 kg/m² (+2.3 SDS)]. She was born at term, with weight = 3.2 kg, length = 50 cm, and HC = 38 cm. Cranial MRI was normal. Thyroid hormone evaluation showed central hypothyroidism: TSH 2.09 mIU/L (N : 0.5-4.5) and free T4 6.8 pmol/L (N : 10-23), with normal TSH response to Thyrotropin-Releasing Hormone (TRH) test (peak TSH : 22.65 mIU/L). Other pituitary hormones were normal and sequencing of TRH gene and TRH receptor gene were normal.

**Results:** Levothyroxin treatment (3 µg/kg/d) and developmental support were initiated, and psychomotor development improved: at 13 years old, she is in 6th grade. Her height remained at +1 SDS, in agreement with genetic target height, BMI increased (BMI = 30.5 kg/m² at 13 years, + 2.2 SDS), and she remained macrocephalic (HC = 62.5 cm, +5 SDS). On levothyroxin treatment (1.44 µg/kg/d), TSH levels were suppressed (< 0.1 mIU/L), FT4 levels were in the upper half of

normal (11 to 25 pmol/L), but FT3 levels were elevated (5.8 to 12.5 pmol/L, N : 3-6).

The unusually high FT3 levels on levothyroxine treatment despite appropriate FT4 levels together with macrocephaly led us to suspect a THRA gene mutation.

An undescribed heterozygous variant in the THRA gene, c.817A>G, at codon 273 was identified. The mutation was located in the hormone-binding domain, and predicted to be deleterious by in silico methods. FT3 level at 2 years of age, measured from stored sample, was 9.8 pmol/l (N : 3-6).

**Conclusions:** CONCLUSION: When isolated central hypothyroidism is identified (from TSH and FT4 measurements), it is necessary to measure FT3: in case of isolated increased FT3 level or decreased FT4/FT3 ratio, TRHA gene must be suspected.

P3-1722

A NON FAMILY CONGENITAL NON-AUTOIMMUNE HYPERTHYROIDISM SECONDARY TO AN ACTIVATING MUTATION IN THE THYROTROPIN RECEPTOR GENE

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**Objectives:** TSH receptor (TSHR) activating germline mutations are a rare cause of neonatal non-autoimmune hyperthyroidism (nNAH). This form of hyperthyroidism persists indefinitely. Surgery or radioactive iodine is indicated eventually.

**Methods:** We report a case of severe congenital hyperthyroidism without family history of thyroid disease. **Results:** The female patient was born in the 41<sup>st</sup> week of gestation, birth weight was 2590 gr. (SDS -1.45). She was hospitalized since birth due to choanal atresia, congenital heart disease, and supraventricular extrasystoles and received amiodarone for two days. At 21 days of life she was admitted to our institution. Thyroid function test confirmed the diagnosis of hyperthyroidism (TSH <0.03 µIU/mL and FT4

4.57 ng/dL). Neither TSHR nor TPO antibodies were detected. She was started on *methimazole* (MMI) (0.5 mg/kg/d) and propranolol (1 mg/Kg/d), with poor response. Currently, she is two years old. On clinical examination: body weight was at 0.49 SDS, height: -1.25 SDS and has normal head circumference. Goiter was not detected. Under MMI treatment 0.86 mg/Kg/d serum thyroid profile was: (TSH <0.03  $\mu$ U/mL and FT4 1.76 ng/dL). Therefore *TSHR* mutation was suspected. Genomic DNA sequencing of all exons and flanking intronic regions of *TSHR* extracted from peripheral blood cells of the patient, her parents, and brother was performed. Molecular studies revealed a heterozygous point mutation c.1897G>C; p.Asp633His at the sixth transmembrane domain of *TSHR* in exon 10. This variant was predicted to be deleterious by *in-silico* analysis using SIFT, Mutation Taster, and PolyPhen-2. Thyroid function was normal in parents and brother and no *TSHR* mutation was detected. The same *TSHR* point mutation was reported in hyperfunctioning thyroid insular carcinoma in somatic thyroid cells, but has never been congenitally reported. In the absence of *TSHR* mutation in the parents or brother, a de novo variant or a post zygotic mutation in the patient, could be proposed.

**Conclusions:** Misdiagnosis of nNAH might result in irreversible consequences, because of inadequate treatment. In the presence of p.Asp633His variant in the *TSHR*, prompt thyroidectomy is recommended due to the high risk of thyroid carcinoma.

P3-1723

#### BRAIN-LUNG-THYROID SYNDROME (BLTS) IN A MEXICAN PATIENT WITH A NOVEL INTRAGENIC DELETION IN NKX2-1

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**Objectives:** To describe the phenotype and a novel deletion of NKX2-1 gene causing BLTS in a Mexican patient.

**Methods:** A Mexican male patient, the third sibling of an endogamous marriage, had normal weight and length and no abnormalities at neonatal thyroid screening. At 22 months of age, he was referred to hospital because of recurrent respiratory tract infections in a setting of developmental delay. Physical examination showed prominent forehead, depressed nasal bridge, umbilical hernia (0.5 cm), scoliosis, simian crease and Sydney line in both hands and bilateral 5<sup>th</sup> toe clinodactyly. Karyotype (15 metaphases), Microarray based Comparative Genomic Hybridization (aCGH) were normal. At 3 years 10 months a thyroid function test reported

subclinical hypothyroidism, thyroid physical examination, ultrasound (US) and scintigraphy were normal. At 6 years he was referred to a neurologist and diagnosed with extrapyramidal syndrome of unknown etiology. At 8 years, a new thyroid function tests showed TSH 28.9 mIU/L, FT4 1.4 ng/dL, and levothyroxine (LT4) was started (2.3 mcg/kg/dose); he continued with LT4 treatment until 10 years 5 months, when it was discontinued with a TSH of 10.2 mIU/L and a FT4 of 1.2 ng/dL; then, being restarted with substitution at 13 years (2.1 mcg/kg/dose) with a TSH of 31.5 mIU/L and a FT4 of 1.2 ng/dL and continued until present. Head computed tomography (CT) was reported normal, and a brain magnetic resonance imaging (MRI) showed a Rathke's cleft cyst. Normal puberty with adequate height and weight were achieved.

**Results:** PCR and Sanger Sequencing of the entire coding region of NKX2-1 and its intro-exon boundaries in lymphocyte DNA from the patient revealed a novel homozygous 253 bp deletion in exon 2.

**Conclusions:** Subsequent presentation of the clinical features of the BLTS made its early diagnosis difficult. Congenital hypothyroidism may be absent at birth or be mild enough to escape detection by neonatal screening. Strikingly, the deletion is not detectable in neither parent, suggesting the existence of germinal mosaicism. Germinal mosaicism should be considered in the identification of genetic defects in NKX2-1.

P3-1724

#### THYROIDITIS AND GONADAL FAILURE IN A GIRL WITH THYROID HORMONE AUTOANTIBODIES, CASE REPORT.

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**Objectives:** Background.

Different results have been reported regarding the presence of thyroid hormone autoantibodies (THAA) in the people with thyroid disorders[1, 2]. Those patients are found because of discrepancy between physical findings and laboratory data[3].

A girl with THAA and gonadal failure is presented along with the challenge in her diagnosis.

**Methods:** Birth date: 19 November 1999

10 years old female with goiter. Ultrasound: multinodular goiter. Physical exam: HR: 88 RR: 22 AT: 80/60 Weight: 28kg Height: 131.5cm. Goiter. Tanner: Breast: II Pubic: I. Reflexes: Slow relaxations phase. Positive Thyroglobulin and Peroxidase antibodies, TSH elevated (Table 1). Thyroiditis was Diagnosed and L-thyroxin initiated.

Through evolution, asymptomatic; TSH levels descended and Free T4 elevated (Table 1). Upper extremities reflexes increased. Pubertal development normal but irregular menses. Final Height normal for her.

In 2014 L-Thyroxin was removed, TSH levels increased and FT4 elevated, asymptomatic. Pituitary adenoma was studied (normal MRI May/2015); or a mutation in Thyroid hormones receptor (negative Feb/2016).

The presence of THAA is suspected, with positive results (Table 1). Amenorrhea is present; her FSH elevated with undetectable estradiol. Ultrasound: ovaries diminished in volume. Autoimmune oophoritis is studied (antibodies negative July/2016), L-thyroxin was reinitiated with normalization of the TSH and FT4. Estradiol detectable

**Results:** N/A

**Conclusions:** Although THAA were described over 50 years ago, the results of thyroid function test in the presence of THAA might cause misdiagnoses and mistreatments by endocrinologists who still ignore the existence of THAA. Further studies are necessary in this patient to explain all the pathology seen in different organs

1. Sakata, S., et al., *Prevalence of thyroid hormone autoantibodies in healthy subjects*. Clin Endocrinol (Oxf), 1994. **41**(3): p. 365-70.
2. Benvenga, S. and F. Trimarchi, *Thyroid hormone autoantibodies in Hashimoto's thyroiditis: often transient but also increasingly frequent*. Thyroid, 2003. **13**(10): p. 995-6; author reply 996.
3. Lee, M.-N., et al., *Thyroxine (T4) Autoantibody Interference of Free T4 Concentration Measurement in a Patient With Hashimoto's Thyroiditis*. Annals of Laboratory Medicine, 2017. **37**(2): p. 169.

Table 1.

Date	TSH (0.4 - 4 µIU/ml)	TT4 (8.5 - 12.5 ng/dl)	FT4 (0.8 - 1.3 ng/dl)	TT3 (70 - 180 ng/dl)	FT3 (1.8 - 6 pg/ml)	L-Thyroxin Dose in µg - total (per kg) *not good adherence	Thyroglobulin (0.8 - 55 ng/ml)	Peroxidase AB (0 - 35)	Thyroglobulin AB (0 - 40)	Thyroxin AB (Neg <100%)	Triiodothyronin AB (Neg <100%)	LH (prepubertal <0.2 pubertal 0.4 - 12 mIU/ml)	FSH (prepubertal 0.3 - 3 pubertal 1 - 11 mIU/ml)	Estradiol (0.1 - 56 ng/ml)	Antimüllerian hormone ng/ml
28/04/2010	13.9	4.8	1	150	4.8	0	0.6	>1000	957						
22/10/2010	6.71	5.5	1.2	155	5.5	*50 (1.62)									
16/02/2011	2.5	8.9	2.1			*62.5 (1.93)									
27/07/2011	0.237	9.1	4			62.5 (1.78)		>1000	354						
10/02/2012	2.46	11.1	4.6	182	4.8	62.5 (1.5)									
07/08/2012	1.49	12.1	5.6	161	5.2	75 (1.69)									
06/02/2013	0.018	16.5	>6	158	5.6	100 (2.33)		>1000	615						
01/08/2013	0.019	15.8	5.4	132	5.4	100 (2.18)	0.5								
13/02/2014	0.014	13.9	5.7			100 (2.3)									
22/05/2014	0.105		4.6			75 (1.6)		>1000	469						
14/08/2014	7.22	9.5	5.4			0									
02/10/2014	4.36	9.9	5	119	3.7	0								4.1	228
29/05/2015	7.46	11.2	3.8	113	4.6	0									
11/04/2016	7.43	10.3	3	137	4.5		<0.2					38.7	74.5	<20	
18/05/2016												42.4	77.8		<0.1
25/06/2016									794	150					
05/08/2016	3.26		2.4	111		12.5 (0.26)						40.4		23.2	

P3-1725

**THYROID HORMONE RESISTANCE: TRIAC (3,5,3'-TRIIODOTHYROACETIC ACID) EXPERIENCE**  
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**Objectives:** Thyroid hormone resistance is a disease characterized by reduced sensitivity to thyroid hormone in

cell membrane, metabolism and nuclear receptor. The clinic signs of thyroid hormone resistance are goiter, sinus tachycardia, attention deficit hyperactivity disorder and laboratory signs are high level of free T4 and normal level of TSH.

**Methods:** N/A

**Results:** A 10 year-old girl was admitted our clinic complaints of palpitation and nervousness. Her weight and height were 27 kg (3-10 p) and 132.8 cm (3-10 p). On physical examination heart rate was 150/dk beats/min; blood pressure was 90/60 mmHg and her thyroid was stage 1. Her thyroid function tests were: total T3 2,4 ng/ml (0,9-2,3), free T3 6,17 pg/ml (1,7-3,7) , total T4 12,9 µg/dl (5,9-12,9), free T4 2,33 ng/dl (0,7-1,48), TSH 3,29 µIU/ml, thyroglobulin 15,2 ng/ml (0,2-70) and negative antibodies of thyroglobulin and thyroperoxidase. In the genetic analysis of the patient suspected of thyroid hormone resistance, the P453A c.1357C> G mutation was detected heterozygously on the exon10 of the THRB gene. B-blocker therapy was initiated in the patient who continued to have palpitations and tachycardia. Patients who did not benefit from B-blocker treatment regressed clinical complaints after Triac (3,5,3'-Triiodothyroacetic Acid) therapy, provided thyroid function tests with euthyroidism. **Conclusions:** Among THRB gene mutations 453 mutation is the most common. In our case, the receptor affinity of T3 is reduced to 17% as a result of alanine substitution of proline amino acid due to guanine transversion instead of cytosine in codon 453 at exon 10. This case is shared for the Triac (3,5,3'-Triiodothyroacetic Acid) treatment experience in Tyhroid Hormone Resistance.

P3-1726

**CHALLENGES IN DIAGNOSIS AND TREATMENT OF HYPERTHYROIDISM POST HEART TRANSPLANTATION**  
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**Objectives:** To describe the obstacles to diagnosis of hyperthyroidism in a girl who underwent heart transplantation.  
**Methods:** A 17.5-year-old girl suffering from bipolar disorder presented with weakness, head ache and weight loss. Cardiomyopathy had led to heart transplantation 26 months earlier. Regular treatment consisted of tacrolimus, mycophenolate sodium, acetylsalicyl acid, duloxetine hydrochloride, folic acid and magnesium diasporal. The patient had been treated with amiodarone for 2 months prior to transplantation. A diagnostic cardiac catheterization with contrast medium was done 4 months before admission. At

admission TSH was <0.008 mIU/L, FT4 59.5 pmol/l, FT3 22.8 pmol/l. Physical findings included diffuse goiter and mild tremor. Tremor had been present since the transplantation and was considered to be a side effect of tacrolimus. Heart rate was 95-105/min, blood pressure 95/55 mmHg. These were constant since transplantation and are regarded as normal for a denervated heart. Eyes, skin and deep tendon reflexes were normal.

**Results:** CRP, antibodies to TPO, thyroglobulin and TSH receptor were all within normal range. Thyroglobulin level was elevated. A Technetium -99m thyroid scan showed very low uptake. MIBI thyroid scan showed reduced uptake as well. None of the currently administered medications could have been associated with thyroid dysfunction. Mixed-type amiodarone-induced thyrotoxicosis (AIT) was diagnosed. Methimazole therapy was not effective and prednisone therapy was instituted, leading to complete recovery.

**Conclusions:** Heart-transplanted patients treated with amiodarone before transplantation are at high risk to develop thyroid dysfunction. Since classical clinical signs such as heart rate and blood pressure are altered, thyroid functions should be routinely monitored in these patients. AIT may develop even several years after treatment cessation and is not associated with dose or duration of therapy. Both MIBI scan and thyroglobulin serum level are important for the diagnosis of the AIT type.

P3-1727

#### TRANSIENT CONGENITAL HYPOTHYROIDISM IN A PREMATURE GIRL DUE TO THYROID-STIMULATING HORMONE RECEPTOR BLOCKING ANTIBODIES

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**Objectives:** Thyroid autoantibodies occur in 5-15% of fertile women. Thyroid receptor antibodies (TRAB) are capable of crossing placenta, and in 0.01% of pregnancies they will cause transient congenital hyperthyroidism often in cases where the mother is known to have Graves' disease. Transient congenital hypothyroidism is much less common.

**Methods:** We present a girl with transient congenital hypothyroidism born by spontaneous labour at gestational age 31+1. Her mother was treated with levothyroxine due to a recent diagnosis of TRAB positive autoimmune hypothyroidism. The mother's TRAB levels were elevated to 1130-1580 IE/l (reference range <1 IE/l).

**Results:** At birth the girl was 1618g (-1 SD) and 41cm (-0.5 SD), and she had a full APGAR score. She did not display any symptoms of hypothyroidism until day six of life, where she started having aspirates from her nasogastric tube and developed hyperbilirubinemia. This collided with a finding of increased thyroid stimulating hormone to 1083 mIU/l (reference range 0.6-8.1 mIU/l). The girl's TRAB level was very high (1210 IE/l). Enteral levothyroxine, phototherapy and IV fluids were commenced. Ultrasound showed a normally sited thyroid gland, and an electrocardiogram was normal. The

girl's symptoms wore-off shortly after starting levothyroxine. She was discharged at corrected 40 weeks of age, and at that time the dose of levothyroxine was 50/37,5ug on alternating days.

By corrected age 3 months, TRAB levels had decreased to 0.4IE/l, and a slow wean of levothyroxine took place until corrected age 6.5 months, at which point treatment was ceased. The girl is now 2 years of age, and she is still attending our outpatient clinic. Bloodsamples and developmental milestones have all been normal.

**Conclusions:** This case underlines the importance of testing for TRAB during pregnancy in case of maternal autoimmune thyroid disease. Neuropsychological delays may result in case of insufficient intrauterine thyroid hormone exposure and delayed treatment of hypothyroidism post partum. Follow-up of patients with transient congenital hypothyroidism is essential.

P3-1728

#### MATERNAL AMIODARONE CAUSING NEONATAL GOITER AND HYPOTHYROIDISM

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**Introduction:** Chronic maternal exposure to iodine-containing medications can cause neonatal goiter, hypothyroidism or hyperthyroidism. The anti-arrhythmic drug, amiodarone, is 37% iodine by weight and has a structure that resembles free T4. We report a case of an infant with goiter and neonatal hypothyroidism secondary to maternal amiodarone use.

**Methods:** N/A

**Results: Case Report:** This girl was born at 37 weeks gestation to a 29 year old mother with 3 pre-pregnancy episodes of cardiac arrest secondary to ventricular fibrillation. The mother began amiodarone 4 years prior to conception, and the dose was increased 2 months prior to delivery for worsening palpitations. Maternal thyroid labs remained normal throughout pregnancy. No goiter was noted on a prenatal ultrasound at 23 weeks gestation, but at 36 weeks, the fetal thyroid circumference was 12 cm (>95<sup>th</sup> percentile). The baby was delivered by elective cesarean section. APGARs were 7, 8 at 1 and 5 min respectively, and she had a birth weight of 6 lb 1 oz. She was intubated due to apnea. She was noted to have a significant goiter measuring 7 by 8 cm at birth which was soft to touch. TSH immediately after birth was 195 mIU/L, free T4 was 0.55 ng/dL, and total T3 was 132 ng/dL. Levothyroxine 37.5 mcg once daily was begun on day 1 and lowered to 25 mcg once daily on DOL 23. On DOL 27, she had a TSH of 0.69 mIU/L, free T4 of 1.82 ng/dL, and the goiter had decreased to 2-3 cm bilaterally. Levothyroxine was then decreased to 12.5 mcg once daily. At age 2 months, TSH was 0.16 mIU/L and free T4 was 1.69 ng/dL, so levothyroxine was discontinued. Because the baby was formula fed after birth, there were no issues with transfer of amiodarone through breast milk.

**Conclusions:** Amiodarone can lead to a significant iodine load for both mother and fetus, as iodide crosses the placenta freely. This iodine overload results in decreased organification (Wolff-Chaikoff effect). Failure to escape from this effect results in persistent inhibition of fetal thyroid function. Therefore, close monitoring of fetal thyroid function during pregnancy and after delivery is important, even if maternal thyroid function is normal.

P3-1729

#### NEONATAL GRAVES DISEASE: REPORT OF TWO CASES IN VIETNAM.

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**Objectives:** Neonatal graves is a transient and rare form of hyperthyroidism which occurs in 1 – 2% babies born from mothers with Basedow disease due to trans placental passage of IgG stimulating TSH receptors (TRAb). Herein, we reported two Vietnamese cases with neonatal graves disease.

**Methods:** This is case series report including clinical course, investigations and outcome of treatment.

#### Results: Case reports

**Case No. 1:** The 7 days old boy admitted to pediatric emergency with chief complains of tachycardia. He is 1st child of the family, 32 weeks of gestation with birth weight of 1800 gram. Rashes on his face and tachycardia were recognized at 2 days after birth. His mother was diagnosed with Basedow 1.5 month before pregnancy and was treated with Carbimazole for 1 month and one dose of radioiodine. On the admission, he presented with tachycardia (180bpm), poor weight gain (150 gram/week). Plasma T3, FT4, TSH levels were 8.5 nmol/l; 111.59 pmol/l; 0.009 UI/l, respectively. He was treated with Thyrozol 1mg/kg/day and propranolol 2mg/kg/day. 1 week after treatment, his condition was stable: normal heart rate (140 bpm), normal plasma T3, T4, TSH levels with 2 nmol/l; 90 nmol/l and 0.181 UI/l, respectively; gained 250 gram/week. **Case No. 2:** The 35 days old girl admitted to pediatric emergency with chief complains of fever, tachycardia. She is 1st child of the family, 38 weeks of gestation with birth weight of 2300 gram. She presented with irritation, sweating, poor sleeping, poor weight gain (300 gram/25 days) at 7 days of age and fever at 13 days of age. Her mother was diagnosed with Basedow at 6 months of gestation (T3: 6.49 nmol/l, T4: 200 nmol/l, TSH: 0.03 UI/l, TRAb: 40 UI/ml) and was treated with PTU. On the admission, she presented with tachycardia (190bpm), a goiter, bulge eyes. Plasma T3, T4, TSH levels were 6.7 nmol/l; 526.4 nmol/l; 0.0001 UI/l, respectively. She was treated with Thyrozol 1mg/kg/day and propranolol 2mg/kg/day. 1 week after treatment, her condition was stable: normal heart rate (150 bpm), normal plasma T3, T4 levels with 3 nmol/l; 136 nmol/l, respectively; gained 200 gram/week.

**Conclusions:** Newborn babies from mothers with Basedow should be screened and follow up for hyperthyroidism to avoid mortality due to thyroid storm.

P3-1730

#### RARE CASES OF THYROID STORM IN ADOLESCENCE

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**Objectives:** Thyroid storm is a life-threatening status induced by severe exaggeration of thyrotoxicosis. Incidence of thyroid storm is very low in children. Here we report four cases of thyroid storm in adolescence.

**Methods:** Patient presentations on admission were as follows. Case 1: 10-year-old boy came to emergency unit presenting with abdominal pain, diarrhea and high fever for three days. He was drowsy status on admission. Free T4 level was 7.81 ng/dl (normal range 1.00-1.80 ng/dl) with undetectable TSH level. Thyroid-stimulating hormone receptor antibody (TSAb) was positive (637 %) (normal range, less than 120%). Case 2: 16-year-old girl was admitted with generalized tonic clonic seizure lasted for 5 minutes. She had been diagnosed with Graves' disease 3 years prior to admission. She was not taking methimazole for several months. Her mental status was drowsy. Free T4 level was 2.95 ng/dl with undetectable TSH level. TSAb was 245 %. Case 3: 14-year-old boy presented with high fever and diarrhea for a week and also presented with auditory hallucination. His consciousness was unclear so that he could not even answer his name. Free T4 level was 7.65 ng/dl with undetectable TSH level. TSAb was 567 %. Case 4: 14-year-old girl was admitted with high fever, frequent vomiting, diarrhea and disturbance of consciousness. She was in a coma and very severe condition. Her vital signs were as follows: BT 39.5 °C, HR 148 /min, blood pressure undetectable. Free T4 level was 3.48 ng/dl with undetectable TSH level. TSAb was 246 %.

**Results:** All cases had neurological symptoms. Three of four patients had gastrointestinal manifestations. Graves' disease was the cause of thyrotoxicosis in all cases. The degree of hyperthyroidism was not more profound than patients with uncomplicated thyrotoxicosis. Case 1, 2 and 3 responded well with thyroid-suppressive therapy; lugol's iodine, methimazole, hydrocortisone and beta-blocker. However, case 4 was suffering from acute stroke with probable brain infarction. She was dead due to multiple organ failure on day 5 of admission.

**Conclusions:** Gastrointestinal and neurological symptoms were main manifestations before admission. Thyroid storm could lead to fatal outcome even with proper thyroid-supportive therapy.

# TREATMENT WITH VANDETANIB IN A 11 YEARS OLD BOY WITH ADVANCED MEDULLARY THYROID CARCINOMA

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**Objectives:** -

**Methods:** -

**Results:** -

**Conclusions:** Case report

An 11 year old boy had a longstanding history of hypotonia and gastrointestinal symptoms. Electromyography suggested a motor polyneuropathy. Gastrointestinal symptoms started at 3 months of age with diarrhea alternating with constipation. Since the age of 8 years he presented loose stools and incontinence, requiring diapers and home education. No definitive diagnosis was made. Before admission to our hospital a spinal and CNS MRI revealed a heterogeneous multinodular goiter (MNG) with multiple cervical and mediastinal adenomegalies. Physical exam showed a lean boy (BMI:12.5), with normal stature and marfanoid phenotype, thick eyelids and lips and multiple small whitish nodules on his tongue. Cervical examination revealed a MNG with cervical adenomegalies. TSH was 8.25 mU/l with normal thyroid hormones, negative thyroid antibodies, circulating calcitonin 58085 pg/ml (RV:0 - 46) and normal catecholamines. Cervical ultrasound showed left dominant heterogeneous nodule with increased central vascularization and microcalcifications, and 2 small right nodules with microcalcifications with multiple abnormal lymphadenopathies. FNAB was positive for medullary carcinoma (MTC) with positive wash out for calcitonin. Bone scan was negative but multiple pulmonary metastases were found on CT. Protooncogen RET mutation c.2753T>C.p.M918T was found in exon 16 confirming MEN 2B syndrome. He underwent partial thyroidectomy with left neck dissection. In the presence of a locally and distant metastatic MTC treatment with vandetanib (100 mg/day) was started. After the first month calcitonin decreased by 90%. Currently after 7 month of treatment his serum calcitonin is 9000 pg/ml. Gastrointestinal symptoms dramatically improved and allowed school reinsertion. Photosensitivity was the only adverse event and was managed with local treatment. Although with a short time of treatment, vandetanib has stabilized his illness and allowed a better quality of life.

# WHOLE EXOME SEQUENCING IN CONGENITAL HYPOTHYROIDISM HIGHLIGHTS A NOVEL PHENOTYPE WITH HYPOPLASIA IN THYROID PEROXIDASE (TPO) MUTATIONS

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**Objectives:** Primary congenital hypothyroidism (CH) affects about 1:3000 newborns worldwide and is mainly caused by defects in thyroidal development (thyroid dysgenesis, TD) or hormone synthesis. A genetic cause can be identified in less than 10% of patients with TD. Our aims were to identify novel candidate genes in TD patients, taking advantage of next-generation sequencing tools.

**Methods:** We applied whole exome sequencing (WES) in two families: a consanguineous Tunisian family (one affected child with thyroid hypoplasia) and a French family (two siblings with CH: hypoplasia and thyroid in situ). Exome enrichment was performed using the SureSelect Human All Exon V6 kit and the resulting libraries were sequenced on an Illumina HiSeq 2500. Variants were filtered according to type of variation, frequency in public and in-house databases, *in silico* prediction tools and the inheritance mode. Findings were validated by Sanger sequencing and familial segregation was performed.

**Results:** By WES we have unexpectedly identified three different variants in thyroid peroxidase (*TPO*) gene. A homozygous missense mutation (c.875C>T, p.Ser292Phe) was found in the Tunisian patient with severe thyroid hypoplasia. In the second family, the two siblings with thyroid hypoplasia and thyroid in situ were compound heterozygous (c.387delC/c.2578G>A, p.Asn129Lysfs\*80/p.Gly860Arg) for *TPO* mutations. Both mutations were previously described in patients with goitrous CH.

**Conclusions:** We report here the first cases of *TPO* mutations in patients with CH and thyroid hypoplasia. These cases highlight the importance of screening for *TPO* gene mutations not only in goitrous CH, but also in normal size or hypoplastic thyroid and broaden the clinical spectrum of described thyroid phenotypes. Finally, these findings are added to previous recent evidence for *SLC26A4* and *DUOX2* mutations, manifesting as at least two different phenotypes, dyshormonogenesis and resistance to thyrotropin phenotype.



**THYROID RECEPTOR ANTIBODY (TRAB) NEGATIVE  
MATERNAL AUTOIMMUNE THYROID DISEASE (ATD)  
ASSOCIATED WITH NEONATAL THYROTOXICOSIS: A CASE  
REPORT AND RETROSPECTIVE REVIEW**

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**Objectives:** Screening for neonatal thyrotoxicosis is based on the presence of TRAB in mothers with hyperthyroid autoimmune thyroid disease (ATD). We report a delayed diagnosis of neonatal thyrotoxicosis and findings of our retrospective case review of neonates born to mothers with Graves Disease.

**Methods:** We describe clinical and biochemical course of an infant with delayed diagnosis of neonatal thyrotoxicosis due to negative maternal TRABs, and discuss TRAB assays in this context. We conducted a retrospective case review of neonates referred to our tertiary paediatric endocrine unit between January 2008-January 2017, for risk of thyrotoxicosis secondary to maternal hyperthyroid ATD.

**Results:** The mother's hyperthyroid ATD was diagnosed on screening early in pregnancy and treated with high dose Propylthiouracil through pregnancy. Maternal TRAB were negative when assayed on eight occasions during and after pregnancy, with two different laboratories using a fully automated human TSH M22 based TRAB assay. However both baby and his mother had positive TRABs on a second generation assay used by our hospital laboratory. Following normal thyroid function tests (TFTs) on day 4 (Table) the baby presented multiple times to emergency departments with classic symptoms including being jittery, and losing weight despite voracious feeding. This however this did not prompt checking of TFTs. At five weeks he was 160gm below birth weight. At 6 weeks planned repeat TFTs revealed thyrotoxicosis, with the infant needing treatment with Lugol's iodine for a week, followed by six months of Carbimazole and thyroxine. Craniosynostosis is being monitored.

**Conclusions:** As TRAB assays have become increasingly sensitive and specific, reliance on them to direct neonatal followup has increased, as reflected in guidelines published by Van der Kaay et al in Pediatrics 2016. We also found from our retrospective case review, that no infants of TRAB negative mothers had transient thyroid disease. However, as our case demonstrates, no assay has hundred percent sensitivity. This emphasises the importance of clinical signs and history including maternal hyperthyroid disease requiring thionamide therapy during pregnancy, which should prompt close monitoring of neonates even if TRABs are negative.

PLEASE SEE TABLE IN NEXT COLUMN

	D4	D44	D52	D60	D67	D75	D82	D97	D106	D129
TSH mU/L	3.34	<0.005	<0.005	<0.005	<0.005	<0.005	0.01	0.01	0.03	0.01
fT4 pmol/L	28.7	35.2	29.8	48.9	47.2	16.8	22.6	23.4	14.6	24.9
fT3 pmol/L		16	12.5	22.4	17.9	7.5	11.9	8.6	6.6	7.5
TRAB U/mL			2					<1		
TPO U/mL			107					77		

**IN IODINE INDUCED THYROTOXICOSIS, STEROID THERAPY  
TODAY COULD KEEP THE SURGICAL KNIFE AT BAY.**

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Medicine , Columbus, OH, United States*

**Objectives:** To report a case of iodine induced thyrotoxicosis (IIT) secondary to iodine containing dietary supplement which was refractory to management with methimazole (Tapazole) therapy, however, responsive to corticosteroid therapy.

**Methods:** Case Report

**Results:** A 17 year- old- Caucasian female presented with a history of an intermittent goiter for five years, simultaneously with normal thyroid function tests (TFT's). TFT's after a 3 month history of fatigue were: TSH < 0.015 (0.4-4 µU/mL), free T4 ≥ 6 (0.7- 2.1 ng/dL) and total T3 651 (50- 200 mg/dL).Thyroid Stimulating Immunoglobulin (TSIg), anti-thyroglobulin, anti- thyroid peroxidase and TSH receptor antibodies were all negative. Despite methimazole therapy for six weeks, 0.7 mg/kg/day, hyperthyroidism proved refractory to medical management with TFT's showing: TSH< 0.015, free T4 > 6 and total T3 572. Though Thyroglobulin (ICMA) level was 1,091 (3- 34 ng/mL), uptake on Iodine- 123 thyroid scan was suppressed. Thyromegaly, gland heterogeneity without nodules were seen on thyroid ultrasound (US) while hyperemia was absent on Color Doppler Interrogation utilized for vascular flow. Complete nutritional history revealed consumption of an iodine supplement prescribed by a non- allopathic practitioner containing at least seven times the Recommended Daily Allowance (RDA) of 150 mcgs/day iodine since five years prior, contributing to the Jod- Basedow phenomenon. Urinary spot iodine and 24 hr urinary iodine were both elevated at 1615 (70- 530 mcg/g) and 861 (26- 705 mcg/L), respectively. Though surgical consult was obtained, surgery was cancelled once TFT improved with Prednisone 30 mgs initially once daily for two doses with TFT's now: TSH < 0.015, free T4 4.3 and total T3 298 with normalization of free T4 and total T3 after two weeks and normalization of urinary iodine level after three weeks of therapy.

**Conclusions:** A trial of corticosteroids should be utilized in the management of IIT which can present with similar findings to amiodarone induced thyrotoxicosis type 2 (characterized as a destructive thyroiditis) which is recalcitrant to thionamide therapy. If successful, corticosteroids may delay or prevent

surgical management thus avoiding possible complications with the latter approach.

P3-1735

#### A CASE OF THYROGLOBULIN MUTATION IN CONGENITAL HYPOTHYROIDISM CONFIRMED BY DIAGNOSTIC EXOME SEQUENCING

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**Objectives:** Congenital hypothyroidism can be caused by various etiologies which include thyroid gland dysgenesis or dyshormonogenesis. Mutation of the gene thyroglobulin resulting in defects of thyroglobulin (Tg) synthesis can be characterized by goitrous congenital hypothyroidism and absent or low levels of thyroglobulin.

**Methods:** Sanger sequencing of gene TSHR (TSH receptor) and diagnostic exome sequencing of 23 genes associated with congenital hypothyroidism were performed.

**Results:** The male newborn was brought to the hospital due to the elevated TSH level on newborn screening test. Initial thyroid function test showed that 3.17 ng/dL of total triiodothyronine, 0.228 ng/dL of free thyroxine, and more than 100 mIU/L of TSH. Serum level of thyroglobulin was 5.53 ng/mL without thyroglobulin antibody, Thyroid sonography revealed diffuse parenchymal disease of both thyroid gland, highly suggestive of thyroiditis.

After the thyroid hormone replacement, serum levels of thyroxine, triiodothyronine, and TSH became normalized and thyroglobulin level was less than 1 ng/mL.

Initial DNA sequencing of gene TSHR (TSH receptor) showed no mutation. We performed diagnostic exome sequencing of 23 genes associated with congenital hypothyroidism which revealed Tg gene mutation of p.Cys1264Arg (in exon 17) and p.Gln1353\* (in exon 19). Family study showed maternal Tg mutation of p.Cys1264Arg and paternal Tg mutation of p.Gln1353\*. Mutation of Tg with p.Gln1353\* seems to be novel.

Now he is taking synthroid of 75 ug daily. His intelligence is good with weight of 22.2kg (75-90 percentile) and height of 117.8 cm (90-95 percentile).

**Conclusions:** Here we report a case of congenital hypothyroidism caused by novel mutation of the gene thyroglobulin in a 5 year and 5 month old boy who has been taking thyroid hormone since the age of 16 days.

P3-1736

#### THYROID PROFILE IN INFANTS WITH NUTRITIONAL MARASMUS

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**Objectives:** Nutritional marasmus is still prevalent in developing countries. Disorders of thyroid function have been reported in patients with marasmus.

The objective of the present study is to evaluate the levels of thyroid hormones in infants diagnosed with marasmus at the time of diagnosis and after reaching a normal weight for age and sex.

**Methods:** Prospective study of patients from one to 11 months of age, diagnosed with nutritional marasmus. Plasmatic levels of thyrotropin (TSH), thyroxine (T4) and triiodothyronine (T3) were determined at the time of diagnosis and after reaching normal weight for age and sex, when properly fed.

**Results:** We studied 47 patients with nutritional marasmus; 41 (87% of the total) had altered thyroid function at the time of diagnosis: In 29 (71% of those affected), there were low T3 values, with T4 levels being normal; 12 (29%) showed low values of T3 and T4. TSH levels were normal in this group of patients.

Values of T3 and T4 were normalized when patients reached a weight adequate for age and sex.

**Conclusions:** The alterations of the thyroid function observed in infants with nutritional marasmus (the decrease in T3 and T4 levels were evidenced), do not require replacement therapy with thyroid hormone, since once the patients reach the adequate weight for the age and sex, the thyroid profile normalizes.

P3-1737

#### THYROID AUTOIMMUNITY IN PEDIATRIC PATIENTS WITH CHRONIC IDIOPATHIC URTICARIA

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**Objectives:** The term Chronic Idiopathic Urticaria (CIU) applies when the cause of urticaria remains unknown; this is the case in 75% of patients with urticaria. Some patients with CIU have serological features of thyroid autoimmunity. The aim of the present study is to investigate thyroid autoimmunity in pediatric patients diagnosed with chronic urticaria.

**Methods:** A prospective study of patients younger than 15 years of age with a diagnosis of CIU, in which the values of TgAb (thyroglobulin antibodies), TPOAb (thyroperoxidase antibodies), TSHRab (antibodies against TSH receptor), triiodothyronine (T3), thyroxine (T4) and TSH (thyrotropin) were determined.

**Results:** We studied 21 patients with CIU. Nine (42.9% of the total) presented thyroid autoimmunity: Six (28.6%) had elevated TPOAb and in three (14.3% of the total) high TgAb and TPOAb values were found. Subclinical hypothyroidism (elevated levels of TSH with normal T3 and T4 values) was diagnosed in four patients (19%).

**Conclusions:** Thyroid autoimmunity was evidenced in several patients with CIU; subclinical hypothyroidism was diagnosed in some cases.

We recommend the investigation of thyroid autoimmunity in patients with CIU.

P3-1738

#### THYROID FUNCTION AND STRUCTURE IMPROVE AFTER WEIGHT LOSS IN OBESE CHILDREN

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**Objectives:** Thyroid function and structure are often altered in obese subjects. A raised TSH together with a thyroid echographic pattern resembling that of Hashimoto's thyroiditis have been described. The real cause is not known although the inflammatory status might play a role. The aim of this study was to verify whether the alterations in function and structure may improve after weight loss and to evaluate the role played by inflammation.

**Methods:** We evaluated 44 subjects (22m, 22f) at baseline and after 1 year of dieting and life style changes. Seven subjects who did not lose weight and one with anti-thyroid antibodies were excluded. The data available for the final analysis were therefore from 36 children (17m, 19f). We evaluated: i) clinical characteristics [BMI SDS, tricipital (TS) and subscapular (SS) skinfolds, % fat mass (FM), % fat free mass (FFM), systolic (sBP) and diastolic blood (dBP) pressure, waist/hip ratio(W/H)], ii) inflammatory markers [total leucocytes and the subtypes, the neutrophil:lymphocyte ratio, HR-C-reactive protein (HR-PCR)], iii) thyroid function (fT4, TSH) and thyroid structure (thyroid score, grade 1 to 5; grade 5=max inflammation)

**Results:** After one year, BMI SDS decreased significantly ( $2.31 \pm 0.5$  vs  $1.98 \pm 0.6$ ;  $p < 0.001$ ) as well as TS ( $27.1 \pm 4.9$  vs  $23.5 \pm 3.9$  mm;  $p < 0.001$ ), SS ( $23.6 \pm 4.2$  vs  $21.6 \pm 4.8$  mm;  $p < 0.01$ ), TS+SS ( $50.7 \pm 8.3$  vs  $45.1 \pm 8.1$  mm;  $p < 0.001$ ), %FM ( $36.3 \pm 6.3$  vs  $34.2 \pm 6.8$ ;  $p < 0.05$ ), W/H ( $0.67 \pm 0.06$  vs  $0.63 \pm 0.06$ ;  $p < 0.001$ ), systolic BP ( $106 \pm 16.4$  vs  $99.5 \pm 11.6$  mm/Hg), diastolic BP ( $63.6 \pm 11.5$  vs  $59.3 \pm 6.2$  mm/Hg;  $p < 0.05$ ), while %FFM increased significantly ( $63.7 \pm 6.3$  vs  $65.8 \pm 8.8$ ;  $p < 0.05$ ). HR-PCR decreased significantly ( $3.1 \pm 0.9$  vs  $2.6 \pm 1.1$  mg/dl;  $p < 0.01$ ) while the other inflammatory parameters did not change. fT4 remained stable, while TSH decreased significantly ( $3.83 \pm 2.1$  vs  $3.03 \pm 1.0$  mU/L;  $p < 0.05$ ) as well as the thyroid score ( $1.79 \pm 1.0$  vs  $0.76 \pm 0.9$ ;  $p < 0.0001$ ). Multiple regression analysis showed that the degree of BMI SDS reduction was the most important factor influencing the improvement in the thyroid score ( $R^2 = 0.39$ ;  $\beta = 0.62$ ;  $p < 0.001$ ).

**Conclusions:** Fat excess is the most important factor negatively influencing the function and the structure of the

thyroid. A significant improvement of both parameters following weight reduction supported this assumption.

P3-1739

#### REFERENCE INTERVALS FOR THYROID STIMULATING HORMONE AND FREE THYROXINE FOR KOREAN TEENAGERS: BASED ON KOREA NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY 2013 TO 2015

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**Objectives:** This study aimed to establish the reference range of serum thyroid stimulating hormone (TSH) and free T4 (fT4) in Korean children and adolescents. We also evaluate the association of TSH and fT4 level according to age, sex, thyroid peroxidase antibodies (TPOAb), obesity, and socioeconomic status (SES).

**Methods:** We analyzed data from 1,021 subjects (537 male) aged 10 to 19 who underwent thyroid function test including TPOAb in the Korea National Health and Nutrition Examination Survey VI (2013-2015).

**Results:** The reference interval of serum TSH and fT4 were 0.70 to 7.03 mIU/L and 1.00 to 1.63 ng/mL. Based on these references, the prevalence of subclinical hypothyroidism was 1.27%. Positive TPOAb were found in 2.7% of subjects (males 1.9%, females 3.7%). TSH is negatively correlated with age. Free T4 is positively correlated with age only in male. Thus, fT4 was higher in male than female. There were no significant differences of TSH and fT4 levels according to obesity status, SES and positive TPOAb status. Only, subject in 4<sup>th</sup> quartiles (UI/Cr > 595 µg/g) showed higher mean TSH than others.

**Conclusions:** The serum TSH and fT4 reference levels in the Korean teenagers based on healthy population were established. This study provides important baseline information for understanding patterns of thyroid dysfunction in children and adolescents.

P3-1740

#### INCIDENCE RATE OF CONGENITAL HYPOTHYROIDISM IN NOTRE DAME DE SECOURS UNIVERSITY HOSPITAL - BYBLOS - LEBANON

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**Objectives:** Congenital hypothyroidism (CH), occurring approximately 1/2000 to 1/4000 newborns, is one of the most common preventable causes of mental retardation. The aim of the study is to determine the incidence of CH in our hospital and some characteristic factors of the disease (sex,

preterm delivery, length and weight at birth, head circumference, maternal age, and consanguinity).

**Methods:** A total of 8364 newborns were screened by measuring newborn TSH, over a period extending between January 2009 and December 2015. The applied technique is based on measuring venous blood TSH which is different from using blood spots. The sample included every newborn having a TSH level at birth  $>20\text{mIU/L}$ . Since birth, the newborns' detailed medical records were followed upon and analyzed using SPSS 22.

**Results:** Out of 8364 screening tests done, the number of newborns having  $\text{TSH}>20\text{mIU/L}$  was 669. When TSH was repeated, 636 patients presented a normal level while 33 children were diagnosed with congenital hypothyroidism (15 boys and 18 girls), giving an incidence of 33: 8364 (1: 253) which is uncommonly high. As for the characteristics, we noted a significant association between CH and the age of the mother (p-value 0.03), newborn weight (p-value 0.04), and gestational age (p-value 0.01). The other variables studied (sex, length at birth, head circumference, consanguinity of the parents), were not associated with CH. It is important to mention that 36 mothers out of 631 gave birth to 74 children having all  $\text{TSH}>20\text{mIU/L}$  at birth. Therefore, giving birth to a child with  $\text{TSH}>20\text{mIU/L}$  may affect the probability for the same mother to have another offspring with  $\text{TSH}>20\text{mIU/L}$  (to be studied in further researches).

**Conclusions:** The incidence of congenital hypothyroidism is about 1/253 in NDS Hospital-Byblos. The risk of having a baby with CH increases with increasing maternal age. Whereas, the risk of the disease decreases when the weight of the newborn increases [OR=0.8 (0.6-0.9)] and decreases when the gestational age is  $\geq 37$  weeks [OR=0.3 (0.1-0.7)]. The use of venous TSH gives a rapid result, thus allowing faster treatment initiation.

P3-1741

#### CONSUMPTIVE HYPOTHYROIDISM CAUSED BY HEPATIC HEMANGIOENDOTHELIOMA: A RARE CASE REPORT

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**Objectives:** consumptive hypothyroidism caused by Hepatic Hemangioendothelioma(HHE)was rare reported in the Worldwide.This is the first report in China. This report investigate the diagnosis and treatment of the Consumptive Hypothyroidism due to HHE.

**Methods:** Review literature and retrospective analysis the data of a case with Consumptive Hypothyroidism due to HHE admitted in our hospital.

**Results:** A male infant born at 38+4 weeks gestation was admitted at the age of two months with pneumonia. The patient's neonatal screening is normal.On routine examination,he had a distended abdomen with11.5 cm of hepatomegaly. Enhanced computed tomography scan of the abdomen showed an enlarged liver containing multiple lesions consistent with hemangioendotheliomata.Full blood count, clotting profile and live

r enzymes were all normal with the exception of thyroid dysfunction.Following the resolution of his pneumonia, he was received the interventional therapy with tumor blood supply artery.But the intractable serious Hypothyroidism was persistence. Although L-

T4 dose was increased to  $200\mu\text{g/day}$ , TSH was not suppressed and free T3 level remained low. Thyroid dysfunction was thought to be due to type 3 iodothyronine deiodinase activity expressed by HHE. L-

T4 therapy was changed to thyroxine tablet, which includes both T4 and T3, in doses of 480mg per day, and euthyroidism was attained within 2 months. Thyroid function course over the period of hospitalization showed in figure 2.3 months later , Repeat CT and ultrasonographic examinations showed that the hemangioendotheliomas shrank in size. Thyroid hormone requirement was reduced and treatment was discontinued after regression of the HHE. At the most recent visit, the patient was 3years old and off treatment. His growth and neurological development were normal for age and he was euthyroid.

**Conclusions:** The pathophysiology of this condition can be summarized as an increased type 3 iodothyronine deiodinase activity and catalysis of the conversion of thyroxine (T4) to reverse triiodothyronine (rT3), and of T3 to diiodothyronine (T2) by this enzyme. Hypothyroidism develops when the rate of inactivation of thyroid hormones surpasses the rate of their production, and this phenomenon is known as "consumption hypothyroidism".

#### POSTER SESSION 3

Saturday, September 16, 2017, 12:00-1:00pm

##### P3 - Type 1 diabetes

P3-1800 – P3-1849

P3-1800

#### THE LEVEL OF STRESS AMONG PARENTS OF DIABETIC CHILDREN IN SAUDI ARABIA

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**Objectives:** Parenting children with Type 1 diabetes (T1D) creates a sense of burden in the parents' minds especially when they struggle with their children's management. This raises the level of stress and may further adversely affect children's diabetes control. Our study aimed to assess the different levels of stress parents experience in caring for children with Type 1 diabetes.

**Methods:** The study was conducted at King Abdullah Specialized Children's Hospital and the diabetes center of King Salman Hospital, Riyadh, Saudi Arabia, between February and May 2015. This study used a validated Pediatric Inventory for Parents (PIP) questionnaire. The instrument was translated into Arabic using internationally accepted guidelines. Parents were interviewed using two 5-point Likert scales and rated for the frequency and perceived difficulties and stressful events they face while caring for their sick children.

**Results:** The study included 390 parents. The total frequency (Mean 64.9/210, SD 7.529) and the total difficulty (Mean 65.3/210, SD 9.448) indices of parental stress were compared with variables of suspected association with stress. Of these, the frequency of hypoglycemia, father's level of education and occupation, marital status, HBA1C were associated with increased level of stress (P value < 0.05). Comparatively, the total difficulty index correlated with marital status, occupation of father, number of children, the mother and father levels of education and HBA1C (P value < 0.05). The level of stress correlates with the level of HBA1C. It is increased in couples that were separated and reduced in employed parents.

**Conclusions:** Parents' of T1D children in Riyadh experience a considerable level of stress emphasizing the importance of addressing these issues thoroughly during routine clinic visits.

P3-1801

#### INTEREST AND ACCEPTABILITY OF DIVE (DIABETES VIRTUAL EDUCATION), A SERIOUS GAME DEDICATED TO DIABETES EDUCATION.

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**Objectives:** The use of serious video games as educational support appears suitable for diabetes education in children and adolescent and interesting to respond to the increase in TPE needs in T1D. DiVE is a serious game that brings knowledge to paediatric patients thanks to video, games and simulation in a numeric environment. Patients can also express their experience thanks to a moderated social network.

**Methods:** Pilot study (11 weeks) to evaluate interest, playability and acceptability of DiVE as a support for diabetes education. Patients recruited in 11 paediatric centres. Data recorded: number of connections, total time of connection, percentage of success in assessment quizz included in the game. Patients were asked to complete a satisfaction survey at the end of the study.

**Results:** 33 patients have logged on to the game at least 3 times. B/G: 51/49% - Median Age 12.5 years (9.5 to 18). 21 satisfaction survey completed. 425 recorded connexions (309 in the first month, 83 in the second, 33 in the third) an average of 6 connexions per day. Progress through the game ranged from 2 to 76%, most of the patients completed at least 20% of the levels. Total connexion time was 5 days 2 hours and 43 minutes. Percentage of success in assessment quizz ranged from 49 to 67%. 75% of the patients liked the game graphics and 66% found it easy to use. 80% found the content interesting and it brought a better understanding of the disease to 70% of the participants. 80% enjoyed videos and cartoons graphics and content. The level of difficulty was adapted for 92%. 53% said that the game has helped them to better understand their blood glucose changes and 81% reported the social network to be helpful.

**Conclusions:** DiVE can be used as a support for diabetes education in children and adolescents to provide knowledge and to promote self-administered care. This pilot study also showed use that the number of level must be reduced and the content of some educative videos further simplified. The in game training program should be less linear to allow a direct access to all the educative content. A moderation of the virtual community created by the game is also critical to sustain patients' interest and to allow them to share their experience of the disease.

P3-1802

#### PATIENT -PHYSICIAN TELEVISITS FROM HOME ARE FEASIBLE AND WELL ACCEPTED BY "TECH SAVVY" PATIENTS WITH T1DM AND THEIR FAMILIES

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**Objectives:** Management of T1DM requires frequent adjustments to the insulin regimen to meet the changing needs of the children and young adults. Video consultations by endocrinologists to support pediatricians, diabetes educators, and school nurses have been proposed to alleviate the travel burden for patients living far from a diabetes center. We aimed to evaluate the feasibility and patient satisfaction with direct patient – endocrinologist televisits from home replacing three of four clinic visits a year.

**Methods:** A 1-year prospective descriptive pilot study was performed in English speaking patients with T1DM, who were capable of providing glycemic data electronically and connecting via Vidyo on-line from home. Evening hours for televisits were offered. Patients with A1c >12%, history of <sup>3</sup> 2 DKA admissions in the past 2 years, and pregnant females were excluded. Protocol included 2 clinic visits; one at baseline and one at study completion, and 3 quarterly televisits. Treatment satisfaction surveys, DTSQ status and

change (Bradley et al 2007) were administered to patients and/or parents.

**Results:** Ten patients (7 males) were recruited: 1 child (9y), 5 adolescents (13-18y), and 4 young adults (18-21y); all Caucasian; nine had private insurances; nine had parents with college education or were in college themselves. The average distance to clinic was 44 mi. Three patients dropped out, all young adults. Average A1c (+/-SD) was 7.4(+/- 0.5)% at baseline and 7.5(+/-0.5)% at the end of the study. No DKA admissions were documented, but one hypoglycemic seizure. Length of the televisits averaged 34 min. Patients' and parents' average DTSQ status scores (+/-SD) were 48.4 (+/- 3.8) out of 60 and 57.4 (+/- 6.3) out of 72 and improved with the intervention: average DTSQ change scores (+/-SD) were +11.4 (+/- 5.9) out of -/+ 30 and +13.2 (+/- 8.0) out of -/+36 respectively.

**Conclusions:** Televisits performed directly with an endocrinologist from home in combination with a yearly clinic visit are feasible and very well accepted by "tech savvy" patients with T1DM and their parents. Televisits should be considered and reimbursed as an option in pediatric diabetes care.

P3-1803

**ANALYSIS OF GLYCEMIC VARIABILITY AND HYPOGLYCEMIA USING A CONTINUOUS SUBCUTANEOUS GLUCOSE MONITOR (CGMS) IN PATIENTS WITH TYPE 1 DIABETES MELLITUS LESS THAN 15 YEARS OLD CONTROLLED AT THE HOSPITAL NACIONAL DE NIÑOS "DR. CARLOS SÁENZ HERRERA " IN THE PERIOD FROM AUGUST 1, 2013 TO AUGUST 31, 2015; SAN JOSÉ, COSTA RICA.**

*Fred Cavallo-Aita, MD, Caja Costarricense del Seguro Social, San José, Costa Rica; Pablo Aguilar-Morales, MD; Roberto Bogarín-Solano, MD; Orlando Jaramillo-Lines, MD; Erick Richmond-Padilla, MD, Caja Costarricense Seguro Social, San José, Costa Rica*

**Objectives:** The Diabetes Control and Complications Trial (DCCT) has shown metabolic improvement with intensive insulin therapy; meanwhile, complications such as hypoglycemia are more frequent. Glycemic variability is also a concern that's increasingly related to micro and macrovascular complications. The use of insulin pumps (CSII) associated with CGMS has shown a reduction in the incidence of hypoglycemia in comparison to multiple dose insulin regimen. Few centers worldwide conduct variability and hypoglycemia studies using CGMS in diabetic patients without a CSII. This is the first study of this type in our country.

**Methods:** This is an observational retrospective study with patients 15 years old or less diagnosed with type 1 diabetes mellitus, with multiple daily insulin injections and an ambulatory CGMS done. Data of glycosylated hemoglobin, number of diurnal, nocturnal and severe hypoglycemia, variability index, treatment and recognition of hypoglycemia symptoms prior to placement of Medtronic iPro2 was gathered. Same variables were obtained 1 and 3 months later after the CGMS and treatment modifications.

**Results:** A total of 33 patients were studied, 18 male and 15 female (54.5% and 45.4%, respectively). Once the CGMS analysis was performed, the average of the glycemic excursions was 25.7 episodes, the mean MAGE obtained in the patients was 235.8 mg/dL, and the patient's MODD was 80.2 mg/dL. The number of diurnal hypoglycemia in a week was significantly lower after the CGMS and treatment adjustment (mean basal 5.52, after 1 month 3.79 and after 3 months 3.03,  $p < 0.0001$ ). Similarly was the comparison between mean number of episodes of nocturnal hypoglycemia (basal 1.33, after 1 month 0.82 and after 3 months 0.33,  $p < 0.0001$ ). A higher dose of insulin (basal mean dose 0.85 U/kg/day, SD 0.37, versus 0.93 U/kg/day, SD 0.38,  $p < 0.0001$ ) and a lower HbA1c value (basal 8.02%, SD 1.24 versus 7.76%, SD 0.96,  $p < 0.0001$ ) was observed in the same period.

**Conclusions:** We have a high glycemic variability in some patients with type 1 diabetes mellitus and multiple dose insulin regimen. The use of CGMS generates benefits in the reduction of diurnal, episodes of severe and nocturnal hypoglycemia, with improvement in the reduction of HbA1c.

P3-1804

**TARGETING CELLULAR CALCIUM HOMEOSTASIS TO PREVENT CYTOKINE-MEDIATED BETA CELL DEATH**

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**Objectives:** Cytokine-mediated beta cell loss is a major pathogenic component of type 1 diabetes. Although endoplasmic reticulum (ER) calcium depletion is known to play a role in cytokine-mediated beta cell death, currently there are no treatments targeting ER calcium homeostasis to delay the progression of type 1 diabetes. The following study was designed to determine if pharmacologic modulation of cellular calcium levels could ameliorate cytokine and ER stress-mediated beta cell death.

**Methods:** INS1-E rat insulinoma cells were pre-treated with calcium-modulating compounds (dantrolene, sitagliptin, pioglitazone, and verapamil) and then exposed to cytokines (IL1- $\beta$  and IFN- $\gamma$ ) or thapsigargin (a direct ER calcium depleting agent which inhibits the sarcoendoplasmic reticulum pump Ca2+ ATPase). Experiments were then performed analyzing cytosolic and ER calcium levels, ER stress levels, SERCA activity, and apoptosis.

**Results:** Of the calcium-modulating compounds studied the ryanodine receptor blocker dantrolene and the dipeptidyl peptidase IV (DPPIV) inhibitor sitagliptin both prevented activation of the calcium dependent pro-apoptotic protease calpain and significantly reduced cytokine and ER stress related beta cell death. In addition sitagliptin was shown to

prevent cytokine mediated inhibition of SERCA activity restoring functional ER calcium release in beta cells.

**Conclusions:** Our results confirm that ER calcium depletion followed by an increase in cytoplasmic calcium levels is essential in cytokine-mediated beta cell death. In addition, our findings indicate that ER and cytoplasmic calcium stabilizers can prevent cytokine and ER stress mediated beta cell death and may present novel therapies to prevent beta cell death in type 1 diabetes.

P3-1805

#### **FACTITIOUS HYPOGLYCEMIA IN CHILDREN AND ADOLESCENTS WITH DIABETES: TRICKS OF THE TRADE**

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**Objectives:** Factitious hypoglycemia is a condition of self-induced hypoglycemia due to surreptitious administration of insulin or oral hypoglycemic agents. In adults, it is an uncommon, but well known clinical entity observed in individuals with and without diabetes. We describe one case and analyzed the existing literature on factitious hypoglycemia to identify common characteristics of affected children and adolescents, report diagnostic pitfalls, and to examine whether information on long-term outcomes exists.

**Methods:** Our case of an adolescent with type 1 diabetes (T1D) with self-induced hypoglycemia of several years duration highlighted 2 diagnostic pitfalls: 1) use of highly specific insulin assays masked the presence of exogenous insulin, i.e. assay results reported no/low insulin concentrations at times when exogenous insulin caused hypoglycemia, 2) administration of exogenous insulin via the priming function of the patient's insulin pump was not recognized because insulin used for priming is not included in the display of daily insulin doses. The systematic literature review was conducted in PubMed, Google Scholar, Embase, and Web of Science using the terms "factitious", "surreptitious", "Münchausen", "pediatric diabetes", and "hypoglycemia." We extracted information on presentation, age, gender, blood glucose control, other medical conditions present, and follow up.

**Results:** 83 articles were identified of which 14 met the inclusion criteria (describing 39 cases). All but one individual had T1D and the majority was female (63%). Average age was  $13.5 \pm 2.0$  years with the youngest patient presenting at age 9.5 years. Blood glucose control was poor (HbA1c  $12.1 \pm 4.0\%$ ). In 35% of cases reviewed, psychiatric disorders were mentioned as contributing factors. Only three reports provided follow up beyond six months.

**Conclusions:** Factitious hypoglycemia typically occurs in adolescent females with T1D of long duration. Awareness of this differential diagnosis and knowledge of diagnostic pitfalls may facilitate future diagnoses. Little information exists on effective treatments and long-term outcome.

P3-1806

#### **PSYCHOMETRIC ANALYSIS USING CHILD BEHAVIOR CHECKLIST (CBCL) IN TYPE 1 DIABETIC TURKISH CHILDREN FROM TWO DISTINCT DEMOGRAPHIC AND GEOGRAPHICAL REGIONS**

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**Objectives:** Diabetic children need an individualized self-management plan that includes insulin regimen, self blood glucose monitoring, physical activity and a healthy diet which may bring a significant psycho-social and emotional burden. In present study we investigate the psycho-social status and mental health of pediatric T1DM patients and evaluate its impact on glycaemic control.

**Methods:** Study included 98 pediatric T1DM patients followed in paediatric endocrinology clinics from Diyarbakir (DDG, n=50), an eastern city and Antalya (ADG, n=48) a western city, and 43 healthy controls from Diyarbakir (DCG, n=20) and Antalya (ACG, n=23). Data for T1DM patients' characteristics extracted from their hospital records. Emotional and behavioral problems were evaluated using Turkish version of The Child Behavior Checklist (CBCL) 4-18. In children, depression was rated using The Children's Depression Inventory (CDI). A higher CDI score suggested as higher depressive state. Data obtained from T1DM patients were compared to those of age&sex matched healthy controls from both cities. To evaluate the relationship between psychological status of patients and its relationship with glycaemic control, we assessed the HbA1c levels and duration for diabetes onset.

**Results:** Patients from the DDG had a longer duration of diabetes compared to those of the ADG group, while, HbA1c levels were not statistically different (Table 1). Comparison of T1DM patients and controls revealed no statistically significant difference in neither CBCL nor CDI scores. CBCL and CDI scores were significantly higher in DDG compared to ADG, DCG and ACG, whereas, there was no statistically significant difference between ADG vs. Controls vs. DCG vs. ACG (Table 1). Correlation analysis revealed a negative impact of the duration of T1DM on both CBCL and CDI scores. HbA1c was not found related to the test scores.

**Conclusions:** T1DM had brought much more psycho-social burden into patients from Diyarbakir, an eastern city, compared to controls and T1DM patients from Antalya, a western city. Better scores detected in the ADG may related



shorter duration of the diabetes or discrepancies in regional and/or familial socio-demographic features. To further elucidate this discrepancy larger scale studies required.

Table 1. Clinical characteristics, CBCL and CDI scores of pediatric T1DM patients and healthy controls from Diyarbakir and Antalya cities

	DDG (n=50)	ADG (n=48)	DCG (n=20)	ACG (23)	P value
Age (year)	12.1±3.4	11.5±2.8	12.2±4.4	12.6±2.7	0.589
Gender (F/M)	32/18	26/22	10/10	12/11	0.622
Diabetes duration (year)	6.2±2.5	2.9±1.2			0.000
HbA1c(%)	10.4±2.9	9.5±2.6			0.115
Childhood Depression Inventory score	9.4±4.3	6.9±4.1	8.2±5.9	9.4±4.8	0.000
Internalization score	0.47±0.27	0.20±0.23	0.28±0.21	0.34±0.29	0.000
Externalization score	0.37±0.22	0.20±0.25	0.24±0.17	0.27±0.26	0.001

DDG: Diyarbakir Diabetes Group, ADG: Antalya Diabetes Group, DCG: Diyarbakir Control Group, ACG: Antalya Control Group

P3-1807

IDENTIFICATION OF MONO TO OLIGOGENIC FORMS OF DIABETES IN SWITZERLAND USING A SINGLE TEST

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**Objectives:** Monogenic diabetes is a heterogeneous group of metabolic disorders due to a single gene defect. The majority of patients still remain undiagnosed, because of lack of access to genetic testing. A correct diagnosis is important for treatment optimization.

The aim of the study was to identify the etiology of diabetes in patients/families with clinical suspicion of monogenic diabetes using a single test.

**Methods:** A cohort of Swiss pediatric and adult patients with a suspected monogenic diabetes, including NDM, autoantibody negative type 1 diabetes mellitus, type 2 diabetes mellitus diagnosed before the age of forty-five years without metabolic features and syndromic diabetes were asked to participate in the study. The analyses were performed by a targeted next-generation sequencing (NGS) assay sequencing over 300 potential diabetes genes using the Haloplex technology. All the identified variants were confirmed by Sanger sequencing.

**Results:** So far we have analyzed 224 Swiss diabetic probands by NGS. At diabetes onset the mean age was 27.5 ± 15 years (mean ± SD), HbA1c 67 ± 30 mmol/mol and 74 patients (33%) were < 18 years old.

We identified 185/224 (83%) patients with at least one mutation/variant in the selected 323 genes. Eighty patients (36%) presented at least one mutation/variant in one of the 13 putative MODY genes. Variants in the GCK gene were the most frequent and present in 47/224 (21%) patients. Variants

in HNF1A gene were identified in 15/224 (7%) of the patients. Among patients with a GCK mutation 3/47 (9%) were positive for another MODY gene mutation/variant (ABCC8, BLK, HNF1A, NEUROD1) and 22 different mutations of GCK could be identified.

Eight of the GCK (17%) patients were unnecessarily treated with an oral glucose-lowering agent and 5 (10%) with insulin.

**Conclusions:** This study shows that monogenic diabetes was diagnosed in 34% of the Swiss cohort and 2% had oligogenic diabetes involving more than one MODY gene mutation/variant. GCK diabetes was identified in 21% of the patients.

Using the targeted NGS as a clinical diagnostic test could clearly improve the identification of monogenic and oligogenic diabetes.

P3-1808

TELEHEALTH REMOTE PATIENT MONITORING: AN EFFECTIVE TOOL FOR IMPROVING OUTCOMES IN CHILDREN WITH POORLY CONTROLLED DIABETES

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**Objectives:** To explore the effectiveness of Telehealth remote patient monitoring (RPM) in decreasing HbA<sub>1c</sub> and diabetes related emergency room (ER) visits and/or hospitalizations in children with poorly controlled diabetes.

**Methods:** Mississippi Medicaid provides coverage for telehealth RPM for patients who have had 2 or more ER visits or hospital admissions for diabetes related illnesses within the past 12 months. Using this criterion, a total of 36 patients with diabetes were enrolled over a period of 12 months. Each patient received a kit, which included an iPad along with a linking blood glucose meter and test strips. The telehealth nursing staff was able to see the patient’s glucose readings in real time as they monitored. Nurses provided patients and caregivers rapid feedback regarding RPM data, self-care advice, education by telephone, text messaging or face-time video chat through the iPad, in addition to timely follow up with the diabetes team. Patients received daily education modules and were reminded to take their insulin injections as scheduled.

**Results:** All but one patient had type 1 diabetes, 33 were on multiple daily insulin injections and 3 were on insulin pump therapy. The median age was 14 years (range 5 to 18). A total of 23 patients stayed in the program for 3 months or more. At the time of analysis, the duration of enrollment ranged from 11 days to 12.6 months, with mean duration being 5.2 months. Sixteen patients (44.4%) have experienced an average decrease in HbA<sub>1c</sub> of 1%; eight patients (22.2%) had an increase and 12 (33.3%) exhibited no change thus far. The hospital encounter frequency decreased from 2.6 to 0.7 visits per patient per year. Patients dropped out due to various reasons: poor connectivity(4), patient perceived intrusiveness (5), equipment malfunction (1), and insurance denial/lapse of

insurance (3). Majority (92%) of the patients enrolled were covered by Medicaid insurance.

**Conclusions:** Telehealth RPM can be an effective tool in improving diabetes outcomes such as decrease HbA<sub>1c</sub> and diabetes related hospital encounters over a short period of time resulting in significant cost savings.

P3-1809

#### FREQUENCY OF ISLET CELL AND ANTI-GAD ANTIBODIES IN NEWLY DIAGNOSED CHILDREN WITH TYPE 1 DIABETES MELLITUS.

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**Objectives:** To establish the frequency of islet cell and Anti-GAD antibodies in newly diagnosed Turkish children with type 1 diabetes mellitus.

**Methods:** A retrospective study was undertaken including patients who diagnosed with Type 1 diabetes mellitus in our paediatric endocrinology clinic, between June 2013 and March 2017. Data from medical carts of 134 children and adolescents (63 female) with T1DM were analysed. Median age of patients at diagnosis is 9.3 years (0.9-18.0 years). The patients was classified as positive for anti-GAD antibodies, positive for islet cell antibodies, positive for both antibodies and positive for anti-GAD or islet cell antibodies.

**Results:** Among the 134 children with type 1 diabetes mellitus, 72 (53.7%) were positive for anti-GAD antibodies, 41 (30.6%) were positive for islet cell antibodies, 25 (34.7%) were positive for both, and 88 (65.7%) were positive for anti-GAD or islet cell antibodies. There were no significant differences in median age of patients, HbA<sub>1c</sub>, C-peptide levels and sex distribution at diagnosis between groups.

**Conclusions:** Positive test results for anti-GAD and/or islet cell antibodies in patients at diagnosis with type 1 diabetes mellitus is not point out differences in clinical findings in this cohort.

P3-1810

#### VASCULAR DAMAGE IS ASSOCIATED WITH ADIPOSITY IN CHILDREN WITH TYPE 1 DIABETES

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**Objectives:** Cardiovascular disease is a major complication of type 1 diabetes (T1D) traditionally thought to manifest in adulthood. Recent evidence suggests that cardiovascular damage is present in children with T1D. We sought to investigate the effect of T1D duration and adiposity on

carotid intima media thickness (cIMT), a subclinical indicator of atherosclerosis, in children with T1D.

**Methods:** This was a cross-sectional pilot study of children aged 9 to 17 years (n=45) with T1D of short duration (6 months-2 years) or long duration (≥5 years). Glycemic control (A1C), serum HDL cholesterol (HDL), z-scores for adiposity markers (BMI; waist circumference, WC; and waist/height ratio, WHtR), systolic blood pressure (SBP) and diastolic (DBP) were collected, and relationships to T1D duration and cIMT determined. A subset of children (n=27) had 24-hr ambulatory blood pressure monitoring (ABPM) performed.

**Results:** Of the children recruited, 60% were female and 49% had T1D for a short duration. BMI z-scores were higher (p=0.059) in the long duration group 0.57 [-0.19,1.25]; median [interquartile range] compared to the short duration group 0.10 [-0.20, 0.58]. There were no differences between long and short duration groups, respectively, in age 14.9 years [12.42, 16.31] vs 13.2 [11.09, 16.15], A1C 7.8% [7.2, 8.7] vs 7.5 [6.3, 7.9], SBP z-score -0.31 [-1.05, 0.72] vs -0.16 [-0.65, 0.09] or DBP z-score -0.28 [-0.63, 0.23] vs -0.37 [-0.79, 0.11]. Adiposity markers were associated with cIMT in unadjusted models [BMI z-score (p=0.007), WC z-score (p=0.009), WHtR z-score (p=0.024)] and remained significant after adjustment for disease duration and A1C [WC z-score (p=0.009), WHtR z-score (p=0.036), BMI z-score (p=0.008)]. Disease duration and A1C were not associated with cIMT. Abnormalities in 24hr ABPM were observed in 65% of children (n=17), with no difference between groups. Notably, only 3 of these children had an abnormal single clinic BP measurement. Abnormal 24hr ABPM was not associated with cIMT or adiposity markers.

**Conclusions:** Adiposity is associated with cIMT in children with T1D, independent of disease duration and A1C. These data highlight the importance of addressing adiposity in children with T1D to prevent cardiovascular complications.

P3-1811

#### EFFECTIVENESS OF CONTINUOUS SUBCUTANEOUS INSULIN INFUSION PUMP THERAPY DURING FIVE YEARS OF TREATMENT ON METABOLIC CONTROL IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS

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**Objectives:** To determine the effect of long-term continuous subcutaneous insulin infusion therapy (CSII) on metabolic control in children and adolescents diagnosed with type 1 diabetes mellitus (T1DM) and compare it to those treated with multiple daily insulin therapy (MDI) over the same time period.

**Methods:** Fifty-two T1DM patients treated with CSII between 2004 and 2011 and monitored for at least 1 year previous to and for at least five years following CSII initiation were included in the study. Thirty-eight age matched patients in

the same age group with a 5-year follow up on multiple daily insulin therapy (MDI) were included as control group.

**Results:** Mean age of the subjects, duration of diabetes and duration of CSII therapy were 17.0±4.8 years, 10.7±2.8 years and 7.7±1.5 years respectively. Mean HbA1c in the year prior to CSII initiation was 7.3±1%, while mean HbA1c during the first year of treatment was 7±0.7%. Mean HbA1c at the end of 5 years on CSII was 7.8±1.3%. Initial and 5th-year mean HbA1C levels of subjects receiving MDI therapy were 7.9±1.08% and 8.6±1.8%. Mean HbA1c values were lower in subjects receiving CSII therapy throughout follow-up (p<0.05). The study group was sub-divided by age as follows: Group 1, 0-5 years (n=16), Group 2, 6-11 years (n=18) and Group 3, 12-18 years (n=18). HbA1c was compared between the groups and there was no significant difference during follow up. Basal and total insulin doses were significantly lower in the CSII group compared to the MDI group at all observation periods.

**Conclusions:** Although mean HbA1c values were not within accepted good metabolic control limits with CSII at the end of 5 years follow-up, it produces better HbA1c control at all time points and in all age groups compared with MDI. CSII is a more effective long-term therapy than MDI in children and adolescents with Type I DM.

P3-1812

**β-KLOTHO IN PATIENTS WITH TYPE 1 DIABETES.**

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**Objectives:** To assess the serum concentration of B Klotho in patients with T1D and determine the correlation of this hormone with duration of diabetes, metabolic control or insulin dose.

**Methods:** Children and adolescents with T1D (n:58; age: 6-18 years) and a healthy control (C) group (n:63; age:4-18 years ) was studied. Both groups were matched by age and BMI. β-Klotho levels were determined by ELISA (Cusabio,Japan). Mann-Whitney’s U test and Spearman’s correlation was used. Results are expressed as mean ±SEM.

**Results:** Both groups had similar age and height. Higher β-Klotho levels were observed in girls with T1D compared to girls in C group. A negative correlation between Klotho levels and T1D duration was observed ( r = - 0.327, p= 0.012).

\*p < 0.05 TD1 Girls vs Control Girls

	T1D Girls (29)	Control Girls (37)	T1D Boys (29)	Control Boys (26)
Age (years)	13.6±0.6	12.5±0.5	12.8±0.5	12.0±0.6
BMI (Z- Score)	0.91±0.16	0.92±0.16	0.39±0.13	0.82±0.21
B-Klotho (ng/ml)	238.0±30.9*	171.8±19.0	182.7±20.9	205.3±22.0

**Conclusions:** This is the first study that has evaluated β-Klotho serum levels in patients with T1D. Higher levels of β-Klotho in T1D girls and decreasing levels in both genders were observed. Future studies should evaluate the mechanism and consequences of elevated β-Klotho in patients with T1D.(Fondecyt 1110240 & 1170895).

P3-1813

**FREQUENCY OF GENITAL FUNGAL INFECTIONS AND ANTIFUNGAL SENSITIVITY OF FLUCONAZOLE IN CHILDREN AND ADOLESCENTS WITH T1DM**

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**Objectives:** Aim of this study is to determine the frequency of genital fungal infections and antifungal sensitivity of fluconazole in pediatric patients with type 1 diabetes mellitus (T1DM).

**Methods:** The study groups included 67 females mean age 12.7±2.9 years with T1DM and 63 non-diabetic control females mean age 11.7±3.6 years without immunodeficiency or chronic drug use. After demographic characteristics of both groups were recorded, all participants underwent genital examination with assistance of a healthcare provider. Blood and urine samples were collected; in addition, genital smear samplings were performed in all participants. Samples were evaluated bacteriologically and mycologically and fluconazole sensitivity was determined in Medical Microbiology Department of Medical Faculty, ERU. Results were compared between diabetic and control groups.

**Results:** Although genital complaints were found to be more common among diabetic patients, no significant difference was detected in culture results between diabetic and control groups. In study, fungal agents have been isolated in 55,2 % of diabetic patients and in 23.8 % of control subjects. C.glabrata was the most common strain isolated in diabetics (48.6%) while C. albicans was more common in controls (40.0%). All strains were found to be sensitive to fluconazole, as strains with native resistant being exception. When diabetic group was assessed in itself, cut-off value of for blood HbA1C level was identified as 8.9±0.5% and it is related with isolation of fungal agents grew was detected with 80% of reliability in cases with HbA1C level above the cut-off value. In terms of BMI, susceptibility to fungal infections has been also evaluated in diabetic group and there is no correlation between the fungal infection susceptibility and the BMI of diabetic patients. Patients who have been following for 1 year with T1DM diagnosis have higher risk for fungal infection.

**Conclusions:** Diabetic patients with HbA1c above 8.9% and the patients who have been following up for 1 year should be assessed for fungal infection regardless of complains. The genital smear samples should be obtained periodically during

follow-up. Fluconazole should be preferred in the treatment option due to its advantages.

P3-1814

#### PHYSICAL GROWTH AMONG CHILDREN WITH TYPE 1 DIABETES MELLITUS ON CONVENTIONAL AND INTENSIVE INSULIN THERAPY

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**Objectives:** Long term glycaemic control in children with Type 1 Diabetes Mellitus (T1DM) affects physical growth and development. Intensive insulin therapy (IIT) is shown to have better glucose control as against conventional Insulin therapy (CIT). A large proportion of children in developing countries are still on CIT due to various reasons. This study was planned to compare physical growth among children with T1DM using Conventional or Intensive insulin therapy.

**Methods:** In this cross-sectional observational study, children of either sex, 5 to 15 years old with T1DM for at least 3 years, without any co-morbidities and on either of the insulin regimens, were enrolled. Out of 154 children enrolled, 54 were on CIT, 50 on IIT and 50 were healthy controls. Weight, Height and BMI z scores were calculated using the CDC charts. Pubertal stage was assessed by Tanner's method. To see the effect of various disease-related factors on growth; HbA1c records, frequency of sugar testing, diet plan, calorie intake, previous hospitalizations, frequency of DKA etc. were recorded.

**Results:** There was significant difference in mean age at enrolment ( $12.2 \pm 3.01$  Vs  $10.81 \pm 2.98$  years;  $p = 0.00$ ) and mean duration of disease ( $5 \pm 2.02$  Vs  $3.97 \pm 1.56$  years;  $p = 0.004$ ) in CIT and IIT groups respectively. Mean age at onset of diabetes in CIT group ( $7.5 \pm 3.46$  years) was similar to IIT group ( $6.4 \pm 3.18$  years;  $p = 0.12$ ). Average HbA1c level over past 3 years in CIT group was  $9.41 \pm 1.78$  gm% and in IIT group was  $8.5 \pm 1.37$  gm% ( $p = 0.010$ ). Height for age (HAZ) and weight for age (WAZ) Z scores were higher in IIT group; HAZ of  $-0.18 \pm 1.48$  Vs  $-0.94 \pm 1.30$  ( $p = 0.007$ ) and WAZ of  $-0.35 \pm 1.34$  Vs  $-0.59 \pm 1.37$  ( $p = 0.38$ ). Mean BMI was higher in CIT group;  $18.66 \pm 3.45$  Vs  $17.25 \pm 2.43$  kg/m<sup>2</sup> ( $p = 0.019$ ). Percentage of boys who had genital stage 2 or more was higher in CIT group (77.4%) compared to IIT group (59.3%);  $p = 0.41$ . Also, there was no significant difference in proportion of girls achieving Breast stage 2 (87 Vs 83%) and menarche (83 Vs 77%) in CIT and IIT groups respectively.

**Conclusions:** In children with T1DM for at least 3 years, there was significantly higher HbA1c, higher BMI z scores and lower HAZ scores in children receiving CIT when compared to IIT. There was no significant difference in attainment of puberty in two groups.

P3-1815

#### ORAL HEALTH IN YOUNG CHILDREN WITH TYPE 1 DIABETES MELLITUS

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**Objectives:** Knowledge about the risk factors for oral pathology among children with type 1 diabetes mellitus (T1DM) is essential for establishing appropriate preventive and therapeutic strategies. We compared the oral health of youngsters with T1DM with that of non-diabetic children according to dietary and hygiene habits, dental caries history, gingival health, saliva secretion, saliva composition and number of mutans streptococci (MS, pathognomonic for early childhood caries) colonies in the saliva. We also examined a possible association between glycemic control and oral health among T1DM children.

**Methods:** The T1DM children were examined by pediatric dentists who scored their oral health status using three indices: decayed (D), missing (M) or filled (F) teeth ("DMFT" for permanent dentitions and "dmft" for primary dentitions) for caries parameters, and the plaque index (PI) and gingival index (GI) for periodontal parameters. Age-matched siblings and friends of the study children comprised the control group.

**Results:** The T1DM children ( $n = 24$ , age  $8.2 \pm 2.4$  yr) had higher MS levels, a higher prevalence of caries, and significantly higher salivary Na levels compared to the controls ( $n = 30$ , age  $6.4 \pm 2.7$  yr). Caries history, evidence of current periodontal disease, oral health-related behaviors, PI and GI findings, and other salivary parameters were similar for both groups. Glycemic control did not influence oral health status.

**Conclusions:** T1DM children may bear potential compromised oral conditions, making early identification of those at high risk essential for preventing oral complications. Salivary MS counts may be a useful tool to identify T1DM children at increased risk for developing caries.

P3-1816

#### DM1 - CLINICAL AND LABORATORIAL EVALUATION INCLUDING THE LOSS OF FOLLOW-UP ANALYSIS OF PATIENTS FROM AN UNIVERSITY CENTER

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**Objectives:** Type 1 Diabetes Mellitus is one of the most prevalent chronic diseases in the pediatric group. Objective: to describe epidemiological data, clinical characteristics, treatment scheme, control of treatment and

loss of follow-up of patients with DM-1 from a tertiary hospital.

**Methods:** It was a retrospective, descriptive study evaluating patients seen between April 2008 and July 2016.

Data were obtained from medical records.

The insulinization scheme was classified as conventional ( $\leq 3$  applications/day without correction), intensified ( $\leq 3$  applications/day with corrections) and intensive ( $\geq 4$  applications/day with corrections).

The mean of the last 3 HbA1c was considered.

The control of the disease was evaluated in those patients with more than 1 year of the disease who were consulted in the last 6 months of the period and was considered ideal (HbA1c  $< 7.5\%$ ) or inadequate (reasonable HbA1c between 7.5 and 10% and bad HbA1c  $> 10\%$ ).

**Results:** Out of 390 patients recorded in the entire period 176 were included to evaluation.

The mean HbA1c of the group was  $9.3 \pm 1.8\%$  (4.8 to 16.8) and was considered ideal for 11.3%, reasonable for 60.2% and poor for 28.5%.

There was no difference in the distribution of HbA1c means between the conventional ( $9.83 \pm 1.85$ ), intensified ( $9.65 \pm 2.19$ ) and intensive ( $9.19 \pm 1.64$ ).

Patients with HbA1c  $< 7.5\%$  used an average insulin dose lower than patients with inadequate control ( $p = 0.015$ ).

Eleven patients had chronic complications: nephropathy (7); retinopathy (2); nephropathy / retinopathy association (2).

Out of 178 patients who were no longer in follow-up, 42 had been transferred to other services.

Out of the 134 who had abandoned the follow up 48 were less than 10 years old at the last consultation.

**Conclusions:** The metabolic control was unsatisfactory for this population and there was no difference in HbA1c between the treatment schemes.

The drop-out rate was considered to be high and worried.

P3-1817

#### NEW ALGORITHM FOR MODIFICATION OF INSULINOTHERAPY DURING EXERCISE IN MDI AND INSULIN PUMP-TREATED CHILDREN WITH TYPE 1 DIABETES

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**Objectives:** To determine the influences of algorithm-based insulin adaptation on the evolution of subcutaneous glucose (SG) after a standardized aerobic exercise in children and adolescents treated with continuous subcutaneous insulin infusion (CSII) or multiple daily injection (MDI) regimen.

**Methods:** Eleven CSII- and 13 MDI-treated patients performed two 30-minute sessions of moderate to vigorous (70% of age-based maximal heart rate) exercise on a treadmill under continuous glucose monitoring (CGM). First sessions were scheduled without insulin modification (TT#1) while patients performed second sessions (TT#2) after preemptive algorithm-based insulin dose modifications.

**Results:** CSII-treated patients had their glucose control improved during TT#2 (mean of  $141 \pm 56$  mg/dL vs  $144 \pm 80$  mg/dL in TT#1;  $P < 0.05$ ) with up to 86% of SG levels within targets during 16 hours post-exercise. Contrarily, SG levels did not normalize during TT#2 in MDI-treated patients who experienced higher rates of hyperglycemia during the afternoon snack. Insulin adaptations did not modify immediate post-exercise drops in blood glucose during TT#2 in either group. As compared to TT#1, CSII-treated patients had reduced rates of hypoglycemia during 4 hours post-TT#2 (from 19.5% to 2.1%;  $P < 0.01$ ) and had shorter duration of nocturnal hypoglycemia ( $35.5 \pm 12.8$  vs  $204.7 \pm 165$  minutes;  $P = 0.04$ ) whereas in the MDI group no changes in percentages of hypoglycemia were observed during TT#2.

**Conclusions:** Our study shows the differences existing between pump and MDI-treated children and adolescents in their potential to bring glucose levels within therapeutic targets during and after aerobic exercise. Using tailored algorithmic adaptations of insulin administration, CSII users were more successful than MDI-treated patients in alleviating their rates of hyper- and hypoglycemia during most of the 24-hour periods following exercise. This advantage may partly be accounted on higher levels of precision in fine-tuning insulin adjustments under CSII therapy, as no quantitative and qualitative differences in self-monitoring and adjusted insulin dose were observed between groups.

P3-1818

#### EVALUATION OF THE IMPACT OF CARBOHYDRATE COUNTING (CHC) EDUCATION IN DIABETIC PATIENTS TREATED IN INTENSIVE INSULINIZATION SCHEME

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**Objectives:** Analysis of the relationship of the clinical-laboratorial condition of the patient before and after the diet habit change obtained through the carbohydrate count (CHC), and the knowledge previously existent and the newly learned regarding diets and the adequate treatment.

**Methods:** Analytical and prospective observational study. Sample of 11 patients with DM1 assessed regarding their knowledge in relation to the disease. Analysis of the clinical-laboratorial relationship before and after the intervention, during a 9 month period through monitoring at the Pediatric Endocrinology Ambulatory of the CHS.

**Results:** 11 patients with ages 4 to 12 were evaluated, 63.64% were male and 36.36% female. There was a 21.6% improvement of the general knowledge regarding the disease and a 15.68% reduction of the HbA1c levels after the start of the CHC and the new diet habits.

**Conclusions:** The CHC education associated with the change in diet habits have a direct influence towards the better glycometabolic control of the patients, since the general knowledge regarding DM1 after the educational intervention

and the observed parameters of the reduced HbA1c levels have improved.

P3-1819

#### **POSITIVE PARIETAL CELL ANTIBODIES IN CHILDREN WITH TYPE 1 DIABETES MELLITUS**

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**Objectives:** The objective of this study was to investigate the prevalence of parietal cell antibodies (PCA) and subsequent autoimmune gastritis (AIG) in children with Type 1 diabetes mellitus (T1DM).

**Methods:** A retrospective chart review was performed on T1DM patients who were screened for PCA in the endocrinology division from January 2009 to July 2014. Data collected included age at T1DM diagnosis, PCA positivity, and presence of other autoimmunity (thyroid, celiac, or adrenal antibodies). In those with PCA positivity, gastrin, hemoglobin, vitamin B12, and endoscopy results were also collected. Categorical data were analyzed with chi square test and continuous data with the unpaired t-test.

**Results:** 983 patients with T1DM had PCA testing performed at least once. The prevalence of PCA positivity was 5.7% (n=56). PCA positivity was associated with female sex (7.7% of females vs 3.8% of males; p=0.009), positive thyroid antibodies (15.1% with PCA, 3.6% without; p<0.005), and positive adrenal antibodies (35.3% with PCA, 5.1% without; p<0.005). The mean age at T1DM diagnosis and presence of celiac antibodies were not associated with PCA positivity. In those with PCA positivity, gastrin was elevated in 50% of the 56 with measured gastrin; anemia was present in 25% of the 52 with a CBC; vitamin B12 was normal in all 44 tested subjects. 33.9% of those with PCA had a GI referral (n=19), and of those, 68.4% had endoscopy performed (n=13). 46.2% (6/13) of those who underwent endoscopy met criteria for AIG.

**Conclusions:** The prevalence of PCA in T1DM at our institution was 5.7%, consistent with previous studies, as was the association of female sex and presence of thyroid and adrenal autoantibodies with PCA positivity. Hypergastrinemia was the most common laboratory abnormality in those with PCA positivity. Almost 50% of youth who underwent endoscopy had findings consistent with AIG. However, screening in 983 patients led to a diagnosis of AIG in only 0.6% of the patients. Future studies will need to explore whether early detection of hypergastrinemia and AIG in youth with T1DM leads to decreased morbidity from complications and thus support screening in youth with T1DM.

P3-1820

#### **POLIMORPHISMS RS2187668 AND RS7454108 IN HLA CLASS II REGION ARE STRONGLY ASSOCIATED WITH TYPE 1 DIABETES IN SOUTHERN BRAZILIAN CHILDREN**

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**Introduction.** Etiology of Type 1 Diabetes (T1D) is multifactorial with involvement of genetic and environmental factors. The human leucocyte antigen (HLA) genotype accounts for approximately 50% of the genetic susceptibility to T1D, with the haplotypes *DRB1\*03:01-DQA1\*05:01-DQB1\*02:01* and *DRB1\*04-DQA1\*03:01-DQB1\*03:02* (DR3/DR4-DQ8) associated with the highest-risk. Several studies have demonstrated the possibility to predict HLA alleles from existing single nucleotide polymorphisms (SNPs).

**Objectives.** In this case-control study, we correlated the frequency of the polymorphisms rs2187668 and rs7454108, which are associated, respectively with the alleles *DQA1\*05:01-DQB1\*02:01* and *DRB1\*03:02*, in healthy and T1D children.

**Methods:** Study group was composed by 300 children (under 12 years of age), 169 healthy controls and 131 with type 1 diabetes (n=131), that were genotyped to identify the polymorphisms rs2187668 and rs7454108 using fluorescent probes (TaqMan®, Life Technologies) in real-time polymerase chain reaction (Real Time PCR 7500fast™ System, Life Technologies). The study was approved by the institutional Ethics Committee.

**Results:** The allele frequencies (95%CI) in the groups T1D and healthy controls, respectively, were to rs2187668 T allele 33,2% (28-39) and 11,2% (8-15), p<0,001, and to rs7454108 C allele: 33,2% (28-39) e 10,1% (7-13), p<0,001. The polymorphisms were in Hardy-Weinberg equilibrium (p>0.05), except rs7454108 in T1D group (H-W; P=0.003). Analyzing the frequency of heterozygous subjects for the two polymorphisms (CT+TC), the T1D group presented 29% and the control group 2.4% (Odds ratio; OR=16.8; p<0.001). The others genotypes combinations presented minor discrimination between groups. Genotyping these two polymorphisms is a standardized, fast and low cost method compared to traditional HLA genotyping.

**Conclusions:** The polymorphisms are strongly associated with T1D, and present potential to HLA risk screening for disease in the studied Brazilian population.

### POSTPRANDIAL INFLAMMATORY MARKERS LEVELS IN TYPE 1 DIABETES MELLITUS CHILDREN AND ADOLESCENTS

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**Objectives:** Even a short term increase of postprandial glycemia promotes inflammation markers such as IL-6, TNFRI, sRAGE and IL-1 $\beta$  responsible for development of long term complications in T1DM children and adolescents. Aim of the works is defining to what extent the value of postprandial hyperglycemia affect the levels of the inflammatory markers in T1DM childre and adolescents.

**Methods:** The study involved 71 patients aged 7-17 years diagnosed with T1DM with treatment duration from 6 to 60 months. Patients with other diseases were exluded. IL-6, TNFRI, sRAGE, IL-1 $\beta$  levels were measured in the morning on fasting at blood glucose levels within 80-120 mg% range and also at 1,2,4 hours after standard meal (Nutridrink) with the use of ELISA test.

**Results:** The levels of glucoes and IL-6 were signifiantly increasing and the levels of sRAGE and TNFRI were significantly decreasing in the postprandial period. Also there were proved:

- negative correlation between the level of sRAGE and the level of glycemia in the 2 hour of the study ( $r=-0,39$ ,  $p=0,002$ )
- positive correlation between the level of IL-1 $\beta$  and the level of glycemia in the 4 hour of the study ( $r=0,24$ ,  $p=0,043$ )

In the presented work the changes in the values of glycemia and inflammatory markers between the examination in 0' and 1 hour after the meal were evaluated too. It has shown:

- negative correlation between the amplitude of the glucose levels marked in 0' and in 1hour of the study and the amplitude of IL-1 $\beta$  in the same period ( $r=-0,26$ ,  $p=0,030$ )

**Conclusions:** 1. Postprandial glycemia and postprandial differences in the glucose levels can be decisive in the creation of inflammatory process.

2. Metabolic disorders occuring within the first hour after meal sustain the inflammatory state in the sequent hours in postprandial period.

P3-1822

### NOVEL AND TRADITIONAL RISK MARKERS FOR DEVELOPMENT OF DIABETIC NEPHROPATHY (DN) IN YOUTH WITH T1D

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**Objectives:** Several studies have shown that elevated serum uric acid (SUA) levels and blood pressure (BP) are associated with development of microalbuminuria and DN in adults with T1D. In addition, renal hyperfiltration (assessed by GFR) may be the earliest hemodynamic abnormality and may be linked with an increased risk of DN. The purpose of this study was to evaluate the relationship between SUA and GFR with albuminuria and diabetes control (by HbA1c) in youth with T1D.

**Methods:** As part of an ongoing study, 98 consecutive youth with T1D who fulfilled International Society of Pediatric and Adolescent Diabetes (ISPAD) criteria for DN screening were evaluated [89% Caucasian, 49% male, mean age 15.8 $\pm$ 2.9 years, duration of T1DM 7.1 $\pm$ 3.6 years, 2-year average HbA1c: 8.1 $\pm$ 1.3%, mean systolic BP (SBP) percentile: 54 $\pm$ 24, mean diastolic BP (DBP) percentile: 69 $\pm$ 17]. Albuminuria was assessed by albumin/creatinine ratio (ACR) (median [IQ range]: 9.45 [5.5 – 20.2] mg/g). eGFR was calculated per the Cystatin-C based Zappitelli method (mean eGFR: 99.9 $\pm$ 20.8 ml/kg/1.73m<sup>2</sup>).

**Results:** SUA did not correlate with ACR ( $r=-0.057$ ,  $p=0.60$ ), age or duration of T1D. There was also no difference in mean SUA levels by quartiles of ACR (3.9 $\pm$ 1.1, 3.7 $\pm$ 0.7, 3.9 $\pm$ 0.9, 3.6 $\pm$ 1.1 mg/dl, lowest to highest quartile respectively,  $p=0.7$ ) or between those with normal vs abnormal ACR (3.8 $\pm$ 1 vs 3.6 $\pm$ 0.9 mg/dl,  $p=0.33$ ). While eGFR correlated with HbA1c ( $r=0.278$ ,  $p=0.009$ ) it only tended to correlate with ACR ( $r=0.193$ ,  $p=0.07$ ). SUA did correlate negatively with eGFR ( $r=-0.319$ ,  $p=0.002$ ), even after adjusting for gender, age and diabetes duration. eGFR correlated significantly with DBP percentile ( $R=0.26808$ ,  $p=0.01$ ), however, this was not true for SBP percentile ( $R=0.07606$ ,  $p=0.50$ ). Neither SBP or DBP percentiles correlated with ACR.

**Conclusions:** Our preliminary findings show that increased eGFR may be associated with increased ACR as well as higher HbA1c, and DBP, suggesting a potential for measuring risk of DN progression. SUA levels may not play a role until later in the course of DN. Further studies at a larger, longitudinal scale will be necessary to confirm these findings.

P3-1823

### METFORMIN LEVELS AND ADHERENCE IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES ENROLLED IN A 12 MONTH RANDOMISED CONTROLLED TRIAL

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**Objectives:** Metformin is increasingly used in addition to insulin in children with Type 1 diabetes (T1D). Metformin pharmacokinetics have not been studied in children with T1D and objective measurements of adherence are lacking. We



aimed to evaluate metformin exposure in relation to vascular function in T1D children enrolled in a randomised controlled trial (RCT).

**Methods:** Ninety T1D children (13.6±2.5 years, 41 boys, 5.5±3.8 years duration) participated in a 12 month double blind, placebo RCT investigating the effects of metformin on vascular function [ACTRN12611000148976] (Anderson J et al. BMC Pediatr 2013). Primary outcome (vascular function), secondary outcomes, metformin plasma concentrations and adherence were evaluated at baseline 3, 6 and 12 months. Metformin plasma concentrations (mg/L) were measured by ultra performance liquid chromatography - tandem mass spectrometry and the area under the curve (AUC) was calculated to determine metformin exposure per dose. Adherence was assessed by prospective electronic monitoring using Medication Event Monitoring System (MEMS) and tablet count. Adequate and optimal adherence was defined as 50-79% and ≥ 80%.

**Results:** Metformin improved vascular function by 3.3 percentage units (95%CI 0.3, 6.3, p=0.03), HbA1c decreased by 0.96% (10.5 mmol/mol) [95%CI -1.5(16.7), -0.39(4.3), p=0.001] and insulin dose was reduced by 0.2 units/kg/day (95%CI -0.26, -0.07, p=0.001). Median [IQR] metformin trough plasma concentration was 0.36[0.2-0.5]mg/L. Median [IQR] adherence by MEMS over 12 months was 75.5%[56-92]. MEMS and tablet count adherence were highly correlated (r=0.9, p<0.0001). Adherence decreased over time in both groups (p=0.003), without differences in adherence rates between groups. Median [IQR] adherence by MEMS at 3, 6 and 12 months was 88.9%[64.9-95.0], 78.8%[46.9-90.5] and 67.5%[44.4-89.1], respectively. Metformin exposure (AUC x adherence) was associated with improvement in vascular function (estimated  $\beta$  0.14, se 0.06, p=0.03) and a trend for HbA1c (estimated  $\beta$  -0.03, se 0.01, p=0.07). No relationship was seen with insulin dose (p=0.4).

**Conclusions:** Suboptimal adherence to metformin at less than 80% still provides some clinical benefits to children and adolescents with type 1 diabetes.

P3-1824

#### RATE OF PREMATUREITY IS SIMILAR AMONG PEDIATRIC TYPE 1 DIABETES MELLITUS PATIENTS AND THE GENERAL POPULATION

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Professor, Hadassah Hebrew University Medical Center, Jerusalem, Israel; Yarden Tenenbaum-Rakover, MD, Ha'Emek Medical Center and the Rappaport Faculty of Medicine, Technion, Haifa, Israel; Marianna Rachmiel, MD, Assaf Haroffeh Medical Center, Tel Aviv University, Zerifin, Israel

**Objectives:** The incidence of type 1 diabetes mellitus (T1DM) has increased in recent decades, as has the incidence of preterm births (<37 weeks). Our aim was to evaluate the association between T1DM and preterm births, especially early prematurity (<34 weeks).

**Methods:** A national cohort study, including linkage of data from 13 pediatric diabetes centers and Israeli National Registries, which contained all patients with T1DM born during 2000-2013. The studied parameters were: ethnicity, gestational age, birth season, age and season at T1DM diagnosis, and presence of autoimmunity in family. The prevalence of prematurity among T1DM was compared to the general population registry of 2000-2013.

**Results:** The study population included 1341 T1DM patients, 52.7% males, mean age was 11.27±2.25 years (1.5-15.33 years). The general non-diabetic population, included 2,046,215 subjects. No significant difference was demonstrated between the prevalence of premature birth or early premature birth in T1DM patients and the general population (9.0% vs. 7.9%, p=0.08, and 2.4% vs. 2.0%, p=0.15, respectively). No seasonality in T1DM birth was detected in preterm, as well as term-born patients. Prematurity was not associated with younger age of T1DM presentation. No difference was detected between preterm-born and term-born T1DM patients in diagnosis seasonality, birth weight, age at diagnosis and family history of autoimmune diseases.

**Conclusions:** This is the largest population based study, and the first in the Middle East geographical area, indicating that prematurity, including early prematurity, is not associated with T1DM, nor a predictor of earlier age of T1DM diagnosis.

P3-1825

#### MULTICENTRIC STUDY OF METABOLIC CONTROL IN TYPE 1 DIABETES MELLITUS WITH THE USE OF FLASH GLUCOSE MONITORING SYSTEM AND DEGREE OF SATISFACTION

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**Objectives:** Real time glucose sensors (RTGS) may improve treatment and quality of life in type 1 Diabetes Mellitus (DM1)

**Objectives:** To evaluate changes in metabolic control (HbA1c) before and after RTGS and degree of satisfaction

**Methods:** 63 DM1 patients (28M / 35F) were enrolled by 5 hospitals, age at diagnosis 6.7-3.5 years, multidose treatment 78% vs CSII 22% with RTGS more than 3 months.

Variables: Hb A1c before / after RTGS, HbA1c during RTGS related to capillary blood glucose (BG); time in hypoglycemia (<70) measured by sensor. SPSS v19.0 analysis

**Results:** Hb A1c was lower  $-p<,000-$  with RTGS ( $7,10 \pm 0,5$  vs  $7,34 \pm 0,6$ ); with a significant decrease  $-p<,000-$  in the number of capillary BG ( $2,8 \pm 1,8$  vs  $8,3 \pm 3,5$ ). The time (%) in hypoglycemia was acceptable ( $6,2 \pm 4,7\%$ ), , without episodes of severe hypoglycemia in any patient.

HbA1c was compared with variables: 1. Time in hypoglycemia (<10% vs > 10%), 2-capillary BG performed (4) during RTGS.

HbA1c values <7% are associated with increased time in hypoglycemia  $-p,003-$ . There is no relationship with the number of capillary BG performed (NS).

In relation to the Satisfaction Questionnaire (Table 1): 1 = worst score (or nothing) and 10 = best score (or much)

**Table 1**

Satisfaction Questionnaire ( RTGS)	Score 1-10
Your quality of life has changed	8,2
It's comfortable for you	9
You would recommend their use	9
Hypoglycemia has decreased	7,4
Hyperglycemia has decreased	4,2
Capillary BG agrees with ( RTGS	6,8
How do you rate the price	1,4
How do you rate the decrease in number of capillary BG	9,3
How do you rate the RTGS's glycemic trends	9,1
How do you value the possibility of frequent consultation	9,8

**Conclusions:** 1. Metabolic control is similar or better with RTGS. 2. The number of capillary BG is drastically reduced, and this decrease does not affect Hb A1c; 3-The degree of global satisfaction is high, except for the price.

P3-1826

#### ARTERIAL STIFFNESS AS MEASURE OF CARDIOVASCULAR RISK IN LEAN AND OBESE ADOLESCENTS AND ADOLESCENTS WITH TYPE 1 DIABETES

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**Objectives:** Cardiovascular disease (CVD), the major cause of death worldwide, is the end result of vascular aging and atherosclerosis, having its origins in childhood. Pediatric patients harboring classical CVD risk include obese and diabetic patients. Noninvasive methods used to evaluate vascular function include intima-media thickness (IMT) and arterial stiffness (AS) assessed with pulse wave velocity

(PWV), arterial compliance (AC) and  $\beta$ -stiffness measurements.

**Methods:** We analyzed parameters of AS in 68 obese adolescents ( $13.27 \pm 2.31$  yrs), 42 adolescents with type 1 diabetes (T1D) ( $14.95 \pm 2.35$  yrs) with T1D duration over 5 years and 38 controls ( $15.02 \pm 1.94$  yrs). AS was assessed using e-tracking ultrasound method (EchoTracking®, Aloka alfa-10). Height, weight, body mass index (BMI) and blood pressure (BP) were assessed in all patients. Lipid levels were measured in obese and T1D patients, while oral glucose-tolerance test (OGTT), insulin level and HOMA index were assessed in obese patients.

**Results:** Significant difference in AS between groups was found for AC ( $P=0,022$ ) and PWS ( $p=0.000$ ) with the lowest compliance and higher velocities found in T1D group. The IMT measurements did not show significant difference between groups. Multiple regression analysis in obese adolescents showed correlation of lower AC in females ( $p=0.041$ ) and in patients with higher systolic BP SDS ( $p=0,032$ ). In adolescents with T1D, duration of the disease was strongest independent determinant of AS for all measures (AC,  $\beta$  and PWV:  $p=0.028$ ;  $p=0.029$  and  $p=0.003$ , respectively) followed by BMI SDS which correlated with PWV and  $\beta$ -index ( $p=0.008$  and  $p=0.033$ , respectively), and HbA1c that correlated with PWV ( $p=0.048$ ). Both systolic and diastolic BP correlated with lower AC (SBP SDS  $p<0,001$ ; DBP SDS  $p=0,049$ ) and higher PWV (SBP SDS  $p=0,023$ , DBP SDS  $p=0,048$ ).

**Conclusions:** Even though obese adolescents have significantly higher body weight and BMI, lower HDL cholesterol and higher BP, early vascular damage was more pronounced in adolescents with T1D. This finding may reveal the influence of hyperglycemia and its consequences on blood vessels as a major risk for cardiovascular health.

P3-1827

#### REAL- WORLD EFFICACY AND SAFETY OF INSULIN DEGLUDEC, AN ULTRA-LONG ACTING BASAL INSULIN, IN BASAL-BOLUS TREATMENT WITH MEALTIME RAPID ACTING INSULIN IN TYPE 1 DIABETES IN INDIAN PEDIATRIC POPULATION

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**Objectives:** Insulin Degludec is a new ultra long acting basal insulin that has not been evaluated in Indian pediatric population. We aim to evaluate the efficacy and safety of insulin degludec (IDeg) as basal-bolus therapy in Indian pediatric patients affected by type 1 diabetes.

**Methods:** The subjects were 30 (17 boys, 13 girls) pediatric & adolescent patients (22 pre-pubertal), with type 1 diabetes started on insulin degludec once daily as basal insulin. All the patients received insulin degludec for at-least 26 weeks along with rapid acting meal time insulin and their pre and post baseline characteristics (anthropometric data (BMI), Age, duration of diabetes), metabolic (HbA1C), insulin requirement (unit/kg body weight per day) and number of hypoglycemia

episodes, were recorded along with the daily self-monitoring of blood glucose.

**Results:** Both fasting plasma glucose (FPG) and HbA1C levels decreased from 156 mg/dl and 9.4 % to 109 mg/dl and 8.6% respectively. Average increase in BMI was from 16.9kg/m<sup>2</sup> to 17.3kg/m<sup>2</sup>. Basal and Bolus insulin requirements were changed from 0.42 unit/kg and 0.49unit/kg to 0.46unit/kg and 0.35 unit/kg respectively. Total insulin requirement decreased by 0.10 unit/kg. None of the patient experienced any DKA episode during the 6-month period. 16.6% patient had experienced at least one symptomatic hypoglycemia episode. None of the patient had severe hypoglycemia episode.

**Conclusions:** These results suggest that insulin degludec may be a safe and effective long acting basal insulin that can be used in Indian pediatric population. In addition we also found that the total requirement of insulin is decreased.

P3-1828

**CONTINUOUS GLUCOSE MONITORING (CGM) VALUES FOR NORMAL CHILDREN- A NEED FOR FINDING NORMAL STANDARDS FOR CHILDREN.**

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**Objectives:** Compared to the short-term glucose monitoring methods (FBG, OGTT, HbA1C), continuous glucose monitoring (CGM) machines provides detailed information about blood glucose values during real life for 3-5 days. However, until now there are no standard criteria to diagnose glycemic abnormalities based on CGM data in children. The aim of this descriptive study was to identify the normal glucose values using CGMS for normal children in order to have a normal reference for this age group. These data were compared to adult standard CGM data published in 2009. \*

**Methods:** Eleven children (age 3-15 years) with symptoms suggestive of hypoglycemia were investigated using CGMS (Medtronic I pro 2 sensor) augmented with capillary blood glucose monitoring (OneTouch Ultra® 2) for 7 days. Four children were excluded as 3 had significant hypoglycemia and one had significant hyperglycemia that was found during the investigation period using CGMS or lab measurements. Therefore, the CGMS data for those seven normal children were recorded and analyzed.

**Results:** Seven children aged (9 +/- 4.4 years) with normal glycemia were investigated. Their BMI SDS (-0.14+/-1.2) and height SDS = -0.09/+ 0.89. Their serum fasting BG measured in the lab was 83 +/- 12 mg/dl. CGM monitoring for 7 days showed that their mean glucose was 98+/-6.5 mg/dl, while the highest was 146 +/-16.1 mg/dl. Their G SD = 15.14+/-4.98 mg/dl and mean MAD % = 9.5+/-4.4 mg/dl. The average number of excursions was 2.5+/-2.3 event /day. The mean percentage of duration (M%D) spent > 140mg/dl was 2+/- 4% and M%D < 70mg/dl was 2+/-3%. These data are comparable to those published for adults. \*

**Conclusions:** This pilot study provides the normal CGMS glycemic data for children. Further larger studies are required for figuring out the normal glucose standards for children

Indicator	Mean Children Value	Mean Adult value*
Mean fasting blood G	83	86
Mean glucose - CGMS	98	104
Glucose SD- CGMS	15	14.2
Highest reading-CGMS	146	144
% time above 140 mg/dl	2	4.1
% time below 70 mg/dl	2	2.7
%time 70-140mg/dl	95	93

\*Diabetes Care. 2009;32(7):1188-1193.

P3-1829

**A PICTURE-BASED CARBOHYDRATE-COUNTING RESOURCE FOR SOMALIS**

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**Objectives:** Carbohydrate counting is an essential task in effectively managing type 1 diabetes (T1D). Somali diet-specific carbohydrate-counting references are lacking, creating an additional barrier to effective diabetes control. The objective of this study was to develop a picture-based carbohydrate-counting resource for Somalis with T1D.

**Methods:** The traditional Somali foods described were selected using a variety of methods. Serving sizes and carbohydrate calculations were tabulated using the United States Department of Agriculture National Nutrient Database for Standard Reference. Carbohydrate-content calculations of home-prepared foods were made by measuring total yield and total carbohydrates of ingredients in the recipe, divided by the number of servings to be consumed. When available recipes were used for food preparation and analysis for more accurate carbohydrate estimation.

**Results:** Photos of prepared Somali foods were compiled into a PDF file. While introductions are written in text, the resource is primarily picture-based, to bypass limited literacy. The resource will be shared free-of-charge via a web link. The link will be updated annually with new information.

**Conclusions:** There is a need to tailor educational materials to address the needs of Somalis with diabetes. We have created a picture-based nutrition resource for carbohydrate-counting traditional Somali foods, and plan to make this freely available to individuals worldwide.

# DEMOGRAPHIC AND REGIONAL DISPARITIES IN INSULIN PUMP UTILIZATION IN A SETTING OF UNIVERSAL FUNDING: A NEW ZEALAND NATIONWIDE STUDY

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**Objectives:** Insulin pumps have been publically funded in New Zealand since 2012 for patients who meet certain clinical criteria; however, the patterns of utilization have not been described. We undertook a nationwide study to estimate the annual proportions of patients with type 1 diabetes mellitus who used a pump between 2012 and 2014, overall, and according to sex, age, ethnicity, socioeconomic position, and region.

**Methods:** We used data from the New Zealand Virtual Diabetes Register and routinely collected national demographic, health, and pharmaceutical dispensing data from the Ministry of Health to identify patients with type 1 diabetes and to calculate the overall, and subgroup, proportions using pumps.

**Results:** Between 2012 and 2014, funded pump use among patients with type 1 diabetes ( $n = 13,727$ ) increased from 1.8 to 9.3 % overall; however, there were differences in uptake according to demographic characteristics and region. In 2014, proportionate pump use was significantly higher in females versus males (adjusted odds ratio (OR) 2.0 [95 % confidence interval 1.8–2.3]), in those aged

**Conclusions:** It is essential to explore the factors driving differential insulin pump uptake, in both New Zealand and elsewhere, if all patients are to have equal opportunity to benefit from intensive diabetes management.

P3-1831

# THE EFFECT OF LIMITED AND STRATEGIC BLOOD GLUCOSE MONITORING ON METABOLIC CONTROL IN AN INDIAN TYPE 1 DIABETES CLINIC

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**Objectives:** DREAM Trust (DT) is a charitable organization that offers free insulin and healthcare to children and youth with type 1 diabetes (T1D) in central India, but historically has not been able to afford routine blood glucose (BG) monitoring. The objective of this study was to assess if the addition of 2 BG tests per day safely improves T1D control over a 21-month period in DT patients.

**Methods:** Prospective cohort study of DT patients  $\leq 23$  years with T1D  $\geq 1$  year and followed at DT for  $\geq 1$  year, who received 2 BG test strips per day from IDF Life for a Child. During the first 9 months of the intervention, DT managed BG monitoring and insulin adjustments with the addition of 2 daily test strips alone. DT was then provided with external recommendations and patient resources to help them teach patients to *strategically* test their BG and make insulin dose adjustments between 9 and 21 months. Participants visited DT at baseline and then every 3 months for routine diabetes care, review of BG, HbA1C measurement, and completion of study questionnaires. The overall impact of the addition of 2 BG tests per day was measured by change in HbA1C from 0-21 months. Difference in HbA1C was also determined between 0-9 months and 9-21 months, and paired t-tests were performed on  $\log(\text{HbA1C})$ .

**Results:** Of 240 DT patients enrolled, 143 missed  $\leq 1$  study visit and completed baseline, 9 month, and 21 month visits (52.4% female, median(IQR) age 16.4 (12.7, 19.2) years). Median(IQR) HbA1C was 10.4% (8.3, 11.9) or 90.2 mmol/mol (67.2, 106.6) at baseline vs. 9.4% (8.2, 10.6) or 79.2 mmol/mol (66.1, 92.4) at 9 months ( $p < 0.001$ ), vs. 9.0% (7.8, 10.8) or 74.9 mmol/mol (61.7, 94.5) at 21 months ( $p < 0.001$  vs. baseline and  $p = 0.01$  vs. 9 months). Adherence to BG monitoring was good with patients completing 67.6% of BG tests. Adherence to timing of strategic BG monitoring, however, was poor. There was no change in acute diabetes-related complications during the study.

**Conclusions:** The addition of 2 BG tests per day significantly improves glycemic control in T1D patients in this low-resource setting. External support and education to direct strategic use of BG monitoring may serve to enhance the improvement in glycemic control.

P3-1832

# USEFULNESS OF LIMITED JOINT MOBILITY IN PREDICTING THE PRESENCE OF EARLY STAGES OF DIABETIC MICROANGIOPATHY IN LIMITED RESOURCE SETTING.

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**Objectives:** To determine the usefulness of limited joint mobility in predicting the presence of early stages of diabetic microangiopathy; Retinopathy and nephropathy.

**Methods:** A longitudinal study involving 24 children with type 1 diabetes mellitus. A single observer performed a survey on 24 children with type 1 diabetes mellitus attending the endocrinology clinic and equal number of age and sex matched children without diabetes attending the children's out patient clinic of the Federal Teaching Hospital Abakaliki. Limited joint mobility was assessed quantitatively with the prayer manoeuvre. Retinopathy was assessed by mydriatic ophthalmoscopy. Microalbuminuria was assessed using early

morning spot urine albumin/creatinine ratio. Serial glycosylated haemoglobin levels was determined. These children were followed up for 3 years.

**Results:** Joint mobility was limited in 63.6% (14/22) subjects.

Mean age at diagnosis of diabetes was 12.4+/-2.3years. Mean duration of diabetes at the time of initial evaluation of LJM was 23.8+/-20.6months. Annual mean HbA1c levels were 11.2%, 10.7% and 10.6%. Microalbuminuria was found in 36.3% (8/22) and retinopathy in 13.6% (3/22). All the subjects with Microalbuminuria and retinopathy had LJM and 18.2% (2/11) of them developed chronic kidney disease. Some subjects (13.6%; 3/22) who had LJM did not have Microalbuminuria or retinopathy.

**Conclusions:** Presence of LJM in some children with diabetes who did not have Microalbuminuria or retinopathy and all the patients with Microalbuminuria and retinopathy may support its usefulness as a predictor of early signs of microvascular complications in patients with diabetes in limited resource settings.

**Keywords:** joint mobility, diabetes, microangiopathy, children.

P3-1833

**IMPROVEMENT OF GLYCEMIC CONTROL AFTER THE SWITCH TO DEGLUDEK IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES**

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**Objectives:** Insulin degludec (IDeg) is a new basal insulin. Few data have been published on IDeg effects in childhood. Our purpose was to longitudinally assess the efficacy and the safety of IDeg in children and adolescents with type 1 diabetes

**Methods:** Thirtyseven patients (12.6±4.89 yrs; 21 males; type 1 diabetes duration 5.50±3.92 yrs; IGlAr treatment at least 1 year) were switched to IDeg once daily. z-score BMI, HbA1c, fasting plasma glucose (FPG), severe hypoglycaemia rates, and insulin dose [IGlar or IDeg plus short-acting/regular] were collected at baseline (T0, during IGlAr treatment), 3 months (T1), and 6 months (T2) after IDeg was started. According to HbA1c levels at T0, patient were included in Group A (n. 20; HbA1c >7.5%; 14.3±4.30 yrs; type 1 diabetes duration 6.54±3.87 yrs) and Group B (n. 17; HbA1c <7.5%; 10.6±4.91 yrs; type 1 diabetes duration 4.28±3.73 yrs)

**Results:** In Group A the switch from IGlAr to IDeg allowed a significant longitudinal change of basal-bolus insulin dose (ANOVA Chi Sqr.=11.8, p=0.008) due to the significant reduction of short-acting/regular mealtime (MT) insulin (ANOVA Chi Sqr.=9.19, p=0.026). Moreover, we found a significant longitudinal decrease of both HbA1c levels

(ANOVA Chi Sqr.=9.41, p=0.009) and FPG (ANOVA Chi Sqr.=8.08, p=0.017) (see Table). No significant longitudinal change was demonstrated in Group B. z-score BMI did not change and no episode of severe hypoglycaemia was reported in both groups.

**Conclusions:** IDeg seems to improve the glycemic control mainly in subject with previous poor control during IGlAr treatment. Despite data from adults with type 1 diabetes, our results in childhood suggest that the dose of IDeg should not be reduced and the MT bolus insulin appropriate replacement doses should be lowered for patients who previously received IGlAr. IDeg might be considered a useful and well tolerated basal insulin also in childhood.

Table - Switch to IDeg: longitudinal changes in insulin dose and glycemic control

	IGlar	IDeg T0	IDeg T1	IDeg T2	Chi. Sqr	p
<b>Group A (n. 20)</b>						
Basal (U/Kg/day)	0.37 ± 0.10	0.35 ± 0.10	0.38 ± 0.09	0.37 ± 0.09	6.03	0.110
Bolus (U/Kg/day)	0.61 ± 0.21	0.60 ± 0.20	0.55 ± 0.18	0.51 ± 0.17	9.19	<b>0.026</b>
HbA1c (%)	8.44 ± 0.71		7.84 ± 0.73	7.90 ± 0.81	9.41	<b>0.009</b>
FPG (mg/dl)	204.5 ± 52.6		180.0 ± 54.6	153.1 ± 28.5	8.08	<b>0.017</b>
<b>Group B (n. 17)</b>						
Basal (U/Kg/day)	0.36 ± 0.12	0.32 ± 0.11	0.36 ± 0.11	0.39 ± 0.11	4.43	0.218
Bolus (U/Kg/day)	0.48 ± 0.16	0.48 ± 0.16	0.43 ± 0.15	0.43 ± 0.18	5.82	0.120
HbA1c (%)	6.61 ± 0.52		6.81 ± 0.92	6.87 ± 0.90	5.64	0.059
FPG (mg/dl)	145.3 ± 22.1		141.5 ± 17.4	136.7 ± 16.2	0.76	0.683

P3-1834

**IN OFFICE RETINAL SCANNER IMPROVES COMPLIANCE WITH DIABETIC EYE SCREENING.**

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**Objectives:** Diabetic retinopathy is a significant cause of eye disease in the adult population and the ADA recommends screening in children with diabetes who are age >10 and have diabetes for 3-5 years. We undertook a survey of diabetic patients and found only 45% of those who should have been screened were and so implemented a quality improvement project to improve the compliance. Our aim was to examine if having an in-office retinal scanner would improve compliance

**Methods:** We purchased a Welch Allyn Retinopathy Screener and after training our staff offered patients the opportunity of having the scan done in office. The procedure takes 5 mins and does not require dilation of the pupils. Scans were performed if the patient met ADA criteria and if they had not had an eye exam in the previous 1 year. The scans are read by a central retinal expert and reported in 48 hours. Families are given a picture of their retina and information about eye disease.

**Results:** There are 1810 T1DM patients and 204 T2DM patients in our clinic. In the first 6 months we performed 206 retinal scans in our office. The testing was done during a diabetes clinic visit and did not increase the time in clinic. Parents and children reported good satisfaction with the scan and particularly the parents appreciated that they did not need to take time off work. Compliance with retinal exam over the 6m period increased to 75% of patients eligible.

Insurance paid for the scans and families did not have separate co-pay.

**Conclusions:** In office Retinal scanning for diabetics is feasible, convenient and improves compliance with the ADA retinal screening guidelines. It is cheaper and faster than seeing a retinal specialist for those who have no other eye disease and improves patient satisfaction.

P3-1835

#### TO STUDY THE CLINICAL PROFILE OF CHILDREN ADMITTED WITH DIABETIC KETOACIDOSIS IN A TERTIARY HOSPITAL IN INDIA

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**Objectives:** To Study the Clinical Profile of children admitted with Diabetic Ketoacidosis in a Tertiary hospital in India

**Methods:** We retrospectively analysed case records of 82 children, 36 males and 46 females who presented with Diabetic ketoacidosis to Manipal Hospital, Bangalore from January 2014 to January 2017. Information regarding personal details, chief complaints, clinical features, laboratory parameters, management and outcome was recorded using a predesigned proforma.

**Results:** The study consisted of 36 males (44%) and 46 females (56%). 70 out of 82 children (85%) were newly diagnosed type 1 diabetics. 32 children (39%) were below 5 years of age, 23 (28%) were between 5-10 years of age and 26 (31.7%) were above 10 years of age. The median time of onset of symptoms to ER admission was 10.36 $\pm$ 6.07 days. At admission, 25% children were in mild DKA, 23% were in moderate DKA and 51.9% were in severe DKA. Among the 12 old patients, the cause for DKA was omission of insulin in 8 (66%) and infection in 4 (33%). The main presenting complaints according to frequency were polyuria and polydipsia (73%), vomiting (29%), abdominal pain (28%).

The mean blood glucose at presentation was 536.17 $\pm$ 163 mg/dl, mean pH was 7.1 $\pm$ 0.16 and mean bicarb 7.99 $\pm$ 3.44. Initial biochemical investigations revealed mean sodium 133.69 $\pm$ 5.77, mean potassium 3.88 $\pm$ 0.87 and mean Blood urea nitrogen 12.79 $\pm$ 5.23. The mean HbA1c at presentation was 12.59 $\pm$ 1.91%. Mean Total leukocyte count was 15324 $\pm$ 7569/cumm.

The average length of ICU stay was 2.09 $\pm$ 0.94 days and total duration of hospital stay was 5.52 $\pm$ 1.52 days. The mean time transition to subcutaneous insulin was 29.34 $\pm$ 7.55 hours and the mean total duration of IV fluids was 43.5 $\pm$ 12.7 hours. The mean insulin dose at discharge was 1.24 $\pm$ 0.33 u/kg. Recurrent DKA was found in 4.8% patients (4/82) and all the four patients had poor compliance with insulin. The incidence of cerebral edema was 6% (4/82). However, there was no mortality in our study group.

**Conclusions:** Diabetic ketoacidosis is a common problem in children with new onset diabetes. The younger the age, the higher the risk of DKA as initial presentation of diabetes mellitus. Poor compliance is most important precipitating factor in known cases of T1DM. Counseling and education of

parents during hospitalization and discharge is very necessary.

P3-1836

#### POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES) COMPLICATING DIABETIC KETOACIDOSIS: A RARE ASSOCIATION IN CHILDREN WITH TYPE 1 DIABETES ?

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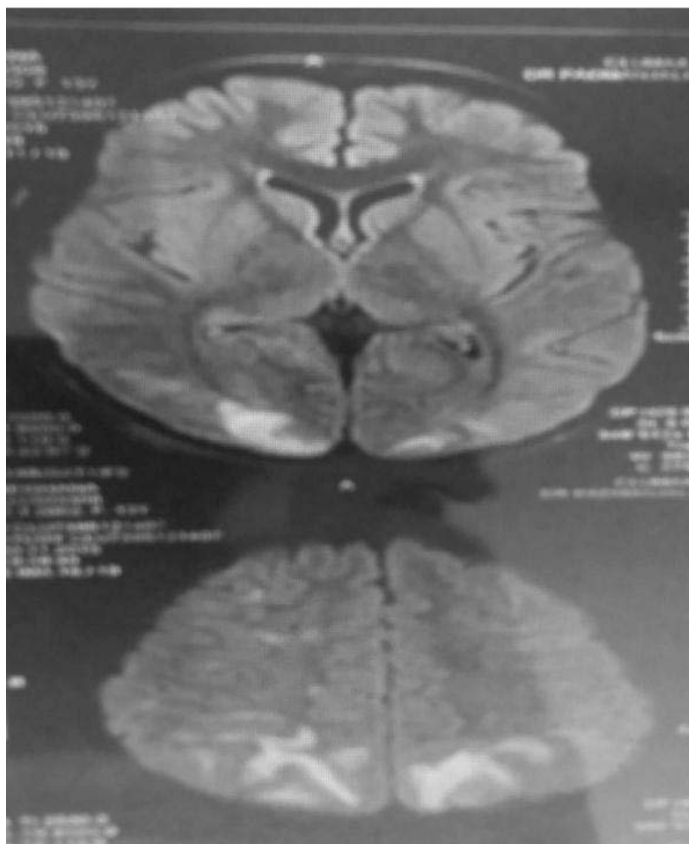
**Objectives:** Posterior reversible encephalopathy syndrome (PRES) complicating diabetes ketoacidosis (DKA) is not commonly heard in children with type 1 diabetes. Here we present a child with DKA followed by development of PRES. We could not identify any obvious trigger factor. We looked into how the DKA may have contributed to development of PRES.

**Methods:** A 13 yrs old girl initially presented with DKA and suspected cerebral edema. She was ventilated for 24 hours. Initial CT brain reported normal. She was discharged on basal bolus insulin regime. She represented to triage 2 days later being drowsy, headache, visual loss and generalised seizures for which she was ventilated and neuroprotected for 72 hours. She was normotensive and normoglycaemic during this episode. MRI brain showed hyperintense areas in subcortical and paraventricular white matter of bilateral fronto- parieto- occipital lobes, suggesting of PRES. Following two weeks, she made a complete recovery without any sequelae.

**Results: Discussion:** PRES is a clinico-radiological entity characterised by headaches, altered sensorium, visual loss and seizures. This is associated with white matter vasogenic edema predominantly affecting the posterior occipital and parietal lobes of the brain. Often also referred as reversible posterior cerebral edema syndrome or hyperperfusion encephalopathy. Most cases of PRES occur with hypertension or immunosuppression, but can occur with many diverse clinical entities. Pathophysiology is under debate, but is related to disordered cerebral autoregulation and endothelial dysfunction. Two mechanisms proposed are cerebral vasospasm which results in cytotoxic edema and cerebral vasodilatation, which results in vasogenic edema. Prognosis is good with mostly self resolving within few days. In our case there was no identifiable triggers but there could be multiple factors causing disordered cerebral autoregulation such as electrolyte disturbances, blood pressure fluctuations, proinflammatory cytokines and beta-hydroxybutyrate which have shown to increase vascular permeability.

**Conclusions:** PRES is often unsuspected by clinicians, recognition of the characteristic imaging findings by radiologists is key to diagnosing this syndrome and should prevent deleterious work-ups or treatments.

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P3-1837

#### TYPE 1 DIABETES, POLYENDOCRINOPATHY AND SJOGREN SYNDROME: A RARE ASSOCIATION IN CHILDREN

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**Objectives:** To report a case of concomitance of type 1 diabetes mellitus, Hashimoto's Thyroiditis, Sjogren's Syndrome and other autoimmune diseases in a female child.

**Methods:** Retrospective review of medical records of a patient with multiple autoimmune diseases followed at the Pediatric Endocrinology unit of Instituto da Criança do HC-FMUSP.

**Results:** Previously healthy girl 1 year and 4 months old was diagnosed with type 1 diabetes due to symptoms, laboratories work up and antibodies positivity (anti-GAD and anti-IAA) and multiple dose injection insulin therapy was

started. In the follow up, autoimmune thyroiditis was diagnosed with positive anti-TPO and anti-TG and treatment with Levotiroxine was started. At the age of 3, she started chronic diarrhea and celiac disease was suspected: she showed positivity for anti-gliadin antibodies, anti-transglutaminase and antiendomysium were negative and intestinal biopsy was suggestive. At the age of 7, the patient presented recurrent polyarthralgia and recurrent parotiditis, which associated with Shimmer Test and salivary gland biopsy suggested the diagnosis of Sjogren's syndrome, despite of negativity for antibodies Anti SS-a/RO and SS-B/LA. At 8 years old, TRAb positivated, so Hashi-Graves thyroiditis became her diagnosis, levothyroxine was suspended and methimazole was started. It is important to state that the mother of the patient has scleroderma and fibromyalgia. The patient has been submitted to flow citometry of T cells (including FOX P3), that showed no abnormalities. Currently, the patient is 12 years old and is been treated with azathioprine, hydroxychloroquine, NPH and ultrarapid insulin, showing moderate diabetes control with HbA1c varying in the last six months between 7,6% - 8,6%. HLA and exome are being processed.

**Conclusions:** This case report demonstrates an association that has not been described so far in the literature: type 1 diabetes or polyendocrinopathy with Sjogren's Syndrome. It should be remembered the possible challenge for endocrinologists on the treatment of patients with multiple autoimmune diseases due to the recurrent use of corticosteroids and other immunosuppressants that may interfere in glycemic control.

P3-1838

#### TYPE 1 DIABETES MELLITUS IN A CHILD WITH RETT SYNDROME

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**Objectives:** We are reporting the case of a 2.6 years old girl with Rett Syndrome who developed type 1 diabetes mellitus at the age of 9 months

**Methods:** A 2.6 years old girl who is a full term baby born by Caesarian section due to fetal distress with a birth weight of 3.2 kilograms, to non consanguineous parents, she was healthy at birth with no neonatal problems. Her development was normal until the age of six months when she started to show regression in her development. At the age of nine months she developed polyuria, polydipsia, and loss of weight for 3 weeks duration and presented with severe diabetic ketoacidosis in which she needed intensive care admission. She was discharged on multiple daily injections of Insulin.

She presented to our endocrine unit at the age of eighteen months, her weight was above the 10th centile, length was below the 5th centile, and her head circumference was 42cm below the 5th centile for her sex and age.



Her speech, language and motor development were below 6 months of age, she had communication dysfunction and stereotyped hand movements with no seizure disorders. She was suspected to have Rett syndrome based on her clinical presentation, so a gene study was requested at the age of 18 months which showed mutation in the MECP2 gene (Xq28). Her investigations at time of diagnosing diabetes showed an Anti-glutamic acid decarboxylase (anti GAD) level that was significantly high (609.3 U/mL, Normal <1.0) which supported the diagnosis of type 1 diabetes mellitus. Her HbA1c was 9.4 %.

MRI of the brain was normal.

This child is currently two years and 7 months, she has regular follow up with the Endocrinologist, Neurologist and physiotherapist. She is only on insulin injections.

**Results:** DNA was extracted from whole blood, sequencing for exon 4 of MECP2 gene showed that the patient has p.R168X(c.502C>T) mutation

**Conclusions:** Rett Syndrome associated with type 1 diabetes is not common, we only found three reported cases with the same condition. Rett syndrome is a rare neurodevelopment disorder and type 1 diabetes is a common disease in childhood, the association of these two diseases are poorly understood still more investigation is needed.

P3-1839

#### SPONTANEOUS POSTPRANDIAL HYPOGLYCEMIA BEFORE INSULIN INTRODUCTION IN EARLY-STAGE TYPE 1A DIABETES MELLITUS

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**Objectives:** The pathophysiology of type 1 diabetes mellitus (T1DM) involves the autoimmune destruction of the pancreatic beta-cells resulting in the loss of insulin-secreting capacity. Over 80% of T1DM cases are positive for islet-related autoimmune antibodies and are designated type 1A DM (T1ADM). Although hypoglycemia is one of the major complications in T1DM, it is almost exclusively observed after insulin treatment. To the best of our knowledge, thus far only one study has described a T1ADM case with hypoglycemia before insulin introduction. We report here two patients with recent-onset T1ADM who developed spontaneous postprandial hypoglycemia during extensive glucose monitoring before starting insulin.

**Methods:** Case review

**Results:** Case 1: A 6-year-old girl presented with polydipsia allegedly for three years. Laboratory results showed mildly elevated HbA1C (6.9 %) and anti-GAD antibody positivity (48.9 U/ml) suggesting T1ADM. Her blood glucose profile before insulin treatment showed spontaneous postprandial

hypoglycemia (46-69 mg/dl) alternating with hyperglycemia (210-347 mg/dl). T1ADM was diagnosed and Miglitol (alpha-glucosidase inhibitor) was administered for six months. Her recent HbA1C remained stable at 7.1%. Her blood glucose levels continued to fluctuate in the manner described.

Case 2: A 3-year-old girl presented with polyuria and polydipsia of 10 days' duration. Laboratory results showed mildly elevated HbA1C (6.6 %) and GAD antibody positivity (28.0 U/ml) suggesting T1ADM. Her blood glucose profile before insulin treatment showed spontaneous postprandial hypoglycemia (47-51 mg/dl) alternating with hyperglycemia (203-354 mg/dl). As blood glucose levels and HbA1C gradually increased in the following six months, rapid-acting insulin was administered at each meal. Long-acting insulin was not used.

**Conclusions:** Hypoglycemic episodes may occur in early-stage T1ADM requiring extensive glucose monitoring to decide the timing of insulin introduction.

P3-1840

#### CANNABIS HYPEREMESIS AND EFFECTS WITH TYPE 1 DIABETES

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**Objectives:** Marijuana is the most commonly abused drug in the world. A known effect of chronic cannabis abuse is cannabis hyperemesis syndrome (CHS). We describe a previously unreported case of CHS complicating the management of type 1 diabetes mellitus (T1DM).

**Methods:** A case report is described.

**Results:** A 21 year-old male with a known history of chronic marijuana use and T1DM with frequent admissions for diabetic ketoacidosis (DKA) presented to the emergency department with sudden onset frequent vomiting and extreme abdominal pain. Symptoms were reportedly worse than prior DKA episodes. Laboratory evaluation was consistent with mild DKA based on acidosis, ketosis, and hyperglycemia. DKA management began with insulin drip and intravenous hydration, but abdominal pain and vomiting worsened despite resolution of DKA within 18 hours, by laboratory assessment. Other evaluation for acute abdominal symptoms were normal, including surgical evaluation, evaluation for pancreatitis, abdominal imaging, and other drug screening. Tetrahydrocannabinol (THC) testing was positive. Emesis and abdominal pain persisted despite bowel reset, anti-emetics, and pain management. Based on his persistent symptoms and chronic marijuana use he received a hot shower. Symptoms resolved within 1 hour of the hot shower, confirming the diagnosis of CHS. He was discharged and counseled to stop marijuana use.

**Conclusions:** CHS is an underreported effect of chronic cannabis use resulting in cyclical episodes of vomiting and abdominal pain. Symptoms are likely a result of effects of gastroparesis during peripheral receptor activation by THC. Temporary resolution of symptoms following a hot shower or

bath is a hallmark feature. Treatment consists of symptomatic therapy and abstaining from cannabis. As THC is adipose stored, lipolysis such as with DKA may cause excessive THC release and produce a hyperemesis effect in chronic users. CHS may occur more frequently with patients who have poorly controlled T1DM and develop DKA. Hyperemesis can also place patients at risk for cyclical periods of DKA. Patients with T1DM should avoid chronic marijuana use, and should be counseled about the risks of CHS and its effect with diabetes.

P3-1841

#### **DUODENAL ATRESIA, INTESTINAL MALROTATION, ANNULAR PANCREAS, GASTRIC AND PANCREATIC HETEROTOPIA AND INSULIN DEPENDENT DIABETES CAUSED BY A NOVEL COMPOUND HETEROZYGOUS MUTATION IN RFX6**

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**Objectives:** Transcription factor RFX6, is essential for endoderm development and pancreatic islet function. Pathogenic variants in RFX6 cause Mitchell-Riley syndrome, a disorder of permanent neonatal diabetes and congenital gastrointestinal defects. We describe a novel compound heterozygous mutation in RFX6 causing severe gastrointestinal defects, growth failure and childhood onset diabetes.

**Methods:** Chart review was performed.

**Results:** A premature female infant presented with annular pancreas, duodenal atresia and intestinal malrotation, repaired via laparotomy. At the age of 8, she had growth failure, normocytic anemia, glucosuria and hyperglycemia and was without polyuria or polydipsia. Islet cell antibody and MODY genetic testing were negative. She was diagnosed with type 1b diabetes and required low doses of insulin. At 10 years of age, she developed epigastric pain and a decline in her hemoglobin. EGD revealed normal esophageal and gastric mucosa and normal pancreatic function. Stool samples were hemocult positive, prompting additional investigation. Capsule endoscopy revealed extensive polypoid lesions in the proximal duodenum. CT enterography and Meckel's scan demonstrated heterotopic gastric tissue in these polyps. A 50 cm resection of the proximal duodenum revealed 11 polyps that were positive for gastrin, ghrelin, pepsinogenC, MUC5AC, MUC2, insulin, PDX1 and amylase staining confirming the presence of antral and fundic gastric, intestinal and pancreatic tissue in these polyps. Duodenal resection led to an improvement in anemia, abdominal pain, weight gain, linear growth acceleration and pubertal progression. Genetic analyses revealed a compound heterozygous mutation in RFX6 (c.1040\_1052del (p. Arg347Lysfs\*18)/ c.2623C>T (p.Gln875\*)).

**Conclusions:** We describe a rare case of Mitchell-Riley syndrome caused by a novel compound heterozygous mutation in RFX6. Our patient had classic features of annular pancreas, duodenal atresia and malrotation. She also had childhood onset diabetes with gastric and pancreatic heterotopia which has been described in two other cases. This case highlights the importance of genetic testing for rare causes of diabetes in patients that present with diabetes and congenital gastrointestinal anomalies.

P3-1842

#### **CONVENTIONAL INSULIN PUMP THERAPY IN TWO NEONATAL DIABETES PATIENTS HARBORING THE HOMOZYGOUS PTF1A ENHANCER MUTATION: NEED FOR A NOVEL APPROACH FOR THE MANAGEMENT OF NEONATAL DIABETES**

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**Objectives:** The enhancer of PTF1A mutation causes developmental defects of the pancreas. This condition can result in insulin-requiring diabetes and exocrine pancreatic insufficiency.

**Methods:** We report two patients with diabetes mellitus harboring the homozygous PTF1A enhancer mutation. The patients had hyperglycemia in the first month of life and were started with subcutaneous insulin injections with NPH insulin. When blood glucose (BG) exceeded 250 mg/dl, a conservative dose of rapid-acting insulin was administered to restore BG to the target range. In cases with documented poor control (persistent hypoglycemia and rebound hyperglycemia), it was decided that the baby would benefit from a continuous subcutaneous insulin infusion pump.

**Results:** But our experience shows that wide fluctuations in BG concentrations despite the strict follow-up was probably due to the absence of circulating glucagon. Further treatment options would overcome this problem, especially for children with pancreas agenesis

**Conclusions:** We could say theoretically that a sensor-augmented insulin pump system and single-hormone (insulin alone) and dual-hormone (insulin and glucagon) artificial pancreas systems may mitigate the severity of hypoglycemia.

P3-1843

#### **SLEEP AND GLYCEMIC CONTROL IN ADOLESCENTS WITH TYPE 1 DIABETES**

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**Objectives:** Increasing evidence link sleep curtailment and circadian misalignment with adverse metabolic outcome. Adolescents might be most affected, given their late sleep timing and early school and work start times. Our aim was to examine the impact of poor sleeping habits on glycemic control in adolescents with type 1 diabetes.

**Methods:** This was a non-interventional multicenter study across Germany recruiting pubertally mature adolescents with type 1 diabetes. Medical records were used to collect information on diabetes duration, treatment and complications. Participants self-reported sleep quality, timing, chronotype and social jetlag – a measure of circadian misalignment. HbA1c was determined at the time of questionnaire response. We used multi-variable linear regression models to examine associations between sleep and glycemic control.

**Results:** 191 patients aged 16.5 years (mean HbA1c 8.0% [64 mmol/mol]) were included in this study. In multi-variable adjusted analyses, sleep quality was significantly associated with HbA1c (mean difference;  $\beta = -0.07$ ,  $p = 0.05$ ). Stratified analysis indicated that this association might be stronger in boys and also in children with migration background. In contrast, neither sleep-duration, sleep debt, chronotype, nor social jetlag were associated with HbA1c. Secondary analyses showed that social jetlag was significantly associated with levels of insulin requirements (mean difference;  $\beta = 0.035$ ,  $p = 0.03$ ).

**Conclusions:** Our study suggests that poor sleep quality is associated with increased HbA1c in adolescents with type 1 diabetes and that higher levels of circadian misalignment are associated with increased insulin requirements. If replicated, our results indicate a clinical relevance of sleep habits in adolescents with type 1 diabetes.

P3-1844

#### EARLY ONSET OF TYPE 1 DIABETES MELLITUS COMORBID WITH COMPOUND HETEROZYGOUS VARIANTS IN CARBOXYL-ESTER LIPASE(CEL) GENE-A CASE REPORT

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**Objectives:** Carboxyl-Ester Lipase (CEL) is predominantly expressed in pancreatic acinar tissue. The mutations in the CEL VNTR are reported a rare cause of mature onset of diabetes in youth, type 8 (CEL-MODY8). The affected subjects develop delayed onset of exocrine pancreatic dysfunction in

2<sup>nd</sup> decade of life, reduced pancreatic volume and lipomatosis. Pancreatic enzyme substitution alleviates the symptoms. Diabetes occurs within the next 20 years, mean age of 27-36 years. Further, insertions in CEL gene is associated with higher risk of exocrine dysfunction in type 1 and type 2 diabetic patients independently. Thus, CEL gene variants may play an important role in MODY, type 1, or type 2 diabetes. Here we reported an infant with Type 1 diabetes, who carries 2 variants in CEL gene, presented with atypical initial clinical presentation.

**Methods:** A 10 month-old female infant presented with 3-week history of otitis media, followed by urosepsis for E. Coli. Subsequent work up is suggestive of type 1 diabetes mellitus, evidenced by elevated HbA1C of 8.4%, detectable insulin (3.5 uIU/mL), and C-peptide (0.645 ng/mL) at glucose of 521 mg/dL. ICA 512, Insulin antibodies, and GAD65 were positive. Islet cell antibodies were negative. Genetic study detected a compound heterozygote for 2 variants in CEL gene (c. 1955C>T and c. 1790C>T). These variants are classified as unknown clinical significance. Both maternal grandparents were diagnosed with “type 2 diabetes” at age 57 years. Mom, her younger siblings, and paternal side of the family, are not aware of any glucose disorders.

**Results:** Now at age 26-month-old, she has been on insulin treatment via CSII. HbA1C is in the range of 8.8-9.2%. She has been thriving well with length and weight around 75<sup>th</sup>% and 75-90<sup>th</sup>% respectively. There is no steatorrhea. She has normal fecal fat, and fecal pancreatic elastase. Abdominal ultrasound was normal.

**Conclusions:** Although CEL gene is highly polymorphic in general population, the co-finding of compound heterozygous variants in CEL gene in this T1DM patient has not been reported previously. The clinical significance is unknown. Due to its delayed presentation in nature, her diabetes course, and exocrine pancreatic function need to be followed up long term. And prompt intervention be generated.

P3-1845

#### INSULIN PUMP THERAPY VS. MULTIPLE DAILY INJECTIONS: A COMPARATIVE ANALYSIS AMONG INDIAN CHILDREN WITH TYPE 1 DIABETES MELLITUS

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**Objectives:** To determine the impact of insulin pump therapy on short and long term glycemic control, Body Mass Index (BMI), rate of severe hypoglycemia and Diabetic ketoacidosis in children, young adults in our population.

**Methods:** Retrospective analysis of data from case records of patients was done. The total number of patients in the insulin pump cohort was 52. Those in the Multi Dose Injections (MDI)

cohort were 63. Matches within defined thresholds were available for all 52 patients on the insulin pump.

The pump and non-pump patients were well matched in respect of baseline characteristics.

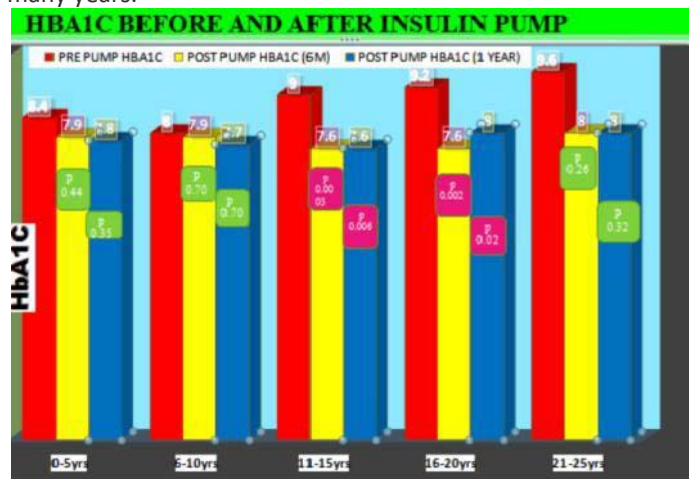
Age of the patients at initiation of insulin pump ranged from 3 to 26 years. Patients were stratified into 5 age groups at 5 year intervals (0-5, 6-10, 11-15, 16-20, 21-25 yrs) and data was recorded as PRE-PUMP and POST-PUMP values. Data included HbA1C (just before initiation of pump, 6 months and 1 year after pump), BMI (at last visit prior to pump and 6 months after pump), episodes of DKA and severe Hypoglycemia (in the 1 year before and after pump). Severe Hypoglycemia was defined as either altered sensorium or seizures associated with low blood glucose.

Of the 52 patients included, we have follow up of 29 patients for up-to 1 year or more. The remaining 23 patients have either yet not completed 1 year after pump initiation or have dropped out.

**Results:** There was a drop in HbA1C across all age groups with insulin pump therapy. This difference was statistically significant in the 11 to 15 year and 16 to 20 year age groups. Body Mass Index also increased across all age groups with Insulin Pump Therapy, though this difference was not found to be statistically significant. Though the incidence of hypoglycaemia decreased in both groups as compared to the indices prior to initiating pump therapy, there was no difference in the rate of complications among the two groups after initiation of pump therapy.

Three episodes of DKA were recorded after pump therapy against five episodes in the pre pump period.

**Conclusions:** In conclusion, we find that among urban Indian children, insulin pump therapy brings forth a significant improvement in glycaemic control, which is sustained over many years.



P3-1846

### TYPE 1 DIABETES OUTCOMES: DOES DISTANCE TO CLINIC MATTER?

*Danya A Fox, MD; Shazhan Amed, MD, University of British Columbia, Vancouver, BC, Canada; Nazrul Islam, PhD, Harvard University, Boston, MA, United States*

**Objectives:** We compared the following outcomes for children travelling varying durations to the type 1 diabetes (T1D) clinic at a pediatric tertiary care center:

1. Frequency of diabetes clinic visits
2. Use of other medical services
3. Glycemic control
4. Satisfaction with diabetes care

**Methods:** Participants were recruited from the T1D clinic at British Columbia Children's Hospital (BCCH). Clinical data were collected by chart review and parent and patient reported outcomes were collected by online surveys (age-permitting). Participants were categorized based on self-reported travel time to BCCH: 2 hours. Descriptive statistics, linear and logistic regression were used, as applicable.

**Results:** Baseline characteristics (age, duration of T1D, insulin regimen, household income) between participants in the 1h group (1-2 h and >2h; N=43) were similar. There was no difference in the frequency of diabetes clinic visits/yr (2.23 1h; p=0.40) and mean A1C (7.90% 1h; p=0.10). However, A1C was significantly higher in patients traveling >2h (N=19) vs 1h were more likely to report barriers to attending clinic, the most common being that the clinic was too far away. They were also more likely to visit an emergency department (ED) in the past year (26% 1h; p<0.05), miss school in the past 30 days (16% 1h; p<0.05), and parents were more likely to miss work (26% 1h; p<0.05). Adjusting for A1C, those who traveled >1h had 2.48 times increased odds (95% CI 1.05-5.83) of visiting an ED compared to the

**Conclusions:** Children travelling longer distances (>2h) to a T1D clinic have worse glycemic control, despite there being no difference in number of diabetes clinic visits/yr. Those who travel >1h to clinic were more likely to visit an ED and children and parents were more likely to miss school and work, respectively. Future research is needed to determine the impact of providing diabetes care closer to home on patient outcomes.

P3-1847

### BURDEN OF THIAMINE DEFICIENCY AMONG CHILDREN PRESENTED WITH DIABETIC KETOACIDOSIS

*Mona Kareem, PhD, Suez Canal university, Ismailia, Egypt; Amina Abd El-Wahab, Professor; Nada S Hassan, MD; Omar Desouki, PhD, Suez Canal University, Ismailia, Egypt*

**Objectives:** To assess the level of thiamine among diabetic children presented with DKA, and its correlation with the degree of acidosis and encephalopathy.

**Methods:** A cross-sectional study was carried on at the Suez Canal University Hospital, Ismailia, Egypt. A convenient

sample of forty diabetic children aged below 18 years, and presented with DKA. The patients were submitted to full history taking, regular examination and laboratory investigations. Thiamine levels were included within the investigations prior to fluids and insulin administration.

**Results:** Among the DKA patients, the mean age of patients was  $8.6 \pm 3.4$  years; the majority of them were females (72.5%) while 37.5 % had a positive family history of DM. 52% of our patients were newly diagnosed as diabetics and 48% of them were already known to have diabetes.

The studied children had their diabetes of  $1.85 \pm 2.6$  years duration, and their HbA1C mean was  $9.96 \pm 2.27\%$  while receiving  $1.08 \pm 0.27$  IU/kg of insulin. DKA triggers were medication non-adherence (32.5%), infection (17.5%), the onset of puberty (5%) and (5%) couldn't clarify a specific trigger, on the other hand. Being newly diagnosed was the cause in 50% of the patients. 42.5% had encephalopathy while more than 50% had moderate to severe acidosis (37.5% and 20 % respectively) at the time of presentation.

The mean thiamine level of the studied group was  $47.37 \pm 28.52$  ng/ml; among them, 45% were found to have absolute thiamine deficiency with levels less than 40 ng/m, PH and HCO<sub>3</sub> level had statistically significant strong positive correlation with level of thiamine ( $r = 0.96, p > 0.01$ ) and ( $r = 0.92, p > 0.01$ ) respectively. While Glasgow Coma Scale had positive but moderate significant correlation with the level of thiamine ( $r = 0.57, p > 0.01$ ).

Stepwise backward regression analysis model of significance best-fitting predictor of the level of acidosis in Diabetic patients presented with DKA was their level of thiamine ( $t = 9.94, p > 0.01$ ).

**Conclusions:** Thiamine deficiency is not uncommon findings among children with diabetic ketoacidosis. It can be predicted by the severity of acidosis and to a lesser extend the degree of encephalopathy. Thiamine can be introduced as a line in the management of the DKA

Table of Multiple Stepwise regression analysis of level of acidosis in Diabetic patients presented with DKA

Model	Unstandardized Coefficients		Standardized Coefficients	T	P-value
	B	Std. Error	Beta		
(Constant)	7.028	0.155		45.49	< 0.01**
Age	0.006	0.004	0.144	1.51	0.14
BMI	0.001	0.003	0.019	0.22	0.82
Thiamine	0.005	0.001	0.873	9.94	< 0.01**
Serum Creatinine	- 0.084	0.051	- 0.136	-1.661	0.11
Cholesterol	-0.001	0.001	-0.141	-1.49	0.14
Hb	0.004	0.013	0.024	0.28	0.77
TLC	-0.003	0.003	- 0.065	- 0.82	0.42

(DKA) diabetes ketoacidosis, (BMI) body mass index, (Hb) hemoglobin level, (TLC) total leucocytic count.  
 \*\* Highly significant p-value at <0.01

P3-1848

### DENTAL HEALTH STATUS AND HYGIENE IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS IN ERZURUM/TURKEY

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**Objectives:** There is disagreement on the effect of diabetes on oral hygiene. The purpose of this study was to assess the oral health and hygiene status of type 1 diabetic patient in Erzurum/Turkey.

**Methods:** In this case control study, periodontal health and hygiene of 20 children and adolescents (7-15 yr of age) with type 1 diabetes mellitus referred to Pediatric Endocrine Clinic and 20 non diabetic control subjects were clinically assessed. The required data such as sex, age, duration of the diabetes, type and number of insulin injections per day were obtained from self-administered questionnaire and the patient's medical records. Participants in both groups were examined for Decay-missing- filled teeth (DMFT); dmft (for primary teeth), oral hygiene using Silnes-Loe plaque index (PI) and gingivitis index (GI).  $P < 0.05$  was considered significant.

**Results:** The mean age of the study and the control group was  $11.6 \pm 3.05$  and  $11.08 \pm 3.25$  yr, respectively. There were no significant difference between two groups in terms of DMFT, dmft and PI indices ( $P < 0.05$ ). The GI index difference was statistically significant in type 1 diabetic group ( $P > 0.01$ ).

**Conclusions:** Apart from higher scores of GI index, frequency of oral and periodontal disease was not different in type 1 diabetic patients compared with healthy subjects. Findings of present study are insufficient to support a significant effect of diabetes on increasing the risk of oral and periodontal diseases. However, children and adolescents with type 1 diabetic should receive oral hygiene instruction.

P3-1849

### A 17-YEAR-OLD GIRL WITH DIABETES MELLITUS TYPE 1 AND DIFFUSE NECROBIOSIS LIPOIDICA DIABETICORUM

Irina V Osokina, PhD, Siberian Federal University, Krasnoyarsk Science Centre of the Siberian Branch of Russian Academy of Science, Krasnoyarsk, Russian Federation

**Objectives:** Necrobiosis lipoidica diabetorum (NLD) is a rare cutaneous complication of diabetes mellitus. NLD is more often met in female. NLD signs are dystrophic infiltrate intradermal changes as spots or dense patches of dark-red to brown color. We report a case of diffuse necrobiosis lipoidica diabetorum in a 17 year-old girl with type 1 diabetes mellitus(T1DM).

**Methods:** Medical history. The baby was born with weight 3400g. The age of the mother at birth of the girl was 37 years. The breast feeding 6 months. In the age of 3 months was measles. T1DM was diagnosed at 9 months in the ketoacidosis. The hyperglycemia, growth delay were observed before 10 years. The patient had a good glycemic control after 10 years. The first NLD lesion had been

diagnosed at the age of 2 years on the back and on the right leg.

**Results:** On physical examination. Height 1.61 m, weight 53 kg. On the skin of the back, on the right hand, on the front surface of shanks - 7 polymorphous hotbeds of necrobiosis lipoidica diabetorum, 60-80 mm in diameter, dark-red and brown with cyanosis. On shanks in centers of NLD hotbeds there is lamellate peeling. A heart rate of 72 beats per minute, blood pressure - 110/70 mm Hg. Pubertal stage: P3 A3 Ma3 Me 0.

Biochemical analysis: HbA1c - 6.8%, glycemia: 110 to 170 mg/L, total cholesterol 378 mg/dL; triglycerides 375 mg/dL (normal 101 to 150), low density lipoprotein 60.1 mg/dL; LH 0.8 nmol/L (normal 4 to 25), FSH 1.9 nmol/L (normal 5 to 20); a thyrotropin 3.2 mIU/l (normal 0.4 to 4.2), a free thyroxine 1.7 ng/dl (normal 0.8 to 2.2); microalbuminuria 99.3 mg/ml.

Histological features of NLD showed foci of collagen degeneration with sclerosis, surrounded by a chronic, mainly perivascular, granulomatous infiltrate, made up of lymphocytes and histiocytes.

Therapy: diet, insulin (Humalog 6-10 U before each main meal; Lantus at bedtime 20 U; 0.75 U per kg); ciprofibrate 100 mg daily.

**Conclusions:** NLD this patient was as result poor diabetes control first years.

**POSTER SESSION 3**  
**Saturday, September 16, 2017, 12:00-1:00pm**  
**P3 - Type 2 diabetes and other carbohydrate metabolism**  
**P3-1900 – P3-1911**

P3-1900

**EARLY ONSET OF METABOLIC ABNORMALITIES IN PEDIATRIC PATIENTS DIAGNOSED WITH FAMILIAL PARTIAL LIPODYSTROPHY**

*Rebecca Brown, MD; Elaine Cochran, MSN, CRNP; Ho Lim Lee, BS/BA; Megan Startzell, RN, MPH, CPH, National Institutes of Health, Bethesda, MD, United States*

**Objectives:** Familial Partial Lipodystrophy (FPL) is a rare disease that may result in premature death. It is characterized by loss of adipose tissue (occurring mostly around puberty) affecting arms, legs, buttocks, and hips. Since FPL is rare and shares clinical characteristics with other metabolic diseases, FPL may easily be missed in pediatric patients. The objective of this study was to examine key clinical characteristics of pediatric patients with FPL.

**Methods:** A cross-sectional analysis was conducted among patients ≤ 18 years with confirmed FPL, who were referred to the NIH for diagnosis and management.

**Results:** From 2003 to 2017, 13 pediatric patients with FPL were referred to NIH. The mean ± SD age was 15 ± 2.5 years; the majority were female (92%) and Caucasian (92%). All

patients had at least one metabolic complication, with most (77%) having ≥ 3 complications. The most common complications were diabetes (76.9%), hyperlipidemia (84.6%), and non-alcoholic fatty liver disease (NAFLD) (84.6%). The age of onset for diabetes was 11 to 17 years, for hyperlipidemia 10 to 17 years, and for NAFLD 10 to 18 years. 30.8% had hypertension and 23.1% had polycystic ovarian syndrome. Among those with diabetes, 85% required anti-diabetic medication and 54% were on insulin, needing an average of 95.7 units/day. Mean serum leptin levels were 10.8 ± 7.2 ng/mL (range 0.95-21.8 ng/mL). Dyslipidemia was consistent with severe insulin resistance syndrome; high TGs, normal LDL-C, and low HDL-C. Among patients with hyperlipidemia, 31% were on lipid lowering therapy. Of 12 patients who had liver imaging, 1 had normal liver echotexture and the remaining 11 all had evidence of hepatosteatosis.

**Conclusions:** Pediatric patients with FPL often presented with severe insulin resistance, hypertriglyceridemia, and hepatosteatosis. Despite the heterogeneity in their clinical presentation of leptin levels, % body fat, and triglycerides, all patients suffered from severe comorbidities due to their underlying lipodystrophy. Early recognition and diagnosis of pediatric patients with FPL is critical for better management strategies to prevent and treat complications.

	Parameter:						
	Triglycerides (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	Fasting Glucose (mg/dL)	HbA1c (%)	Urinary Protein Excretion (mg/day)	Total Fat (%)
Number of Patients	N=13	N=6	N=10	N=13	N=13	N=10	N=13
Mean ± SD	2617.8 ± 3999.3	106.8 ± 25.2	29.7 ± 8.2	182.4 ± 90.9	8.2 ± 2.6	49.7	24.3 ± 6.6
Range	(64 to 11528)	(87 to 155)	(23 to 51)	(85 to 343)	(4.9 to 12.4)	(26.1 to 142.8)	(14.4 to 33.8)

P3-1901

**NON-ALCOHOLIC FATTY LIVER DISEASE IN PEDIATRIC TYPE 2 DIABETES: METABOLIC AND HISTOLOGIC CHARACTERISTICS IN 38 SUBJECTS**

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**Objectives:** Obesity and type 2 diabetes (T2D) are risk factors for non-alcoholic fatty liver disease (NAFLD). However, there is limited understanding of the histologic activity of NAFLD in children with T2D. We studied the relationship between liver histology and metabolic phenotype in obese pediatric patients with T2D.

**Methods:** An IRB-approved retrospective chart review of children with T2D and biopsy-proven NAFLD. Liver slides were scored by one pathologist using the NASH CRN scoring system. High NAFLD activity was defined as NAFLD Activity Score (NAS, range 0-8) ≥ 5. Labs including highest transaminases and lipid panel results ≤6 months of Bx and A1c nearest to Bx were used to correlate with NAS.

**Results:** 38 subjects (21 F, 17 M), 63.2% Hispanic, 15.8% Caucasian, with mean T2D Dx at 13.4±2.7 years, had their first evaluable Bx at 14.3±2.3 years. All were euthyroid. NAS score ≥ 5 was noted in 43% of females and 59% of males (NS), with



mean NAS score  $3.8 \pm 1.6$  and  $4.1 \pm 1.8$ , respectively (NS). Nine (6F, 3M) had  $NAS < 3$  (24%). Parameters close to Bx showed mean  $A1c = 6.9\%$ , elevated  $ALT = 94.7$  U/L,  $AST = 79.3$  U/L, Triglycerides (TG) = 332 mg/dL, and low HDL = 36.4 mg/dL. For those with  $NAS \geq 5$ , ALT varied widely (50-225 U/L). NAS correlated with  $A1c$  ( $r = 0.49$ ), TG ( $r = 0.39$ ), and HDL ( $r = -0.47$ ). HDL was lower ( $p = 0.026$ ) in males (32.2 mg/dL) vs females (40.2 mg/dL). No other gender or ethnic differences were noted. Most received metformin (78.9%) and/or insulin (50%). In 8 subjects with a 2nd Bx (range 1.7-5.6 years later) NAS was equal (37.5%) or improved (62.5%), and mean score went from 3.75 to 2.5 (NS). None received vitamin E. Steatosis was similar or lower, mean going down from 68.1% to 32.8% ( $p = 0.027$ ).

**Conclusions:** High NAFLD activity is common in pediatric T2D, and can be present even with mild transaminase elevation. Lower NAS scores were noted with lower TG, A1c and higher HDL, targets that can be improved with diet and diabetes control. No significant gender or ethnic differences were noted, aside from lower HDL in males. The stability and improvement on a repeat Bx noted in a small subset suggest that control of T2D may be beneficial for NAFLD in children.

P3-1902

#### REFERRALS FOR HYPOGLYCEMIA TO THE PEDIATRIC ENDOCRINE CLINIC: IS IT FOR REAL?

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**Objectives:** Concerns about hypoglycemia in otherwise healthy children is a common reason for referral to pediatric endocrinology. How often true pathologic hypoglycemia is identified among these patients has not been systematically examined. Our objective was to determine the incidence of pathologic hypoglycemia in the outpatient setting among school-aged children and adolescents referred for hypoglycemia.

**Methods:** A retrospective review of otherwise healthy pediatric patients  $\geq 5$  years of age seen in the pediatric endocrine clinic for hypoglycemia was conducted. Variables analyzed included age, gender, BMI SDS, symptoms, previous evaluation, laboratory data and disposition.

**Results:** Charts of 83 eligible patients (60% female) were reviewed. Mean age at referral was  $11.4 \pm 3.9$  years and average BMI z-score was  $0.40 \pm 1.07$ . The most common symptoms were feeling shaky (34%), dizzy/lightheaded (24%), having headaches (24%), diaphoresis (23%), abdominal pain or nausea (19%) and "spells" (19%). Fourteen patients had a history of syncope and three patients reportedly had a previously detected serum glucose  $< 50$  mg/dL. Nineteen patients had been given a glucometer prior to the appointment and many reported treating presumed lows with snacks. Evaluation in the pediatric endocrinology clinic consisted of a Hemoglobin A1c in 41 (49%) and a random serum glucose in 17 (20%), all of which were normal. Twenty-four patients (29%) were sent home with a glucometer and

thirteen (14%) with a prescription for a STAT serum glucose at the time of an episode with no results received to date. Of the six patients (7.2%) hospitalized for a challenge fast, one developed hypoglycemia and was subsequently diagnosed with primary adrenal insufficiency. This patient was an eight year old female with a history of a prior serum glucose of 40 mg/dL.

**Conclusions:** Although non-specific episodic symptoms often generate concerns about hypoglycemia in otherwise healthy children, the probability that pathologic hypoglycemia exists is exceedingly low. Education of primary care providers is needed in order to decrease unnecessary referrals, minimize parental anxiety and avoid disruption to the daily activities of well children and adolescents.

P3-1903

#### ANALYSIS OF INSULIN SECRETORY DYNAMICS DURING ORAL GLUCOSE TOLERANCE TEST (OGTT) IN OBESE PREDIABETIC CHILDREN AND ADOLESCENTS.

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**Objectives:** OGTT is the gold standard test to detect prediabetes and /or Type 2 diabetes. American Diabetes Association criteria for prediabetes: a)  $HbA1c$  5.7- 6.4% b) impaired fasting glucose (IFG)  $\geq 100$  mg/dl and/or impaired glucose tolerance (IGT: post-prandial plasma glucose (PG)  $\geq 140$ ) during an OGTT.  $HbA1c \geq 6.0\%$  is considered high risk (1).

**Objectives:** a) To measure timed plasma insulin (PI) values during an OGTT and to analyze whether they can enhance the interpretation of an OGTT, especially in the normal glucose tolerance (NGT) category.

**Methods:** A retrospective design reviewed OGTT results of 34 obese children and adolescents; 8-17 years of age;  $BMI > 95^{th}$  % and prediabetes. PG and PI values were obtained at 0, 1 and 2 hr during a 75 g glucola challenge OGTT.  $HOMA-IR$  was calculated = fasting glucose X fasting insulin/405 and values  $\geq 3.4$  were considered as insulin resistant (3). T test was used to study differences between group 1:  $HbA1c < 6.0\%$  and group 2:  $HbA1c \geq 6.0\%$ . A pediatric study has suggested that 1 hour plasma glucose  $\geq 132.5$  mg/dl (1h PG) during an OGTT can be considered abnormal (2).

**Results:** Mean age (mean  $\pm$  SD) was  $13.4 \pm 3.8$  years;  $BMI = 29.7 \pm 9.2$ ; 60% were Hispanic and females. **PG:** Two subject had IGT, 2 had IFG and 6 had an abnormal 1 h PG during an OGTT. There were no statistical differences between PG at 0, 1 & 2 hours among the groups. **PI:** One & 2-hour insulin levels (1h PI & 2h PI respectively) were significantly higher in group 1 compared to group 2 ( $p = 0.003$  &  $p = 0.02$  respectively), suggesting a decreasing insulin response from beta cells. Spearman correlation of 1h PI showed trends towards significance with 1h PG & 2h PG ( $p = 0.07$ ). Delta insulin (1h PI- 0h PI) showed statistical significance with  $HbA1c$  ( $P = 0.027$ ).  $HOMA-IR$  showed significant correlations with 1h PI & 2h PI ( $r = 0.6$ ;  $p = 0.001$ ).



**Conclusions:** Our results suggest: 1) Follow up OGTT's will be needed to determine the conversion rate to abnormal glucose tolerance in those subjects with an elevated 1h PG (17%). 2) 1h PI, in addition to 1h PG, may be a useful to identify high risk subjects, especially those with HbA1c  $\geq$  6 % in the NGT category 2) HOMA-IR is predictive of timed insulin responses during an OGTT 3) Assessment of insulin values may augment the interpretation of OGTT results, especially in NGT category.

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P3-1904

### USING CRISPR/CAS9 GENE EDITING TO STUDY MOLECULAR MECHANISMS OF CONGENITAL HYPERINSULINISM (CHI)

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**Objectives:** Background: Congenital Hyperinsulinism (CHI) is a heterogeneous genetically determined condition that is characterised by unregulated secretion of insulin from pancreatic  $\beta$ -cells. Aim: To develop models of CHI using CRISPR/Cas9 gene editing in order to study the molecular mechanisms of the disease. The genes targeted are *ABCC8*, mutations of which are most commonly seen in patients with CHI, and *HADH* which is a rare cause of CHI. The Cas9/guide RNA(gRNA) complex binds to the targeted area of the DNA creating double stranded breaks which are then repaired by the non-homologous end joining (NHEJ) technique which leads to short insertions/ deletions (indels) thus causing gene disruptions. The applicability and efficiency of CRISPR/Cas9 gene editing as a tool to generate models to study CHI has been little reported.

**Methods:** sgRNAs were designed using 3 different web tools for predicting on-target and off-target probabilities. The exons 1, 3 and 6 were targeted in the *ABCC8* gene while exons 1,3 and 4 were selected in the *HADH* gene in MIN6 cell lines. sgRNAs were then cloned into the plasmid vector pX330 encoding the *S. pyogenes* Cas9 endonuclease (SpCas9) gene. These constructs were transfected into the MIN6 cells. Gene editing efficiency was determined by the T7 Endonuclease I mutation detection assay and Sanger sequencing.

**Results:** Six sgRNAs have been designed of which two have targeted the *ABCC8* gene at two sites within exons 3 and 6. We demonstrated insertion and deletions (indels) within the genomic DNA of the *ABCC8* gene which shows the potential generation of a knock-out mutation in the *ABCC8* gene of MIN6 cells using the CRISPR/Cas9 gene editing technique.

**Conclusions:** The results of our study so far has demonstrated the potential of the use of Cas9/gRNA system as an efficient reverse genetic tool in studying the molecular mechanisms

underlying CHI. Our future aims are to: conduct further molecular interrogation to confirm the KO in *ABCC8* gene; create a KO allele of *HADH* gene in the MIN6 cell line and further, use the newly generated KO mutant cells, to analyse the function of these genes.

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P3-1905

### THE EFFECT OF MATERNAL DIABETES MELLITUS ON FETAL SERUM EXOSOMAL MICRORNA EXPRESSION

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**Objectives:** Exposure to the diabetic milieu *in utero* has long-term effects on the infant including predisposition to developing type 2 diabetes mellitus (DM2) and obesity.

Exosomes are membrane vesicles secreted by cells and transfer unique microRNAs (miRNA) to recipient cells enabling gene-based communication between cells.

We hypothesize that exposure of maternal diabetes effects exosomal miRNA in the fetal circulation, and miRNA are potential mediators of some of the metabolic effects on the infants.

**Methods:** Umbilical cord serum was collected at delivery from healthy, term offspring of women with type 2 or gestational DM (DM group) and normoglycemic controls undergoing elective Caesarian section. Exosomes were isolated from equal volumes of cord serum and total RNA was isolated. Synthetic *Caenorhabditis elegans* miRNA was added during RNA isolation as spike-in control. Reverse transcription was performed on equal volumes of total RNA and quantitative PCR reactions were performed in triplicate for each miRNA species. Expression of seven miRNAs, miR-126, miR-130b, miR-148a, miR-let 7a, miR-132, miR-29a and miR-222 were compared between the DM and control groups using Mann Whitney U Test. These 7 miRNA were selected as they are known to be regulated by dysglycemia. Results were analyzed using IBM SPSS and p<0.05 was considered significant.

**Results:** All seven miRNAs were detectable in the exosomes (average Cq below 32). Expression of miRNA-let7a was significantly higher in exosomes from diabetic pregnancies. miRNA-130b and miRNA-126 expression approached statistical significance. No difference in the expression was observed for miR-148a, miR-132, miR-29a and miR-222. See Table 1.

**Conclusions:** This study identifies increased abundance of specific miRNAs in the fetal circulation exposed to the maternal diabetic milieu, and these miRNAs are known to play key roles in physiological and pathological processes through regulation of gene expression. The results of this study will provide a foundation for future studies in which we will evaluate the potential cellular targets of these miRNAs

and determine the metabolic mechanisms affected by miRNA.

Table 1: Fold change expression of miRNA between DM versus control groups

	miR-126	miR-130b	miR-148a	miR-let 7a	miR-132	miR-29a	miR-222
DM	1.56	1.41	0.94	1.28	1.29	2.21	1.83
P value	0.082	0.094	0.348	0.044	0.332	0.120	0.202

P3-1906

**COMPLICATIONS OF TYPE 2 DIABETES IN ADOLESCENT PATIENTS: THE RHODE ISLAND HOSPITAL EXPERIENCE COMPARED TO THE TODAY STUDY**

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**Objectives:** The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study was a multi-centered, prospective randomized clinical trial that compared metformin monotherapy, metformin and rosiglitazone, and metformin with intensive lifestyle intervention, on outcomes of youth-onset type 2 diabetes (T2DM). In addition to comparably more difficult glycemic control than similar adult cohorts, the TODAY study noted accelerated onset of complications and comorbidities, thus demonstrating the aggressive nature of youth-onset T2DM. In light of the TODAY study, we wanted to compare glycemic control and associated complications of our local population to the national trial.

**Methods:** We performed a retrospective chart review of pediatric patients with Type 2 diabetes seen at the Hasbro Children's Hospital Pediatric Diabetes clinic from 2003-2013. Inclusion criteria include obese adolescents with diabetes with negative diabetes autoimmune antibody panel and had more than one visit to clinic. We tracked HbA1C, BMI, blood pressure, LDL, microalbuminuria screening, and documented dilated eye exams at five visits over the span of 3 years (at diagnosis, 6 months, 1 year, 2 years, and 3 years).

**Results:** Sixty-five patients (41 F; 24 M) were included in the study. At diagnosis, mean age was 13.8 years, BMI 37.2 kg/m<sup>2</sup>, HbA1c 8.5%. Hypertension (>130/80 or >95% for age/height/sex) increased from a baseline of 17% of all participants to 40% by the end of the study. Elevated LDL cholesterol >130 increased from 17% to 31%.

Microalbuminuria (microalbumin to creatinine ratio >30ug/mg at 2 or more visits) increased from 3.3% to 30%. Finally, only 14 patients had a documented dilated eye exam, and 1 patient had developed diabetic retinopathy.

**Conclusions:** Prevalence of hypertension, hyperlipidemia, and microalbuminuria in our 65 patients increased over three years from time of diagnosis, similar to the TODAY study. Limitations include number of patient charts reviewed and patients who did not receive recommended screening for hyperlipidemia, diabetic kidney disease, and retinopathy. This further emphasizes the importance of adhering to screening guidelines for complications in adolescent patients with Type 2 diabetes.

P3-1907

**TYPE 2 DIABETES IN ADOLESCENTS IN ANNABA; EXPERIENCE OF A PEDIATRIC DIABETES CLINIC**

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**Objectives:** Type 2 diabetes (T2D) is an emerging pathology in pediatrics, whereas it is a characteristic of adult patients, T2D is strongly linked to obesity, which is becoming more frequent in adolescents. The aim of this study is to show the appearance of T2D in adolescents in Annaba, to identify its diagnostic criteria and to explore the risk factors.

**Methods:** In a pediatric diabetes clinic in Annaba, between 2015 and 2016, 8 cases of overweight or obese adolescents were diagnosed with T2D. We analyzed the data of the history, the clinical examination, the biology and the treatment.

**Results:** The age of our patients was between 10.5 and 14.7 years. The population consists of 6 girls and 2 boys. The BMI was between 19 and 38. A family history of T2D was present in all cases. Acanthosis nigricans was present in 4 cases. HbA1c at diagnosis was between 7.9 and 12.8%. C-Peptide was normal (decreased in only one case), biomarkers of autoimmunity of type 1 diabetes (T1D) that were performed were negative. Our patients have no vascular complications. 6 cases were first diagnosed as T1D and treated with insulin and then the treatment was switched to metformin. All our patients are currently on metformin monotherapy. The treatment allows good glycemic control when dietary advice and physical activity are well followed.

**Conclusions:** T2D in overweight adolescents with a family history of T2D needs systematic attention. the discriminating criteria available are the blood insuline level and/or C-Peptide measurement as well as autoantibodies. Screening at 10 years of age for young obese at risk should be considered. Prevention is possible through the fight against obesity and lifestyle changes.

P3-1908

**GROWTH HORMONE THERAPY AMELIORATES INSULIN RESISTANCE IN SEVERE GROWTH HORMONE DEFICIENCY.**

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**Objectives:** To report a case of severe insulin resistance (IR) secondary to growth hormone (GH) deficiency in a patient with newly diagnosed Type 2 diabetes (and a history of other pituitary insufficiencies adequately treated) which was ameliorated by GH supplementation.

**Methods:** Case Report

**Results:** A 17-year-old non-obese (BMI 26 kg/m<sup>2</sup>) Caucasian female with a history of a medulloblastoma diagnosed at 7-years-old, status post brain-stem radiation therapy that developed Thyrotropin (TSH) and Gonadotropin Releasing Hormone (GnRH) deficiencies, presented to our practice. At presentation, though GH deficiency was suspected based on her height, z-score – 3.10, it was reportedly unexplored prior. At 20-years-old, based on glucosuria detected on surveillance at the Oncology clinic and HbA1c of 9.1 (4–5.6 %) with symptoms, diabetes was diagnosed. GAD, ICA-512, IAA, ZnT8 antibodies and MODY testing were negative. Fasting C-peptide was 3 (0.4–2 ng/mL). Insulin therapy was started however; she required frequent dose escalation for hyperglycemia management and her maximum total daily insulin requirement was 2.9 Units/kg/day, initially. Further work-up, which included assessing for cortisol excess, hematological causes of IR such as Hepatitis B and C, hemochromatosis and porphyria cutanea tarda, were all negative. Provocative GH stimulation testing using Arginine-Clonidine was performed based on the presence of pituitary hormonal deficiencies. Peak GH was 0.8 (normal ≥ 10 ng/mL). Brain magnetic resonance imaging (MRI) indicated a small anterior pituitary for the patient's age. GH therapy was initiated, 0.3 mgs daily and titrated upwards based on IGF1 levels. Her HbA1c decreased to 5.9% and 5.3% at 6 and 9 months respectively and insulin therapy requirement decreased to 2 Units/kg/day at 9 months. In addition, quality of life (QoL) indices improved.

**Conclusions:** In individuals with predisposing factors for GH deficiency who develop Type 2 diabetes and profound IR, an exploration of GH-IGF 1 axis should occur when IR cannot be explained by common IR states. GH supplementation may not only ameliorate IR and improve diabetes control, but it may be associated with an improvement in QoL.

P3-1909

#### VITAMIN C PROTECTS AGAINST TNF- $\alpha$ -INDUCED HEPATIC INSULIN RESISTANCE THROUGH SUPPRESSION OF INFLAMMATION

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**Objectives:** Activation of inflammatory pathways by inflammatory cytokines gives rise to insulin resistance. Vitamin C, an antioxidant agent, which has been reported to possess both antioxidant and anti-inflammatory properties. Therefore, The present study was designed to evaluate the effect of Vitamin C on amelioration of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ )-induced hepatic insulin resistance in vivo and vitro.

**Methods:** Insulin resistance was induced by TNF- $\alpha$  in HepG2 hepatocyte cells and Gulo(–/–) male mice. Vitamin C (0.33, 3.3 g/L in drinking water) in mice and Vitamin C (100  $\mu$ mol/L) in HepG2 cells were administered. Glucose tolerance test, insulin tolerance test, hepatic glycogen content, 2-(N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino)-2-deoxyglucose (2-NBDG) uptake and protein expression of insulin receptor substrate-1 (IRS-1), protein kinase B (AKT), glycogen synthase

kinase (GSK)-3 $\beta$  and glucose transporter (GLUT)-2 were estimated as indicators of insulin resistance. Gene expression of interleukin (IL)-6, IL-1 $\alpha$  and protein expression of inhibitor of  $\kappa$ B kinase (IKK)- $\beta$ ,  $\kappa$ B- $\alpha$ , nuclear factor-kappa B (NF- $\kappa$ B), c-Jun NH<sub>2</sub>-terminal kinase (JNK), p38 mitogen-activated protein kinase (p38) and extracellular signal-related kinase (ERK)1/2 were measured as indicators of inflammation.

**Results:** Vitamin C improved impaired glucose tolerance, increased insulin sensitivity, increased glycogen synthesis and 2-NBDG uptake by enhancing insulin signaling pathway IRS-1/AKT/GSK3 $\beta$ /GLUT2 in a TNF- $\alpha$ -induced model of insulin resistance in vivo and vitro. Vitamin C presented strong inhibition effect on TNF- $\alpha$ -associated inflammation, as gene expression of IL-6 and IL-1 $\alpha$  in liver were greatly reduced with suppression of IKK $\beta$  phosphorylation,  $\kappa$ B $\alpha$  degradation and phosphorylation at position Ser32 and inhibition of NF- $\kappa$ B translocation into nuclei. Meanwhile, Vitamin C also significantly inhibited TNF- $\alpha$ -induced MAPK JNK and p38 activation, but no significant inhibitory effect on ERK1/2 activation.

**Conclusions:** These data demonstrated that Vitamin C could inhibit TNF- $\alpha$ -associated inflammation and attenuate hepatic insulin resistance through suppressing TNF- $\alpha$ -mediated inhibition of insulin IRS-1/AKT/GSK3 $\beta$ /GLUT2 signaling. Therefore, Vitamin C might have potential to be applied for treatment of metabolic disorder.

P3-1910

#### DIAGNOSIS OF HEREDITARY SPHEROCYTOSIS WITHOUT ANEMIA DUE TO LOW GLYCATED HEMOGLOBIN IN ADOLESCENT TYPE 2 DIABETES MELLITUS PATIENT: CASE REPORT

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**Objectives:** Glycosylated hemoglobin (HbA1c) reflects average glycemic control for about 3 months and strong predictive value for diabetes complications. Strict glycemic control can make HbA1c reach less than 6.5% but a reasonable HbA1c goal is less than 7% because of hypoglycemia or other adverse effects of treatment.

We report the rare case of a boy with type 2 diabetes mellitus (T2DM) who had no anemia, but was diagnosed with hereditary spherocytosis due to too low HbA1c.

**Methods:** A 13-year-old boy came to the emergency room with abdominal pain. He was diagnosed with diabetic ketoacidosis (DKA; serum glucose 1397 mg/dL, pH 7.12, urine ketone 3+, urine glucose 4+), T2DM (C-peptide 1.89 ng/mL, HbA1c 8.1%), fatty liver (SGOT 16 U/L, SGPT 47 U/L, severe diffuse fatty liver on abdominal sono), hyperbilirubinemia (total bilirubin 2.4 mg/dL, direct bilirubin 0.6 mg/dL). There was no anemia (Hb 16.5 mg/dL) and sonographically negative

spleen, gallbladder. After DKA was controlled, he was treated with metformin.

**Results:** After metformin treatment for 4 and 8 months, HbA1c decreased 4.7% and 3.8%, respectively. Total bilirubin stayed high (1.8~2.9 mg/dL) and there was no anemia. Osmotic fragility test was positive and splenomegaly (13.1cm) was newly developed. He was diagnosed with hereditary spherocytosis and diabetic control was monitored with self-monitoring of blood glucose (SMBG), glycated albumin and fructosamine.

**Conclusions:** Hereditary spherocytosis is hemolytic disorder characterized by anemia, intermittent jaundice and splenomegaly. However, in our case no anemia was noted not only initial but also even with splenomegaly due to well compensation. Short RBC lifespan leads to falsely low HbA1c level.

HbA1c reflects average glycemic control and there can be discrepancy in undiagnosed mild RBC disease. Clinicians should be aware the discrepancy of HbA1c measurement with SMBG

P3-1911

#### **CHANGES IN ANNUAL INCIDENCE IN CHILDREN WITH TYPE 2 DIABETES DETECTED BY URINE GLUCOSE SCREENING PROGRAM AT SCHOOLS IN TOKYO DURING 1975-2015**

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**Objectives:** Changes of annual incidence in children with type 2 diabetes detected by urine glucose screening program at schools in the Tokyo Metropolitan Area during 1975-2015 were studied.

**Methods:** Trends of temporal changes in annual incidence rate were analyzed using a joinpoint regression model developed by Kim et al., and the joinpoints where is an essential change in the log-linear trends were detected. Annual percent change (APC) was calculated for each segmented line regression. Average annual percent change (AAPC) was also calculated for the whole period analyzed.

**Results:** During the study period, a total of 11,652, 205 children, including 7,955,857 primary school children (PSC) and 3,696,348 junior high school children (JHSC), participated in the screening program. Thus, 301 children, including 64 PSC and 237 JHSC, were diagnosed with having type 2 diabetes. The incidence of type 2 diabetes (per 100,000 children-year) throughout the study period was 2.58 in all children, 0.80 in PSC and 6.41 in JHSC. AAPC during the entire study period was estimated as -1.5 (NS), and the incidence significantly increased during 1975-1982 (APC=17.49,  $P<0.05$ ), but tended to decrease during 1982-2015 (APC=-1.01). In PSC, the incidence significantly increased during 1975-2010 (APCC=3.3,  $p<0.05$ ), and tended to decrease during 2010-2015 (APC=-29.61). On the other hand, in JHSC, the incidence hardly increased during the entire study period (APCC=0.06).

**Conclusions:** We speculated that significant increase in the incidence of type 2 diabetes in PSC during 1975-2010 might

be reflected by increase in the frequency of obesity in PSC during the same period, whereas decrease in the incidence during 2010-2015 seems to be influenced by tendency of decline in the frequency of obesity possible due to improvement of lifestyle in PSC after 2010 in Tokyo.