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in Paediatrics

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Abstracts

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PL5

Cracking the pituitary stem cell code across life using single-cell transcriptomics and organoid models

Hugo Vankelecom

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The pituitary gland dynamically remodels during key timepoints of life to meet the prevailing endocrine demands of the organism. Mechanisms underlying this plasticity remain poorly understood. In particular, it is not clear how the pituitary stem cells are involved and biologically behave during pituitary remodeling processes. Indeed, pituitary stem cells remain highly enigmatic regarding cellular complexity, regulatory circuits, niche make-up and functional role. In our studies, we decode the pituitary stem cells' biology at key physiological stages of life and during pathological conditions including local damage and tumorigenesis. To this end, we apply state-of-the-art single-cell transcriptomics and innovative pituitary-derived organoids, *in vitro* models closely recapitulating the stem cells' biology.

Single-cell RNA-sequencing (scRNA-seq) unraveled a high activation modus in the stem cell compartment of the neonatal maturing (mouse) pituitary. Transgenically inflicted local damage, although not inducing extra stem cell activation, is efficiently and fully restored. In contrast, injury at adult age promptly stimulates the pituitary stem cells and is also repaired, although more slowly and incomplete. scRNA-seq and organoid interrogation uncovered interleukin-6 (IL-6) as pituitary stem cell activator, being upregulated after the inflicted damage. At aging, the gland's regenerative capacity fades, coinciding with absence of stem cell activation and IL-6 upsurge following the local injury, attributed to a pronounced inflammatory state in the older gland (i.e. 'inflammaging'). Captivatingly, inquiry of human pituitary omics datasets showed significant translational power of our mouse-based findings. Also, the organoid models closely recapitulated the stem cells' phenotypical and functional aspects according to specific age and pathology. Intriguingly, organoid examination revealed that the old pituitary's stem cells retain intrinsic functionality but are *in vivo* restrained by the obstructive inflammatory microenvironment. Finally, we found that stem cell activation as occurring in the tumorigenic (mouse) gland is also recapitulated in organoid culture, comparable to findings in human pituitary tumor-derived organoids.

Taken together, using innovative approaches we are cracking the pituitary stem cell code across life and pathologies. The resultant pituitary single-cell atlas will uncover stem cell complexity and pathways regulating stem cell behavior in the (remodeling) gland. Our endeavor can eventually translate into therapeutic, regenerative and rejuvenative strategies to counter deficient pituitary function due to damage, disease or aging.

PL6

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PL7

Abstract Unavailable

PL8

Real world use of closed loop insulin delivery

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The development of the artificial pancreas or closed loop for type 1 diabetes, which started as a concept in the last century, took off once continuous glucose monitors became available. The first hybrid closed loop entered the market in 2016, where now several systems compete. This creates the 'luxury problem' of having to choose between different systems. Anonymized CGM data collection from company databases try to address the question whether performance in optimized randomized clinical trial circumstances is mirrored in real world evidence, and whether performance is different across the various age groups. Finally, will we soon see fully closed systems, and what would these look like? All this and more will be discussed at the last plenary session of ESPE 2023!

Symposia

DSD

S1.1

Life-long care for people with 46,XY DSD

Olaf Hiort

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46,XY differences of sex development (46,XY DSD) comprise a very heterogeneous group of people amongst DSD. While some conditions are well characterized on the molecular level, e.g. androgen biosynthesis enzyme deficiency or DSD due to genetic variants in the androgen receptor, many 46,XY DSD patients lack a specific diagnosis, especially those people where gonadal development is affected. A specific diagnosis, however, is helpful to develop an individualized management programme for life-long care.

Standardized care should be offered through specified centres for DSD management offering a multidisciplinary approach for longitudinal assessment. This offer needs to spread from the initial diagnostic work up for the newly diagnosed child and its family to a transition process during adolescence and continuous upkeep through adulthood. With the restriction of surgical procedures altering genital appearance in childhood, we will be more and more confronted with adolescents actively seeking advice for possibilities of bodily appearance. Second, with the postponement of gonadectomy to adulthood or the maintenance of the gonads in situ, we need to develop screening programmes as well as a decision-making process for these patients regarding gonadal management. This adds to queries on hormone therapy during adolescence and adulthood. In association with certain conditions, specialized preventive management has to be developed, e.g. for neuropathy in people with desert hedgehog variants or with MYRF mutations for hyperopia. As in many rare conditions, these management issues need interested experts which have to be part of the network for DSD care. Finally, psychosocial support needs to be offered throughout the life-span to empower all affected person in changing life situations.

S1.2

Studying neglected cell populations of the developing testis and their functions

Serge Nef

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Gonadal sex determination represents a unique model for studying cell fate decisions. However, a complete understanding of the different cell lineages forming the developing testis and ovary remains elusive. The widespread adoption of advanced sequencing technologies, such as scRNA-seq, has provided the field of developmental biology with an opportunity to discover previously unrecognized cell types, such as short-lived progenitors or rare cell lineages. By combining single cell transcriptomic analyses during the critical period of sex determination with in vivo lineage tracing, we will describe the specification and differentiation of several previously neglected gonadal cell lineages that give rise to multiple cell types such as rete testis cells, peritubular myoid cells, as well as fetal and adult Leydig cells.

S1.3

Pathogenesis of testicular dysfunction in Klinefelter syndrome

Kristian Almstrup

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The most common genetic abnormality found among men is the presence of an additional X-chromosome which causes Klinefelter syndrome (KS). KS has an estimated prevalence of 1.5/1000, but only ~40% receive the diagnosis, probably because the phenotype varies considerably. Men with KS often show eunuchoid body proportions, cognitive and psycho-social difficulties, and have an increased risk of developing cardiometabolic diseases. But the most persistent symptoms are small testes, non-obstructive azoospermia, and hypergonadotropic hypogonadism. The additional X chromosome arises due to a non-disjunction during paternal or maternal meiosis and is thought to be subjected to dosage compensation by X-inactivation and expression of the long non-coding RNA, XIST.

In adult men with KS, the testes appear degenerated and typically only contain Sertoli cell-only (SCO) tubules without germ cells, degenerated “ghost” tubules, and Leydig cell hyperplasia. Occasionally, focal spermatogenesis can be observed and is crucial for the ability to father a child by in vitro fertilisation. However, what biologically determines whether focal spermatogenesis can occur and what causes testicular degeneration remains unknown.

With the emergence of bulk RNA- and later single-cell RNA-sequencing, several studies have indicated that the Sertoli cells play a central role in testicular degeneration. Interestingly, earlier morphological studies have described that two different types of SCO tubules exist, in which, the Sertoli cells show differences in the presence of the Barr body. The Barr body represents a dense inactivated X-chromosome and was observed in the type B SCO tubules containing immature-like Sertoli cells but never in the type A SCO tubules containing adult mature-like Sertoli cells. This could indicate a relationship between X-inactivation and the maturity of the Sertoli cells.

Using ultra-sensitive single-molecule RNA and DNA in situ hybridisation with probes targeting XIST and the X chromosome, we show that the undifferentiated type B Sertoli cells highly express XIST and have two X-chromosomes, while the differentiated type A have lost XIST expression and the additional X-chromosome. Hence, the maturity of the Sertoli cells seems related to the loss of the additional X-chromosome. In focal tubules with spermatogenesis, both Sertoli cells and spermatogonia were also found to have lost XIST expression and the additional X-chromosome.

The additional X-chromosome hence seems incompatible with the maturation of Sertoli cells and spermatogenesis, while focal rescue of spermatogenesis can occur in conjunction with a micro-mosaic loss of the additional X-chromosome both in Sertoli cells and spermatogonia.

Hypothalamo-pituitary disorders

S2.1

Abstract Unavailable

S2.2

Abstract Unavailable

S2.3

Abstract Unavailable

Endocrine effects of cancer treatment

S3.1

Safety of GH treatment in cancer survivors

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Cancer treatment may result in development of long-term endocrine complications, including growth hormone (GH) deficiency·[1] Although extensive and careful monitoring has been carried out to establish the safety profile of GH therapy,[2] a relative scarcity of data means that questions persist around its use in survivors of childhood cancer.

The effects of GH on growth and metabolism mean that there is a particular interest in whether GH therapy increases the risk of tumor recurrence or a second neoplasm in childhood cancer survivors.[3] Expert assessment of the available evidence indicates that there is little to indicate that GH treatment causes a new primary cancer or recurrence of previous primary cancer in children; however, there is less evidence in the adult population of childhood cancer survivors, and treatment decisions need to be made on a case-by-case basis.[3] Evidence for an increased risk of secondary or subsequent neoplasms in children who survived cancer is also scarce, but indicates a reduction in risk as the time after onset of GH treatment increases.[3] The cellular effects of GH have also given rise to the suggestion that GH therapy can increase the risk of development of diabetes, although surveillance and clinical data indicate that this is limited to type 2 diabetes in predisposed individuals.[4]

This presentation will review the current best approach to management of growth hormone deficiency in childhood cancer survivors given the available data and discuss the considerations that must be made at initiation of GH therapy, and as it proceeds.

References

1. Robison LL and Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. Nat Rev Cancer 2014;14: 61–70.
2. Stochholm K and Kiess W. Long-term safety of growth hormone-A combined registry analysis. Clin Endocrinol (Oxf) 2018; 88:515–28.
3. Allen DB et al. GH safety workshop position paper: a critical appraisal of recombinant human GH therapy in children and adults. Eur J Endocrinol 2016;174:P1–9.
   Cutfield W et al. Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment. Lancet 2000; 355:610–3.

S3.2

Surveillance for Endocrine Disease in Childhood Cancer Survivors

Wassim Chemaitilly

UPMC Children's Hospital of Pittsburgh, Pittsburgh, USA

Endocrine and reproductive sequelae are among the most commonly reported complications in survivors of childhood cancer and brain tumors with nearly 50% individuals affected. Treatment related hormonal disorders may occur in a delayed fashion as late effects, several years to decades after the completion of cancer or tumor therapy, especially when resulting from the irradiation of the endocrine glands. This phenomenon requires a systematic, risk-based, approach in the screening of survivors in order to allow early diagnosis and treatment. Over the past two decades, several national and regional oncology-led consortia have sought to develop evidence-based long-term follow-up screening guidelines with a more recent effort to harmonize these recommendations through the collaborative International Guideline Harmonization Group. This presentation proposes an overview of the surveillance for endocrine disease in at-risk childhood cancer survivors, including areas of controversy and ongoing investigation.

S3.3

Fertility preservation in children with cancer

Rod Mitchell

MRC Centre for Reproductive Health, University of Edinburgh,
Edinburgh, United Kingdom

Fertility is dependent on the normal development of germ cells, which is controlled by hormones and paracrine factors produced by the somatic cells within the gonads. However, exposure to cancer treatment during childhood can cause damage to the gonads leading to infertility in adulthood [1]. This presentation will explore how various cancer treatments affect gonadal function based on clinical evidence in patients [2], experimental models involving animals and studies utilising human tissues [3]. Options for fertility preservation in children with cancer, including gonadal tissue cryopreservation, will also be described along with the latest information on utilising cryopreserved gonadal tissue to restore fertility in males and females. Finally, this presentation will describe some novel experimental approaches to fertility preservation in males that focus on protecting prepubertal gonads from the damaging effects of cancer treatment.

References

[1] Anderson RA and Mitchell RT et al. Thomas W Kelsey, Norah Spears, Evelyn E Telfer, W Hamish B Wallace. Cancer treatment and gonadal function: experimental and established strategies for fertility preservation in children and young adults. The Lancet Diabetes and Endocrinology 3(7):556-67. 2015.

[2] Lim TE et al. Impacts of platinum-based chemotherapy on subsequent testicular function and fertility in childhood cancer. Human Reproduction Update. 26(6):874-885. 2020.

[3] Tharmalingam MD et al. Cisplatin and carboplatin result in similar gonadotoxicity in immature human testis with implications for fertility preservation in childhood cancer. BMC Medicine. 18(1):374. 2020

Biography

Rod is Professor of Developmental Endocrinology at the MRC Centre for Reproductive Health at the University of Edinburgh. He is also a Consultant Paediatric Endocrinologist at The Royal Hospital for Children and Young People (RHCYP) in Edinburgh.

His research interests are focused on the role of the germ-stem cell niche in prepubertal testis development and function. This includes research into the effects of exposure to environmental exposures and pharmaceuticals (including chemotherapy) on germ cell development and future fertility potential. Rod is clinical and research lead for fertility preservation in prepubertal boys with cancer. His work combines the clinical service for gonadal tissue cryopreservation with research aimed at developing clinical strategies to protect or restore fertility in patients receiving gonadotoxic therapies.

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Twitter: @RodTMitchell

Novel insights and innovations in diabetes

S4.1

Abstract Unavailable

S4.2

Abstract Unavailable

S4.3

Physical interaction between beta and delta cells

Patrik Rorsman

University of Oxford, Oxford, United Kingdom

Diabetes mellitus is a bihormonal disorder involving both insufficient insulin secretion (from the beta-cells(and dysregulation of glucagon secretion (from the alpha-cells). In healthy people, a fall in plasma glucose increases glucagon and stimulates counterregulatory hepatic glucose production. This response is impaired in many patients with type-1 diabetes (T1D). Why this defect develops is unknown but it may lead to fatal hypoglycaemia, which accounts for up to 10% of the mortality in patients with T1D. Somaotstatin (secreted locally by the delta-cells of the islets) is a powerful paracrine regulator of glucagon secretion. We hypothesised that the loss of physiologically adequate counterregulation in T1D is the result of enhanced somatostatin signalling in the islets.

T1D is associated with the autoimmune destruction of the the beta-cells. Because the beta-cells outnumber the delta-cells by a factor >10, delta-cells will be in direct physical contact with several beta-cells. The interaction is so tight that electrical contacts (mediated by gap junctions) form between the two cells. Accordingly, electrical stimulation or inhibition of the beta-cells increase or decrease delta-cell electrical activity/somatostatin release, respectively. There was an inverse regulation between beta-cell number and somatostatin release, which would be consistent with the idea that the beta-cells provide an "electrical brake" on the delta-cells. Thus, experimental approaches that prevent electrical signalling between beta- and delta-cells increased somatostatin secretion under hypoglycaemic conditions. This culminates in supression of counterregulatory glucagon secretion and somatostatin receptor antagonists restore glucagon secretion at low glucose in T1D mice and in isolated human/mouse T1D islets.

These data suggest that agents that reduce somatostatin action/secretion should be considered as an adjunct to insulin therapy. They also suggest a new mode of intercellular communication between different types of cells in the endocrine pancreas and that electrical signals may be (at least) as important as paracine signals. Finally, this concept provides an explanation to the observation that residual beta-cell function (<10% of normal) protects against hypoglycaemia.

Hypothalamic syndromes

S5.1

Abstract Unavailable

S5.2

Abstract Unavailable

S5.3

Abstract Unavailable

Neonatal endocrinology

S6.1

Unravelling the role of epigenetics in reproductive adaptations to early-life environment

Philippa Melamed

Technion-Israel Institute of Technology, Haifa, Israel

Adult reproductive function is affected by early life environments and experiences, pointing to a possible role for epigenetic modifications in directing an adaptive response. Using mouse and cellular models, we have been studying the mechanisms underlying the shorter reproductive lifespan experienced by Bangladeshi women who grew up in Bangladesh as opposed to the UK, a phenotype associated specifically with the greater immune challenges in Bangladeshi childhood and altered DNA methylation signatures. Pre-pubertal colitis in mice similarly leads to later pubertal onset and smaller ovarian reserve. The ovaries of these mice express lower levels of *Srd5a1*, encoding the enzyme 5α reductase-1 that converts testosterone to dihydrotestosterone which plays a role in follicle development and ovarian function. Strikingly, the gene was seen to be hypermethylated at a transcriptional enhancer in these mice and at the orthologous genomic location in the DNA of the women who had grown up in Bangladesh. In mice, expression of this gene increases towards puberty and is upregulated by estradiol, an effect dependent on low levels of the enhancer methylation which normally drop at this time, explaining its pre-pubertal sensitivity to epigenetic modification. These mice also express lower levels of *Srd5a1* in the hypothalamus, where the enzyme plays a role in production of neurosteroids, and its inhibition delayed pubertal onset. However, expression of this gene in the hypothalamus is regulated very differently from in the ovaries, and appeared to be most sensitive in the neonatal stage to the repressive effects of glucocorticoids, which was enhancer methylation insensitive. Our findings shed new light on how early-life events can impact adult reproductive function and explain some of the diverse reproductive phenotypes in women with distinct life histories.

S6.2

Abstract Unavailable

S6.3

The developing HPA axis: establishing diurnal variation in cortisol secretion

Martijn Finken

Emma Children's Hospital Amsterdam UMC, Amsterdam, Netherlands

In adults and older children with adrenal insufficiency, hydrocortisone replacement therapy is based on the assumption that the secretion of cortisol follows a diurnal pattern, with a peak in the early morning, a gradual decline over the day and a nadir at midnight. However, replacement therapy with multiple daily doses of hydrocortisone is unable to exactly match the normal diurnal rhythm of cortisol secretion from an intact hypothalamus-pituitary-adrenal (HPA) axis, with consequences for metabolism.

In infants with adrenal insufficiency mismatch between hydrocortisone dosing scheme and cortisol clock may be even more prominent because of lack of normative data for HPA axis rhythmicity, while its consequences may be larger, considering that in infancy metabolic set point are set for life. Some studies suggest that a rhythm in HPA axis activity might already be present in the fetus, with data showing that markers of the fetal adrenal zone were higher in the afternoon than at other times of the day. However, the exact age at which an adult-type rhythm in cortisol secretion is established, could not be pinpointed, because studies conducted to date took too few samples across the diurnal cycle for the study of HPA axis rhythmicity. Based on the currently available scattered data it is assumed that an adult-type rhythm of cortisol secretion is established somewhere between 2 weeks and 9 months of age. During this talk novel data on HPA axis rhythmicity development will be presented.

Theories of obesity development and their implications on dietary interventions

S7.1

Competing Paradigms of Obesity Pathogenesis

David Ludwig

Boston Children's Hospital, Boston, USA

Conventional treatment for obesity, founded on the First Law of Thermodynamics, assumes that all calories are alike, and that to lose weight one must ultimately "eat less and move more." However, this prescription rarely succeeds over the long term. Calorie restriction elicits predictable biological responses – including increased hunger and reduced energy expenditure – that oppose ongoing weight loss. Indeed, the prevailing Energy Balance Model offers no compelling explanation for what environmental factors have so profoundly altered the biological systems that control body weight. Why has average body mass index increased so rapidly among populations worldwide with relatively stable genetic obesity risk?

The Carbohydrate-Insulin Model proposes a reversal in causal direction: Overeating doesn't drive body fat increase over the long term; instead, the process of storing excess body fat drives overeating. High intakes of processed carbohydrate raise the insulin-to-glucagon ratio, shifting substrate partitioning toward storage in adipose and leaving fewer calories available for metabolically active and fuel sensing tissues. Consequently, hunger increases and metabolic rate slows in the body's attempt to conserve energy. From this perspective, conventional calorie-restricted, low-fat diets amount to symptomatic treatment, destined to fail for most people. A dietary strategy aiming to lower insulin secretion promises to increase the effectiveness of long-term weight management and chronic disease prevention.

S7.2

Does an adiposity force induce obesity independent of a normal energy balance system?

Thorkild I.A. Sørensen

University of Copenhagen, Copenhagen, Denmark

Obesity in humans represents a cumulative retention of a tiny fraction of total energy intake as fat, which is accompanied by growth of the metabolically active, energy demanding, lean body mass. Since the energy balance regulation operates irrespective of the excess fat storage, availability of the required energy supplies is a permissive condition for obesity development. It occurs predominantly among people genetically predisposed and/or living with social or mental challenges. This is usually attributed to increased food intake due to environmental cues and/or increased appetite. However, although experimentally induced excessive food intake may enlarge the fat mass, it does not produce the obesity phenotype, characterized by the resistance to being reduced. I propose a theory in which the body responds to social disruptions as threats of a future lack of food by an adiposity force building a reserve of energy independent of the regulation of the energy balance. It is based on the assumption that our evolutionary development required collaboration in gathering and sharing of food, combined with precautionary measures against anticipated failing food supplies. Social challenges are perceived as such threats, which activate the adiposity force through the brain to instigate the growth of fat and lean mass by neuro-hormonal signaling bypassing the appetite regulation. The signals may induce minor alterations in the balance between adipogenesis and apoptosis in the adipose tissue and between lipogenesis and lipolysis in the adipocytes. If both perceived social threats and food abundance continue, the adiposity force pushes the fat accretion process to continue without inhibition by feedback signals from the fat mass, eventually leading to more obesity, and more so among genetically predisposed. If the theory is right, the challenge is to find ways to reduce or interrupt the signals from the brain to the adiposity stores.

DOI: 10.1159/000533803

S7.3

Abstract Unavailable

Adrenals

S8.1

Abstract Unavailable

S8.2

Abstract Unavailable

S8.3

Abstract Unavailable

Thyroid

S9.1

Abstract Unavailable

S9.2

Is there a role for combined T4 and T3 therapy in hypothyroidism?

Antonio Bianco

University of Chicago, Chicago, USA

The standard of care for the treatment of hypothyroidism is the administration of daily tablets of levothyroxine (LT4) at doses that normalize serum TSH levels. In most patients, this approach elevates serum thyroid hormone (TH) levels and eliminates symptoms of overt hypothyroidism. Nonetheless, treatment with LT4 in adults does not fully normalize the TH economy. Despite normal TSH levels, many patients exhibit a reduction in the serum T3/T4 ratio due to a relative excess of T4 and a relative deficiency of T3; in approximately 15% of the patients, serum T3 is below the normal reference range. New studies have shown that these residual abnormalities in TH homeostasis are due to an unbalance in T4 to T3 deiodination between the hypothalamus/pituitary gland and the other tissues involved in extrathyroidal T3 production. This could be clinically relevant as lower T3 levels could explain the residual hypercholesterolemia, increased utilization of statins, subnormal energy expenditure, and difficulty managing body weight frequently observed in LT4-treated patients. In addition, many adult patients prefer combination therapy with T4+T3; this is also observed in randomized clinical trials. In fact, the number of patients started in combination therapy, synthetic LT4+LT3 or desiccated thyroid extract (DTE) has doubled in the last 10 years. In LT4-treated children with congenital hypothyroidism, the serum T3/T4 ratio was found to be lower, but the utilization of therapy with LT4+LT3 has been limited to cases of consumptive hypothyroidism. Further studies in children with hypothyroidism could explore whether monotherapy with LT4 restores TH signaling in all forms of hypothyroidism.

S9.3

The role of thyroid hormone transporters in brain development and function

Heike Heuer

University Duisburg-Essen, Essen, Germany

Thyroid hormone (TH) transporters are mandatory for proper TH metabolism and action as they facilitate the transmembrane passage of both T4 and T3. Inactivating mutations in the highly specific TH transporter MCT8 (encoded by the X-linked SLC16A2 gene) lead to severe intellectual and motor disabilities presumably due to a strongly diminished TH transport into the CNS and, consequently, an impaired neural development (Allan-Herndon-Dudley Syndrome, AHDS). Apart from a central TH deficiency, AHDS patients exhibit strongly altered TH parameters. In particular, highly elevated serum T3 concentrations causes a thyrotoxic state in peripheral organs thereby affecting e.g. liver, heart, kidney and skeletal muscle function. Different AHDS mouse models have been developed and revealed distinct cell- and organ-specific functions of Mct8 in mediating TH uptake and efflux. Moreover, AHDS mice were successfully exploited to test therapeutic strategies including the application of TH analogs, chaperone treatment and novel gene therapy approaches. In my presentation, I will summarize recent preclinical findings that eventually will pave the ground for an effective treatment strategy for this rare and devastating disease.

Bone

S10.1

Abstract Unavailable

S10.2

Inherited ectopic calcification disorders

Frank Rutsch

Münster University Children's Hospital, Münster, Germany

Ectopic calcifications rarely manifest in the pediatric population. However, especially when present in arteries calcifications are often associated with severe complications. Ectopic calcification can be viewed as a phenomenon arising in a state of imbalance between systemic activators and inhibitors of calcification. Within recent years, research has led to the discovery of intricate networks regulating the systemic phosphate/pyrophosphate ratio, which seems to play an important role in this respect.

I will present an overview of the few inherited monogenetic disorders presenting with early onset ectopic calcification. These disorders can be classified according to the function of the respective disease gene into disorders caused by an altered phosphate/pyrophosphate metabolism, interferonopathies, Gaucher Disease type III and Keutel Syndrome.

The finding of ectopic calcification in early life should alert the clinician and prompt further genetic work-up to define the underlying genetic defect, to establish the diagnosis and to enable appropriate therapy.

S10.3

Abstract Unavailable

Diet, nutrients and the environment

S11.1

Timing of eating and exercise to improve metabolic health in humans

Patrick Schrauwen

Department of Nutrition and Movement Sciences, NUTRIM
School for Nutrition and Translational Research in Metabolism,
Maastricht University, Maastricht, Netherlands

Recently our 24-hour culture has been identified as another lifestyle factor that can cause type 2 diabetes. Technological and societal advances such as electric lighting and digital screens – leading to light exposure that is too dim during the day and too bright during the evening –, shift work, time zone transfers, and round-the-clock food availability disrupt our intrinsic and evolutionarily preserved 24-hour rhythms resulting in a desynchronization between light cues and behavior cues to our circadian system. This mistiming of cues is now thought to be a large contributor to the current metabolic health crisis, a concept known as circadian misalignment. Our internal biological clock sets circadian rhythmicity of a large range in bodily functions, including energy metabolism. We have shown that whole body energy expenditure and skeletal muscle mitochondrial function displays 24h rhythmicity in humans, a rhythm that is disturbed in prediabetic volunteers. Also, we have shown that a rapid day-night shift can lead to insulin resistance. More recently, we showed that also muscle metabolism shows 24h rhythmicity in healthy humans.

Next to light, also food and activity can function as zeitgebers for the molecular clock. Therefore, timing of interventions can be used to improve metabolic health; we and others showed that exercise training in the afternoon may have more beneficial effects compared to exercise training in the morning. Also, time restricted feeding may improve rhythmicity of our metabolism and glucose homeostasis. In this lecture, our latest data on the effects of timing of food intake and exercise on metabolic health will be presented.

S11.2

Abstract Unavailable

DOI: 10.1159/000533803

S11.3

Abstract Unavailable

What's new for the HPG Axis

S12.1

Minipuberty - Looking into the future

Katharina M. Main

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The transient activation of the hypothalamus-pituitary-gonadal (HPG) axis shortly after birth has been described as early as in the 70ies. This discovery has since been applied clinically as a 'window of opportunity' for diagnostic evaluation of patients suspected of endocrine disorders and differences of sex development. With the advent of increasingly more sensitive and specific analytical methods for peptide and steroid hormones produced in the pituitary, gonads, and adrenals our insight into the regulation of this developmental window has improved considerably.

Several research groups have investigated the physiology of this so-called 'mini-puberty' in boys and girls and described its significance for genital growth and functional development. Some of these effects are easily assessed by clinical examination, ultrasound, and blood samples. Recently, our group has been able to perform a long-term follow-up of a mother-child cohort to show that the HPG axis in infancy also is associated with pubertal development and adult reproductive health.

This finding of a reproductive trajectory may not only be important for future clinical care of patients but also for research into adverse influences on reproductive health of future generations. Over the past two decades several groups have shown that in utero and early life exposures to risk factors such as endocrine-disrupting chemicals may have considerable adverse effects on reproductive health. The ability to gain insight into such effects already in infancy is a big advantage considering the long generation time of humans and the urgent need to suggest preventive measures. Thus, pediatric endocrinologists together with scientists from other disciplines can play an important role in unravelling causes for the world-wide increase in infertility and need of fertility treatment which has major societal and personal consequences.

S12.2

SEMA6A drives GnRH neuron-dependent puberty onset by tuning median eminence vascular permeability

Anna Cariboni[1], *Roberto Oleari*[1], *Antonella Lettieri*[1], *Marleen van den Munkhof*[2], *Eljo van Battum*[2], *Carlotta Tacconi*[1], *Marco Spreafico*[1], *Alyssa Paganoni*[1], *Federica Amoruso*[1], *Ivano Eberini*[1], *Leonard Dunkel*[3], *Alessandro Fantin*[4], *Sasha Howard*[3], *Jeroen Pasterkamp*[2]

[1]University of Milan, Milan, Italy. [2]Utretch Medical Center, Utrecht, Netherlands. [3]Queen Mary University of London, London, United Kingdom. [4]University of Milan, Milan, United Kingdom

Innervation of the hypothalamic median eminence by Gonadotropin-Releasing Hormone (GnRH) neurons is vital to ensure puberty onset and successful reproduction. However, the molecular and cellular mechanisms underlying median eminence development and pubertal timing are incompletely understood. Here we show that Semaphorin-6A is strongly expressed by median eminence-resident oligodendrocytes positioned adjacent to GnRH neuron projections and fenestrated capillaries, and that Semaphorin-6A is required for GnRH neuron innervation and puberty onset. In vitro and in vivo experiments reveal an unexpected function for Semaphorin-6A, via its receptor Plexin-A2, in the control of median eminence vascular permeability to maintain neuroendocrine homeostasis. To support the significance of these findings in humans, we identified patients with delayed puberty carrying a novel pathogenic variant of SEMA6A. In all, our data reveal a novel role for Semaphorin-6A in regulating GnRH neuron patterning by tuning the median eminence vascular barrier and thereby controlling puberty onset.

S12.3

Abstract Unavailable

Meet the Expert

MTE1.1

Abstract Unavailable

MTE2.1

Abstract Unavailable

MTE3.1

Abstract Unavailable

MTE4.1

Abstract Unavailable

MTE5.1

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MTE6.1

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MTE7.1

Abstract Unavailable

MTE8.1

Abstract Unavailable

MTE2.2

Abstract Unavailable

MTE3.2

Abstract Unavailable

MTE4.2

Abstract Unavailable

MTE5.2

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MTE8.2

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MTE1.2

Abstract Unavailable

MTE6.2

Abstract Unavailable

MTE7.2

Abstract Unavailable

How Do I…

How Do I…Session 1

HDI1.1

Abstract Unavailable

HDI1.2

Abstract Unavailable

HDI1.3

Abstract Unavailable

How Do I…Session 2

HDI2.1

Abstract Unavailable

HDI2.2

How Do I initiate, support, and follow-up people with T1DM on an automated insulin delivery system?

Revital Nimri

Schneider Children's Medical Center of Israel, Petah Tikva, Israel

Automated insulin delivery (AID) systems are increasingly gaining popularity as a viable therapeutic option for managing type 1 diabetes. These systems hold the potential to significantly improve outcomes for individuals with T1D by reducing the risk of hypoglycemia and hyperglycemia, alleviating the burden of diabetes self-management along with improving overall quality of life. Implementation of the technology requires new knowledge for individuals with diabetes as well as health care professionals. In this 'How Do I' session, we will discuss how to guide individuals with diabetes and the healthcare team about the most effective use of AID systems. Clinical insights acquired from various AID studies will be presented, along with the latest recommendations on how to initiate and follow up with individuals starting AID use. Practical clinical recommendations will be presented through case studies. The discussion will include:

How do I initiate AID therapy for people with diabetes? general recommendations for initiating AID use such as transitioning from previous different therapies, the optimal time to initiate AID, and setting up the AID system.

How do I provide education, training, and support for AID system? AID education should be an integral part of comprehensive diabetes management education. It serves as the peak of the diabetes education pyramid, built upon a strong base of core diabetes knowledge and management, followed by basic education on continuous glucose monitoring (CGM) and pump usage. Essential elements needed for education, training, and follow-up will be reviewed.

How do I provide clinical recommendations for AID system? Clinical treatment considerations for AID use will be discussed such as treatment of hypoglycemia events, exercise management, and timing of user-initialed insulin delivery for meals and sick days. Case studies will be presented.

How do I report and explain AID data? Understanding AID data information and CGM time in ranges.

HDI2.3

Diagnosis and management of hypercholesterolemia

Lorenzo Iughetti

University of Modena and Reggio Emilia, Modena, Italy

Dyslipidemia is a well-known risk factor for cardiovascular disease (CVD). Although familial hypercholesterolemia (FH) has an important impact on CVD, most people with FH are undiagnosed or diagnosed only after their first coronary event. Therefore, early identification of affected individuals is crucial. Total cholesterol levels alone are not sufficient to confirm a diagnosis of FH, because of the extensive overlap in LDL–C levels existing between FH-causing mutation carries and non-carries (non-genetic polygenic hypercholesterolemia) and the high prevalence of modestly severe LDLR mutations that hampers the use of LDL-C cut-offs. Therefore, a diagnostic definition of FH, which supports cholesterol measurements with clinical signs and family history, has to be used. Genetic analysis gives a definitive confirmation.

The cornerstone of lipid-lowering treatment is a healthy lifestyle, but diet alone fails to lower cholesterol levels to acceptable values namely in patients with genetic hypercholesterolemia needing pharmacological treatment.

Statins efficacy is already well established and they are currently the mainstay in the treatment of hypercholesterolemia also in childhood. Statins not only decrease LDL-C, but also have lipid-independent pleiotropic effects, altering inflammatory responses and local atherosclerotic plaque morphology. Considering the safety concerns posed for long-term treatment with statins, screening of liver and muscle enzymes before and during treatment could be envisaged. If liver enzymes are above 3 times the upper limit and/or CK is above 10 times the upper limit and/or patient complains any adverse effects, medication should be stopped. A way to improve the safety of lipid-lowering treatment is to associate different drugs at lower doses. Ezetimibe, decreasing cholesterol absorption through inhibition of Niemann-Pick C1-like 1 protein, could improve the efficacy of statins alone. Moreover, the inhibition of PCSK9 pathway appears one of the most promising novel targets for additional LDL-C reduction. Although we are still far from the complete comprehension of the lipid metabolism, the better understanding of its physiology and pathophysiology has already permitted the introduction of new therapeutic opportunities, namely for patients with severe genetic forms of hypercholesterolemia.

Controversies

CON1.1

Pharmacological manipulation of bone maturation should be used to preserve final height in short children (FOR)

Veronica Mericq

Institute of Maternal and Child Research, faculty of Medicine, University of Chile, Santiago, Chile

Short children who are not GH deficient, often necessitate a different strategy, especially those with acceleration of bone age, which greatly limits height potential and the time available for growth. In this setting the use of agents to delay bone maturation has been explored to improve adult height. Estrogen principally modulates epiphyseal fusion in females and males through ERα. Aromatase inhibitors (AIs) block androgen to estrogen conversion, slowing down growth plate fusion, while allowing normal virilization in males and stimulating longitudinal bone growth via androgen receptor effects on the growth plate. During prepubertal years these are the only agents allowing pharmacological manipulation of bone maturation. Efficacy and safety in different conditions will be reviewed. During puberty GH production rates and growth velocity more than double, and high-dose GH use has shown dose-dependent increases in linear growth, but also can raise insulin-like growth factor I concentrations supraphysiologically and increase treatment costs. Gonadotropin-releasing hormone analogs (GnRHa) suppress physiologic puberty, and when used in combination with GH can meaningfully increase height potential in males and females while rendering adolescents temporarily hypogonadal at a critical time in development. The use of potent oral AIs, has shown that limited use of AIs is a viable alternative to promote growth in pubertal males, particularly combined with GH with an excellent safety profile. Ultimately the best approach for children with growth retardation is early referral to pediatric endocrinology, well before the onset of puberty, so proper diagnoses are made, and tailored interventions started. Careful discussion of these treatments and realistic expectations needs to be discussed with families.

CON1.2

Abstract Unavailable

Novel Advances 2

NA2.1

Abstract Unavailable

NA2.2

Abstract Unavailable

Young Investigators

YI1.1

Abstract Unavailable

YI1.2

Abstract Unavailable

YI1.3

Abstract Unavailable

Working Group Symposia

ESPE Working Group on Disorders of Sex Development

WG1.1

Abstract Unavailable

WG1.2

Abstract Unavailable

WG1.3

Abstract Unavailable

WG1.4

Abstract Unavailable

ESPE Working Group on Obesity

WG2.1

Abstract Unavailable

WG2.2

Environmental contributions to obesity development

Thorkild I.A. Sørensen

University of Copenhagen, Copenhagen, Denmark

The differences between people in degree of obesity within a given population are attributable to a combination of differences in their genomes and in what they have been exposed to in the environment. The heritability, which indicates the proportion of the phenotypic variance that is due to the genomic variation within this given population, is often estimated to a broad range of 40-80%, dependent on methods used (family versus twin studies), and is often interpreted as defining the limits of environmental influences (20-60%). However, this is an important misunderstanding, best exemplified by the rapidly rise of the prevalence of obesity within most populations around the world, which must be due to changes in environmental exposures (i.e. 100% environmental, barring likely minor contributions from assortative mating and migration). The essential questions are which specific environmental exposures induce obesity in the individuals, which have changed over time and thereby induced the obesity pandemic, and which are realistically modifiable. Whereas eating food in excess of the needs can enlarge the fat depots, it does not seem to produce the obesity phenotype, characterized by its resistance to being reduced, so it is necessary to search for other causes and mechanisms of obesity development. The energy value of the stored fat in obesity is always a tiny fraction (usually <1%) of the total energy consumed during obesity development, which is easily trapped from the food. Since obesity development is accompanied by excessively growing and energy consuming lean body mass, persisting food abundance can be seen as a permissive condition for obesity development. When this condition is met, it appears that exposure to a variety of psychosocial disadvantages and adversities along the life course within and between families increases the likelihood of obesity development, even at the pre-conceptional stage. Other environmental factors may play a role, e.g. parental smoking before birth, and many have been proposed, but there remains much uncertainty about the causal roles, both at the individual and population levels, and also about the often presumed interaction with the specific genetic predisposition.

WG2.3

Abstract Unavailable

WG2.4

Abstract Unavailable

ESPE Bone and Growth Plate Working Group

WG3.1

Abstract Unavailable

WG3.2

Abstract Unavailable

WG3.3

Abstract Unavailable

ESPE Working Group on Diabetes Technology

WG4.1

Abstract Unavailable

WG4.2

Abstract Unavailable

WG4.3

Abstract Unavailable

WG4.4

Abstract Unavailable

ESPE Working Group on Paediatric and Adolescent Gynaecology

WG5.1

Abstract Unavailable

WG5.2

Abstract Unavailable

WG5.3

Abstract Unavailable

ESPE Working Group on Gender Dysphoria

WG6.1

Abstract Unavailable

WG6.2

Abstract Unavailable

WG6.3

Abstract Unavailable

ESPE Working Group on Turner Syndrome

WG7.1

Abstract Unavailable

WG7.2

Abstract Unavailable

WG7.3

Abstract Unavailable

WG7.4

Abstract Unavailable

WG7.5

Abstract Unavailable

Ethics in Endocrinology

EE1.1

Solidarity and justice in the Dutch Coverage Lock Policy for Expensive Medicines - public Opinions and Stakeholder Perspectives

Ghislaine van Thiel, Féline Scheijmans, Willem van der Pol, Johannes van Delden, Margot Zomers, Rieke van der Graaf, Sina Fadaei, Marthe Onrust, Roosmarijn van der Wal

University Medical Center Utrecht, Utrecht, Netherlands

Background: Solidarity-based healthcare systems face significant challenges due to the rising costs of new and highly expensive medicines for cancer and rare diseases. The Dutch government introduced the Coverage Lock (CL) policy in 2015 to restrict access to reimbursement for such drugs. The CL has raised controversy around its ethical acceptability. Some claim the CL is necessary to secure solidarity while others have pointed out that its leads to unfair inequalities in access to treatment. However, the CL has not been evaluated in light of the key ethical principles of solidarity and justice. This study aimed to explore citizens' views to validate and improve the CL policy, considering public support as vital for healthcare policy.

Methods: A mixed methods study was conducted comprising a survey among a representative sample of Dutch citizens to assess their views on the CL policy and gauge public preferences for funding decisions and responsibilities related to the CL. Additionally, qualitative interviews were conducted among stakeholders on their perspectives on the CL procedure for the medicine nusinersen, used in treating spinal muscular atrophy (SMA).

Results: The survey revealed that while a majority of Dutch citizens considered the CL policy unjustified, they preferred it over the presented alternatives. In real-world examples of expensive medicines, respondents cited effectiveness, lack of alternative treatment options, and improved quality of life as reasons for positive reimbursement decisions. Unfavorable cost-benefit ratios were the main reason cited for non-reimbursement, with some respondents viewing it as a means to convey that extremely high drug prices are unacceptable. Stakeholders identified emotional impact, procedure duration, transparency, patient-centered decision-making, and unequal access to expensive treatments as key issues related to the CL policy in the case of the drug nusinersen.

Conclusion: Dutch citizens generally support providing expensive medicines to patients in need within existing healthcare budgets. Consequently, they recognize the necessity of controlling access to reimbursement for such drugs. Respondents were remarkably unified in their reimbursement decisions in real-world examples of expensive medicines. Despite concerns, the CL approach has public support due to the lack of alternative solutions. Stakeholders emphasized the need for greater patient-centric decision-making, improved transparency, and faster implementation of conditional reimbursement programs.

EE1.2

Abstract Unavailable

Endo-ERN Symposium

ERN1.1

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Henning Andersen Award Winners

HA1

An integrated roadmap of human fetal adrenal gland development

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Introduction: The human adrenal gland originates from the adrenogonadal primordium at around 4 weeks post conception (wpc) and undergoes marked developmental changes throughout the first half of pregnancy. Several key aspects of adrenal maturation are well-established, such as the formation of a large inner fetal zone (FZ) and synthesis of dehydroepiandrosterone, but many other processes contributing to adrenal gland development and function in humans are still unknown at an anatomical and molecular level. Further insight into human adrenal development has implications of understanding postnatal stress responses, stem cell origin and clinical conditions resulting in primary adrenal insufficiency (PAI).

Methods: In order to develop an integrated map of human adrenal gland development, we combined single cell RNA-sequencing (scRNA-seq) (n=4; 6wpc-19wpc; c.44,000 cells) (10X Genomics), bulk RNA-seq (n=32; 7-11.5wpc, plus 8 controls), spatial transcriptomics (7wpc+4d) (10X Visium), immunohistochemistry (IHC) (n=4 stages), micro-focus computed tomography (microCT) imaging and multiomic-ATAC sequencing (10X genomics) across a key time course between 6-20wpc.

Results: Using this integrated dataset we have elucidated several key aspects of adrenal gland developmental, including: 1) rapid adrenal growth and remodelling, and the generation of fetal adrenal growth curves; 2) marked vascularisation (using surface imaging) and important drivers of vascular endothelial development (e.g., VEGFR1); 3) more marked cell proliferation in the outer definitive zone (DZ) (using cell cycle markers and IHC for KI67) with an early central trajectory of cell differentiation; 4) steroidogenic pathways favouring androgen synthesis in the central fetal zone (FZ), but with DZ capacity to synthesise cortisol and aldosterone with time; 5) the identification of "core" transcriptional regulators (n=17) (e.g. SF-1/*NR5A1*, DAX-1/*NR0B1*) and localisation of a novel cell regulator, HOPX, to the outer DZ; 6) early cell trajectories between the mesenchyme and adrenal cortex, with ligand-receptor interactions (e.g., RSPO3/LGR4) (CellPhoneDB); 7) an enrichment of growth-promoting imprinted genes (e.g. *IGF2*, *PEG3*), especially paternally-expressed genes in the rapidly-expanding FZ; and 8) a potential relation between the specificity of gene expression and the age of onset of primary adrenal insufficiency in infants and children with adrenal disorders. Several key elements linked to adrenal tumour biology were also identified.

Conclusion: These findings reveal new aspects of human adrenal development and have clinical implications for understanding PAI and related postnatal adrenal disorders, such as steroid biosynthesis and the ability of the extreme preterm baby to respond to neonatal stress.

HA2

Effect of omega-3 fatty acids supplementation on renal glomerular and tubular integrity and subclinical atherosclerosis in children and adolescents with type 1 diabetes: A randomized controlled trial

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Background: Numerous studies have evaluated the beneficial effects of omega-3 fatty acids on inflammatory, autoimmune and renal diseases. However, data about the effects of omega-3 fatty acids on diabetic kidney disease in type 1 diabetes mellitus (T1DM) are lacking.

Objectives: This randomized-controlled trial assessed the effect of oral omega-3 supplementation on glycemic control, lipid profile, albuminuria level, kidney injury molecule-1 (KIM-1) and carotid intima media thickness (CIMT) as a surrogate marker for subclinical atherosclerosis in children and adolescents with T1DM and diabetic nephropathy.

Methods: Seventy T1DM patients and diabetic nephropathy were enrolled with a mean age 15.2 ± 1.96 years and median disease duration 7 years. Patients were randomly assigned into two groups; intervention group which received oral omega-3 fatty acids capsules (1 gram daily). The other group received a matching placebo and served as a control group. Both groups were followed-up for 6 months with assessment of fasting blood glucose (FBG), HbA1c, fasting lipids, urinary albumin creatinine ratio (UACR), KIM-1 and CIMT.

Results: Both groups were well-matched as regards baseline clinical characteristics and laboratory parameters ($p>0.05$). After 6 months, omega-3 fatty acids adjuvant therapy for the intervention group resulted in a significant decrease in FBG, HbA1c, triglycerides, total cholesterol, LDL-cholesterol, UACR, KIM-1 and CIMT, whereas, HDL-cholesterol was significantly higher post-therapy compared with baseline levels and compared with the control group ($p<0.05$). Baseline KIM-1 levels were positively correlated to HbA1c% ($r=0.589$, $p<0.001$), UACR ($r=0.647$; $p<0.001$) and CIMT ($r=0.612$; $p<0.001$). Supplementation with omega-3 fatty acids was safe and well-tolerated.

Conclusions: Omega-3 fatty acids as an adjuvant therapy in pediatric T1DM patients with diabetic nephropathy improved glycemic control, dyslipidemia, prevented disease progression and subclinical atherosclerosis among those patients.

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Free Communications

Adrenals and HPA Axis

FC1.1

Investigating intergenerational effects of glucocorticoids

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Background: Animal studies have reported that exposure to synthetic glucocorticoids (sGCs) may lead to inter- and transgenerational effects on offspring phenotype. However, many of these studies are poorly designed, do not account for possible non-epigenetic confounds, and cannot determine the mechanism(s) by which gamete epimutations are induced.

Objectives: Firstly, to determine whether developmental exposure of mice to sGCs at human-relevant doses and routes causes intergenerational and/or transgenerational effects on phenotype through the paternal line; and secondly, to determine whether intergenerational effects of sGCs are due to germline inheritance (including specifically glucocorticoid receptor [GR] activation in germ cells or epididymis only) or confounding by other factors.

Methods: First, wild-type gestating C57BL/6J mice were treated with subcutaneous vehicle or dexamethasone (0.2 mg/kg/day) on gestational days 16-17, and their patrilineal F1-F3 offspring phenotyped. Next, sperm from F1 males exposed antenatally to vehicle or dexamethasone were used to generate F2 offspring via *in vitro* fertilisation, which were also phenotyped. Finally, heterozygous C57BL/6NTac mice expressing a constitutively active GR (*ΔGR*) under a germ cell- (males and females) or epididymis-specific (males only) promoter were mated with wild-type mice and their wild-type offspring phenotyped and compared to controls with two wild-type parents. Phenotypic outcomes assessed were growth, glucose and insulin tolerance, body composition, and various reproductive metrics.

Results: Gestational dexamethasone treatment caused impaired glucose tolerance in F1 and F2 males, and heavier internal genitalia in F2 females, but these findings were not replicated in F2 mice generated by IVF, suggesting a non-germline effect. The F3 phenotype was of increased body weight (males) and altered thyroid hormone levels and body composition (females). Founder mice heterozygous for *ΔGR* had no obvious phenotype, but their wild-type adult male offspring had improved glycaemia regardless of which parental reproductive tissue (male/female germ cells or epididymis) expressed ΔGR; paternal and maternal germ cell, but not paternal epididymal, ΔGR expression also affected offspring body composition in a sexually dimorphic manner.

Conclusions: Patrilineal intergenerational effects of gestational dexamethasone treatment appear to be transmitted independent of the germline. Constitutive activation of the GR in germ cells of either parent causes sexually dimorphic changes in offspring body composition, and improves male glycaemia; the latter effect is also seen with paternal epididymal GR activation. More evidence is required to determine the public health significance of these findings.

FC1.2

The pathophysiologic response of central nervous system due to differently impaired steroidogenesis

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Background: The pathophysiological link between the stress axis and mental health disorders is well established. However, the impact of inborn errors of steroidogenesis on the brain remains elusive. We analysed the brain transcriptome of adult zebrafish with impaired steroidogenesis to study the role of steroid hormones in the development of mental and psychiatric disorders.

Methods: Adult brains from two established zebrafish lines with differentially impaired steroidogenesis, 21-hydroxylase deficiency (*cyp21a2-/-*) and side-chain cleavage enzyme deficiency (*cyp11a2-/-*), were used. We analysed 18 months old male and female wildtypes and *cyp21a2-/-* mutants (6 in each group), and 4 wildtype and 5 *cyp11a2-/-* mutant males (no female mutant progeny as part of the mutant phenotype) that were 12 months old. Following RNA extraction and paired-end sequencing, transcriptomic analysis included differential gene expression (DGE) analysis, Gene Ontology (GO), Gene Set Enrichment Analysis (GSEA), and enrichment analysis of disease-associated genes.

Results: For both mutant lines, the most significantly differentially expressed genes were downregulated, including glucocorticoid-response genes *klf9* and *fkbp5,* as well as chaperone-mediated protein folding heat shock protein *hsp90aa1.2,* and *nfkbiab* involved in the regulation of CNS development. In *cyp21a2-/-* fish, enrichment GO analysis showed dysregulation of chaperone-mediated protein folding and organic acid transport in males, and response to hypoxia in females. Meanwhile, in *cyp11a2-/-* mutants, multiple dysregulations were found for biological processes involved in immune response, provision of energy precursors, and circadian rhythm. For both *cyp21a2-/-* and *cyp11a2-/-* males, GSEA revealed downregulation of processes involved in synapse

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organization and signalling, as well as metabolic processes involved in energy homeostasis. Upregulation was observed for ribosome biogenesis and inflammatory response. In contrast, in female *cyp21a2-/-* fish, the majority of dysregulated biological processes were related to cell division and reproduction. The analysis of the association with human disease identified similar neurological conditions between all mutant groups, including Alzheimer's disease, dementia, cognitive impairment, depressive and mood disorders, and autistic spectrum disorder.

Conclusion: These findings indicate that impaired steroidogenesis affects multiple processes involved in the functioning of the adult zebrafish brain. Synapse signalling and cell energy homeostasis processes are repressed, while inflammatory responses are upregulated. Such dysregulations may impact the pathogenesis of human mental conditions such as dementia and mood disorders. These effects appear to be influenced by sex, suggesting that sex hormones may have important roles in the pathogenesis of mental health disease. Further in-depth research using models of differentially impaired steroidogenesis and altered signalling is warranted.

FC1.3

Generation and Characterization of a novel Humanized CYP21A2 Knock-in Mouse Model for Congenital Adrenal Hyperplasia

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21-hydroxylase deficiency (21OHD) is the most common form of congenital adrenal hyperplasia (CAH) and is caused by mutations in the *CYP21A2* gene. 21OHD causes a wide array of clinical symptoms that result from gluco- and mineralocorticoid deficiency and adrenal androgen excess. In most cases, supra-physiological glucocorticoid doses are necessary which may cause short stature, obesity, hypertension, cardiovascular and metabolic comorbidity with reduced quality of life. Hence, current steroid substitution regimens have significant limitations, so novel therapeutic strategies are required. In recent years, new therapeutic approaches have emerged including new non-glucocorticoid substances interfering with the HPA axis to minimize adrenal androgen production and to lower external glucocorticoid substitution to physiological levels. However, valuable in-vivo models for preclinical testing of such drugs are lacking. Here we present the first viable and humanized knock-in mouse model in which the mouse gene *Cyp21a1* is replaced by the human orthologue *CYP21A2* with the integrated frequent-occurring human point mutation p.R484Q.

Twenty-weeks-old homozygous mice show marked adrenocortical hyperplasia, enhanced expression of the *CYP21A2* gene and a weak increase of *Cyp11a1* and *Cyp11b2* gene expression. Tandem mass spectrometry measurements in mice plasma at 20 weeks show decreased corticosterone and 11-deoxycorticosterone levels in both male and female homozygous animals. Progesterone levels in homozygous mice are significantly higher ($p<0.01$) than in wildtype mice. We also observed increased aldosterone levels in female mutants whereas blood pressure does not differ between wildtype and mutant mice strains. Tetrahydrocorticosterone (THB), a major glucocorticoid metabolite could be detected in 24-hours-urine in wildtype mice but not in homozygous mutant animals. While mutant male mice are fertile with normal appearing testes, females are infertile, remain in the diestrus phase and present with a reduced number of ovarian follicles and lack of corpus luteum.

In parallel, a second mouse strain bearing the I173N mutation was developed. This mutation is frequent in human patients causing simple virilizing or rarely salt wasting CAH. Homozygous mice require dexamethasone treatment during pregnancy and until weaning but are viable without treatment afterwards. Preliminary results show adrenal hyperplasia and alteration in steroidogenic gene expression and steroid profiles.

In conclusion, we demonstrate that the humanized mutant *CYP21A2* mice may represent an excellent animal CAH model to test novel treatment strategies for CAH patients. We believe that this model(s) will facilitate the transition from basic research into clinical application.

FC1.4

Response to Crinecerfont Treatment in Adolescents with Classic Congenital Adrenal Hyperplasia Is Correlated with Elevated Baseline Hormone Concentrations but Not Glucocorticoid Dose

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Introduction: Classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD) is a rare, autosomal disorder characterized by deficiency of cortisol and oftentimes aldosterone, elevated adrenocorticotropic hormone (ACTH), and excess androgen production. In a phase 2 study of adolescents with classic 21OHD, 14 days of treatment with the corticotropin-releasing factor type 1 receptor (CRF1) antagonist, crinecerfont, led to median percent reductions of 69% for 17-hydroxyprogesterone (17OHP), 57% for ACTH, and 58% for androstenedione (A4). Post hoc analyses were conducted to assess whether baseline hormone concentrations and glucocorticoid (GC) dose correlated with treatment response.

Methods: Adolescent males and females with 21OHD and elevated 17OHP concentrations (≥800 ng/dL) received open-label crinecerfont 50 mg twice daily for 14 days. Participants' glucocorticoid and fludrocortisone regimens were maintained stable prior to and during crinecerfont treatment. Pearson correlations between baseline ACTH, 17OHP, A4, and GC dose against the magnitude of change from baseline (CFB) to Day 14 hormone concentrations were assessed using the average value of samples collected during the morning window (0700h and 1000h, before the morning GC dose) as well as the average over the full 24-hour sampling period.

Results: Eight participants (3 males, 5 females; mean age, 15 years [range, 14-16 years]) were enrolled and included for analysis. Baseline GC regimens were hydrocortisone alone (n=6) or prednisone alone (n=2), with median total daily dose (in hydrocortisone equivalents) of 16.2 mg/m^2/day (range, 11.9-18.5 mg/m^2/day). A significant negative correlation was found between baseline concentration and CFB to Day 14 for 17OHP (morning window, r=-0.876 [P=0.004]; 24-hour average, r=-0.904 [P=0.002]), with the greatest reductions from baseline in 17OHP observed in participants with the highest baseline concentrations. Similar relationships were observed for ACTH (morning window, r=-0.949 [P<0.001]; 24-hour average, r=-0.988 [P<0.001]) and A4 (morning window, r=-0.781 [P=0.022]; 24-hour average, r=-0.789 [P=0.020]). No correlation was found between baseline GC dose and CFB to Day 14 for 17OHP (morning window, r=0.007 [P=0.987]; 24-hour average, r=-0.038 [P=0.929]), ACTH (morning window, r=-0.057 [P=0.893]; 24-hour average, r=-0.177 [P=0.674]), or A4 (morning window, r=-0.286 [P=0.492]; 24-hour average, r=-0.290 [P=0.486]).

Conclusions: In adolescents with 21OHD CAH treated with crinecerfont, there was a strong correlation between treatment response and baseline hormone concentration, but not with baseline GC dose. These data suggest that higher baseline hormone concentrations (i.e., worse disease control) predict greater response in children with 21OHD, and that androgen reduction might occur across a broad range of GC doses in this population.

FC1.5

Management of congenital adrenal hyperplasia in the first 90 days of life: a multi-centre I-CAH analysis of contemporary practice

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Aims: Historical I-CAH data shows considerable variation in the management of 21-hydroxylase deficiency (21-OHD) congenital adrenal hyperplasia (CAH) in infancy despite existence of several guidelines. Using the I-CAH registry we analysed contemporary early infancy natural history data, creating benchmarks as part of continuous quality improvement.

Methods: Of 136 infants born in 2018-2023 and treated for 21-OHD CAH within the first 90 days of life, data was available in 121 from 26 centres in 15 countries. The median number of cases included per centre was 3 (range 1,16).

Results: Of the 121 infants (52 male), 90 (74%) were assigned sex at birth. The median (10th-90th percentile) age at presentation was 5 days (0-18) in the 104 infants diagnosed postnatally. 78 (64%) had newborn screening (NBS) but in 35 (45%) the diagnosis was reached prior to the NBS result. Diagnosis based on NBS was more likely in males than females (33/40 vs 10/38, $p<0.0001$). 120 infants (99%) had biochemical diagnosis at a median age of 7 days (2-25.6). In 53 (44%) infants, genetic confirmation was reached by 90 days. Hyponatraemia and hyperkalaemia occurred in 78 (64%) and 79 (65%) infants, with lowest sodium and highest potassium at median ages of 12 days (6.4-30.2) and 12 days (4-28.3), respectively. In 18 (15%) infants hypoglycaemia occurred with lowest level at a median age of 1 day (0-38.2). At 90 days, hyponatraemia and hyperkalaemia were evident in 7/95 (7%) and 20/89 (23%) infants, respectively. Blood pressure measurements were available in 37 (31%) infants and in 13 (35%) they were >95th centile. Hydrocortisone, fludrocortisone and salt were administered in 120 (99%), 116 (97%) and 107 (88%) infants, respectively. At initial hospital discharge, median doses of these three medications were 15.4mg/m^2/day (11.5-34.1), 100mcg/day (50-200) and 3.6mmol/kg/day (1.7-8.88), respectively, and by 90 days the doses for hydrocortisone and salt were lower (both $p<0.0001$). Over the 90 days, there were a total of 190 hospitalisation episodes (including birth) in the 121 infants. The median duration of each episode was 4 days (2-19.8) and total hospitalisation duration in the 90 days per patient was 10 days (3-24). Of the 190 episodes, 44 (23%) had an associated adrenal crisis.

Conclusion: These novel contemporary data from a large number of centres show variation in CAH management over the first 90 days of life. It is expected these data will lead to development of data-driven clinical benchmarks and care standards.

FC1.6

Cardiovascular risk profile in adult patients with congenital adrenal hyperplasia: a cross-sectional study

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Background: Adults with congenital adrenal hyperplasia due to 21-hydroxylase deficiency (21OHD) develop an adverse metabolic and cardiovascular risk profile. Both over- and undertreatment with glucocorticoids are associated with these adverse metabolic effects. There is limited data available of changes in cardiovascular parameters during lifetime.

Objective: This study aimed to evaluate unfavorable changes in cardiovascular and metabolic risk factors in patients with 21OHD, with emphasize on post pubertal young adult patients. When present, it was aimed to examine the contribution of CAH-related parameters such as genotype, glucocorticoid and mineralocorticoid therapy (17-hydroxyprogesterone, androstenedione and renin levels) to these adverse effects.

Methods: A cross-sectional study was performed using data collected from the International multicenter DSD life study. Incidence of cardiovascular and metabolic risk factors (metabolic syndrome (MetS), hypertension, insulin resistance) were compared to healthy reference populations. Putative effects of CAH-related risk factors on cardiovascular morbidity were tested using Cox-proportional hazard analyses. Effects of sex (XX versus XY), smoking behavior, everyday activity, and practice of sports were considered.

Results: A total of 333 post pubertal 21OHD patients mean age 30.6 years (range 15-70 years) in 14 centres from six western-European countries were included. Of those, 192 were classified as young adults, mean age 22.4 years (range 15-30 years). Preliminary analyses showed that the incidence of metabolic syndrome (MetS; 31/230 (13.5%)), hypertension (88/310 (28.4%)), and insulin resistance (14/340 (4.1%)) were increased compared to reference populations. Up to the age of 30, the incidences of MetS (6/131) and insulin resistance (3/186) were low, but hypertension was already observed (33/167 (19.8%)). XY karyotype and smoking were associated with increased risk of MetS. Patients with salt-wasting 21OHD were 1.7 times more likely to develop hypertension in comparison to patients with simple virilizing. Plasma renin levels were not significantly correlated with the presence of hypertension. With or without adjustment for significant effect of smoking behavior and CAH phenotype, suppressed androstenedione (but not 17-hydroxyprogesterone) below the normal limit was associated with increased risk for hypertension. No CAH related risk factors for insulin resistance were identified.

Conclusions: Preliminary analyses showed increased incidence of metabolic and cardiovascular risk factors in adults with 21OHD. Increased incidence of hypertension, already observed in young adults, was associated with suppressed androstenedione levels. This association may reflect (reversable) glucocorticoid and/or mineralocorticoid overtreatment and not reflect long-term morbidity, suggesting that the adverse cardiovascular and metabolic risk profile does not arise before midlife.

Bone, growth plate and mineral metabolism

FC2.1

Hearing loss in pseudohypoparathyroidism (inactivating PTH/PTHRP Signaling Disorder): a prospective study to assess prevalence and predictive factors of hearing loss in 44 patients affected with iPPSD/PHP

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Background: Since the first description of inactivating PTH/PTHrP signaling disorders [(iPPSD, former pseudohypoparathyroidism (PHP)] a remarkable clinical variability was observed, apparently age-dependent. The main clinical features, including PTH resistance, brachydactyly and short stature, develop during middle and late childhood. Hearing loss (HL) is commonly found in iPPSD/PHP. Only a few studies approached the subject of hearing loss in iPPSD/PHP and these have yielded largely divergent conclusions, presumably due to the small size of the investigated cohorts.

Objectives: The aim of our monocentric, prospective study was to analyze the auditory from 44 iPPSD/PHP. Children and adults affected by either iPPSD/PHP and followed in the pediatric or adult departments of endocrinology were included.

Methods: Prospective demographic, clinical data and results of auditory investigations for 44 patients with iPPSDs, followed between March 2019 and May 2020 in the Otolaryngology department and the Calcium Phosphate reference centers for rare diseases at Bicêtre Paris-Saclay Hospital, France, were collected. Air and bone conduction hearing thresholds were determined between 125 and 8000 Hz per octave frequency (125, 250, 500, 1000, 2000, 4000 and 8000 Hz). Hearing thresholds were also analysed by frequency. We analysed the prevalence and predictive factors of hearing loss. Student's T-test or Mann-Whitney test and chi-squared test were used. Clinical predictive factors of HL were assessed using a generalized estimating equation model (GEE), with a threshold of 20 db. The results were compared to hearing norms according to the age and the gender. The primary outcome was the pure-tone average (PTA) calculated as the average of the hearing thresholds at the frequencies of 500, 1000, 2000 and 4000 Hz.

Results: Median [QR] for age at auditory investigations was 15.6 years [9.5, 28.5] (range 3.5 to 56.3 years). Thirty-six patients were diagnosed with iPPSD2 and eight with iPPSD3. Twenty-six of them (59%) were female. Age was correlated to HL (p=0.04). Short stature and the presence of ectopic ossifications were significant predictive factors of hearing loss (p=0.009 and p=0.03 respectively). Eighty-eight ears were considered for the analysis of audiograms. Hearing impairment was confirmed in 17 patients (39%) and 26 ears (30%). The mean difference of PTA between the patients and the norms was 11.4 db (p=0.00002).

Conclusion: We confirm the presence of hearing loss in iPPSD/PHP (prevalence=39%). The combination of short stature and the presence of ectopic ossifications should initiate investigations and auditory follow-up from childhood in iPPSD/PHP.

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FC2.2

First Results of the Global ALPL Gene Variant Classification Project

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Background: Hypophosphatasia (HPP) is an inherited multisystem disorder predominantly affecting the mineralization of bones and teeth. HPP is caused by pathogenic variants in ALPL, which encodes tissue non-specific alkaline phosphatase. A major challenge in diagnosing HPP is interpreting variants in ALPL classified as variants of uncertain significance (VUS) according to ACMG/AMP criteria, creating uncertainty in patients and treating physicians resulting in diagnostic delays.

Objectives: The ALPL gene variant classification project was established to reclassify VUS and to continuously assess and update genetic, phenotypic, and functional variant information in the ALPL gene variant database (https://alplmutationdatabase.jku.at/), an open-access archive for interpretations of the clinical significance of variants reported in ALPL. We aim to report the first results of newly classified variants in this project.

Methods: An international, multidisciplinary consortium of HPP experts has been established to reclassify the submitted VUS using a multi-step process adhering to the ACMG/AMP variant classification guidelines. These steps include a clinical phenotype assessment, deep literature review including artificial intelligence technology, molecular genetic assessment, and in-vitro functional testing (episomal pcDNA3 vectors used in a co-transfection model to express a variant in renal MDCK-II cells to measure ALP residual activity and assess dominant negative effect).

Results: Currently, the ALPL database has 423 variants and 587 genotypes. The number of VUS reclassified/classified by the ALPL gene consortium since its inception in Feb 2021 is 51, as shown in the table below.

Variants	Number of Variants
Reclassified to date	51
-Reclassified with functional testing	25
-Reclassified from literature	7
New submissions classified	19

Out of the 51 classified or reclassified variants, 3 were pathogenic, 24 likely pathogenic, 2 were likely benign, 1 benign, and 21 remained VUS. 68 new genotypes and 50 new phenotypes were added to the variants in the ALPL database. Through studying the submitted and reported phenotypes, we discovered distinct new phenotypes - asymptomatic heterozygote individuals featuring the typical biochemical signature of HPP (c.1225C>T, c.466C>T, c818C>T, c.244G>A, c.244G>C, c.906C>A, c.83A>G and c.299C>T) and heterozygote individuals with massive ectopic calcification (c.1559del and c.1250A>G).

Conclusion: This classification project and the ALPL gene variant database serve the global medical community and widen the genotypic and phenotypic HPP spectrum by classifying ALPL variants based on ACMG/AMP criteria, thus facilitating improved genetic counselling and medical decision-making for affected patients and families and as a repository for clinicians and scientists to query a variant and view evidence of its pathogenicity.

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FC2.3

Hyperparathyroidism after three years of burosumab in children affected with x-linked hypophosphatemia

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Background/Aim: Hyperparathyroidism (HPHT) is a common feature in patients with X-linked hypophosphatemia (XLH) especially when treated with vitamin D analogues and phosphate supplements. Although the exact mechanism is not clear, it is assumed that phosphate supplements taken chronically stimulate parathyroid hormone (PTH) secretion. We prospectively assessed the effect of a novel pathogenetic treatment anti-FGF23 (burosumab) on PTH levels in children with XLH.

Patients and Methods: 37 XLH-children (23 girls / 14 boys; 8.8±3.2 years) were switched from conventional therapy to burosumab and completed at least three years of burosumab therapy. Subjects with secondary HPTH at baseline were excluded from analysis. The biochemical parameters of calcium-phosphate metabolism were measured at baseline (M0) and then every 6 months under burosumab (M6 up to M36). According to our national guidelines, the target serum phosphate upon burosumab was >1.2 mmol/l (>3.7 mg/dl).

Results: After three years of treatment with burosumab, there was a global increase of PTH levels from 39.1±18.2 (M0) to 54.8±27.6 ng/l (M36) (18.5-88 ng/l) (p=0.001). Four subjects of 37 (10.8 %) developed secondary HPTH with mean±SD PTH levels equal to 110±17.9 ng/l. The subjects who developed HPTH tended to be older (10.0±1.2 vs 8.7±3.4 yrs, p=0.43, respectively) and had significantly higher PTH levels at baseline (62.8±22.5 vs 36.3±15.7 ng/l, p=0.004, respectively), in comparison to those without HPTH. Subjects with HPTH tended to have higher levels of serum phosphate at M36 (1.33 vs 1.19 mmol/l, p=0.11, respectively) and higher delta of phosphate increase from M0 to M36 (94% vs 63%, p=0.051, respectively), in comparison to those without HPTH. None of the children developed tertiary hyperparathyroidism.

Conclusion: This is the first study describing the effect of anti-FGF23 treatment on PTH secretion in children with XLH. Although the benefit on phosphate homeostasis and bone mineralization has been fully demonstrated, we suggest that prolonged anti-FGF23 treatment may stimulate PTH secretion thus leading to development of hyperparathyroidism after three years of treatment. Nonetheless, longer follow-up study is needed to better understand and describe this phenomenon.

FC2.4

A real-world study in Germany and Switzerland regarding renal health in children with X-linked hypophosphatemia

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Purpose: X-linked hypophosphatemia (XLH) is the most common hereditary cause of hypophosphatemic rickets. Elevated circulating levels of fibroblast growth factor 23 (FGF23) caused by mutations in the PHEX gene lead to renal phosphate wasting and rickets. Conventional treatment with phosphate salts and active vitamin D is associated with nephrocalcinosis in XLH patients. Mice on a high phosphate diet develop proximal tubular injury. Detailed analysis on kidney health and contributing factors in XLH are lacking.

Methods: To investigate the long-term outcome and its contributing factors in children with XLH we are conducting a prospective observational multicenter study in Germany and Switzerland. Patients are treated with conventional therapy or burosumab, a fully humanized anti-FGF23 antibody. Clinical and biochemical data as well as urine samples are annually obtained. Lithogenic substances and biomarkers for kidney health and their associations e.g. with estimated glomerular filtration rate (eGFR) and nephrocalcinosis are examined.

Results: Currently, 103 patients (62 girls, mean age 13 years) from 32 centers are included in the study. 14% of patients have been treated conventionally for 9.7 years, and 86% of patients have received burosumab for an average of 4.1 years with 4.5 years of conventional therapy beforehand. A reduced eGFR (<90 ml/min/1.73 m2) and/or nephrocalcinosis was noted in 9% and 29.4% of patients, respectively. Microalbuminuria is twice as prevalent in children with XLH as in healthy children (14% vs 7%). The excretion of lithogenic substances (calcium, oxalate, glycolate) is increased in 1.8-22.8%, and the excretion of citrate is decreased in 12.3% of XLH patients when compared to healthy children. The urinary tubular injury markers neutrophil gelatinase-associated lipocalin (NGAL) and Dickkopf-3 (DKK3) are elevated in children with XLH compared to healthy individuals, and chitinase 3-like 1 (CHl3L1) is comparable to that in children with chronic kidney disease. The renal inflammation marker monocyte chemoattractant protein-1 (MCP-1) is elevated in children with XLH and epidermal growth factor (EGF) preserving the capacity of tubular cells to recover is decreased compared to healthy children. Children with XLH showed increased mean z-scores for systolic blood pressure and body mass index (BMI), but blood pressure values were not associated with BMI z-scores.

Conclusions: First analyses show considerable renal comorbidity in children with XLH, including reduced eGFR, nephrocalcinosis, elevated urinary lithogenic substances and increased urinary kidney injury markers as well as elevated blood pressure independent of BMI. A comparison between conventional and burosumab treatment needs to be conducted.

FC2.5

Generation of novel genetic zebrafish models and using RNA-seq analysis to explore the role of ankrd11 gene on bone growth

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Keywords: KBG syndrome, *ANKRD11*, zebrafish, CRISPR/CasRx, Wnt signaling pathway

Background: KBG syndrome (KBGS) is a rare condition caused by variant in ANKRD11 gene, which is characterized by intellectual disability, distinctive facial features, macrodontia of the upper central incisors, skeletal anomalies and short stature. Patients carrying loss-of-function ANKRD11 variants exhibit short stature due to defects of bone development. However, the mechanism of which remains unclear.

Objective: This study aimed to generate a zebrafish model of KBGS by using CRISPR/CasRx method and explore the effects of *ankrd11* on bone growth.

Methods: The mixture of mRNA of CasRx and gRNA targeting ankrd11 gene were generated according to the 2:1 ratio, whose final concentration was 200 ng/μL and 100 ng/μL, respectively. The mixture or CasRx mRNA alone was injected into zebrafish single-cell stage fertilized eggs by microinjection (experimental group vs. control group). Alizarin red and Alcian blue staining were used to analyze the craniomaxillofacial skeletal growth. The gene expression profiles of experimental group and control group were compared using RNA genome wide analysis (RNA-Seq) and RT-qPCR analysis.

Results: The relative level of *ankrd11* gene was 50.9% in experimental group compared to control group ($p<0.05$). Impairment growth, with different degrees of deformity (small head, spinal curvature, pericardial effusion, monocular, slow degeneration of yolk sac, mandibular malformation and undeveloped swim bladder) was observed in zebrafish after knocking down *ankrd11*. Alizarin red and Alcian blue staining of the knockdown zebrafish showed craniomaxillofacial cartilage development defect. Further RNA-Seq and RT-qPCR analysis showed the Wnt signaling pathway was down-regulated in the ankrd11 knockdown zebrafish.

Conclusions: A novel genetic model of KBGS was generated by using CRISPR/CasRx method. It is confirmed that ankrd11 gene regulates bone growth in zebrafish through the Wnt signaling pathway.

FC2.6

Human breast milk-derived exosomes promote growth plate cell lines in vitro

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Introduction: Human breast milk (HBM) contains various components with critical roles in supporting early human growth and development. HBM is highly enriched in miRNAs, short, noncoding RNAs of 18 to 25 nucleotides in length, involved in the development, differentiation, proliferation, metabolism, and death of cells and tissues. miRNAs have been linked to growth control, apoptosis, epigenetic modifications, developmental programming, stem cell differentiation, and increase growth by targeting genes involved in development. The growth plate shows growth activity only with breast milk products for the first six months, and continues to work in the following period in the interaction of other sources and hormones taken with nutrition. This study explores the functions of exosomes derived from HBM on growth plate cell lines in vitro.

Methods: Breast milk exosomes were isolated and characterized by positive CD63 and negative calnexin markers from western blot, nanoparticle tracking analysis and transmission electron microscopy. To assess cytotoxicity-cell viability using an MTS assay, cultured growth plate chondrocytes were incubated with HBM exosomes and the effective dose was determined. As a result of MTS analysis, 200 mg/dl was found to be optimum. In vitro scratch experiments were performed to analyze the effects of exosomes on the migratory capacity of chondrocytes. Cell cycle progression for different doses of exosomes in growth plate chondrocytes was assessed by flow cytometry. Expression of cartilage extracellular matrix components (Types I and II collagen and aggrecan) was assessed using reverse transcription coupled polymerase chain reaction (RT-PCR). As a result of PCR experiments, the amount of increase and decrease in gene expressions were analyzed.

Results: HBM exosomes can be endocytosed and effects of exosome application on growth plate cells were analyzed by MTS, Scratch assay, cell cycle and PCR techniques. After determining the optimum dose with MTS analysis, genes and expressions specific to chondrocytes and extracellular matrices such as aggrecan, type I and II collagen, Sox-9 were analyzed by PCR. HBM exosome treatment significantly attenuated the inhibitory effect of IL-1β on the proliferation and migration of chondrocytes. Exosomes activated signaling associated with extracellular matrix production of chondrocytes, a key signaling event in chondrocyte metabolic activities. It also increased expression of genes specific for growth, extracellular matrix secretory function and survival of cartilage cells. Finally, exosomes significantly increased chondrocyte proliferation and no toxic effects were observed.

Conclusion: In conclusion, our data identified HBM derived exosomes as a crucial regulator of chondrogenesis and may represent a potential strategy for the treatment of growth disorder.

Fat, metabolism and obesity 1

FC3.1

Early childhood height and weight development in children with monogenic obesity: A European multicenter cohort study

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Introduction: Monogenic defects in the leptin-melanocortin pathway result in hyperphagia and severe, early-onset obesity. Knowledge of the natural history of anthropometric parameters in patients with monogenic obesity is essential for diagnosis. However, reliable data on early childhood weight and height development in affected patients are lacking. This study aimed to evaluate the history of height, weight, and BMI development in early childhood in a European cohort of patients with monogenic obesity.

Methods: In this multicenter cohort study, 152 patients diagnosed with biallelic (likely) pathogenic variants in the *LEP* (n=9), *LEPR* (n=54), *POMC* (n=11), *PCSK1* (n=2), or *MC4R* (n=16) gene or diagnosed with monoallelic (likely) pathogenic *MC4R* gene variants (n=60) were included from six European centers (Berlin, Cambridge, Madrid, Ulm, Paris, Rotterdam). Early childhood weight and height data were collected from birth to five years of age. Height, weight, and BMI development were compared between the different forms of monogenic obesity based on the WHO growth reference standards.

Results: Patients with biallelic *LEP*, *LEPR* and *MC4R* variants had a steep increase in BMI and BMI SDS in the first year of life, resulting in a significantly higher BMI and BMI SDS at the age of one year (*LEP*:27.8±3.2kg/m^2, 5.48±1.19; *LEPR*:28.3±5.8kg/m^2, 5.54±1.91; *MC4R*:26.2±7.3kg/m^2, 4.47±2.45) than in patients with monoallelic *MC4R* variants (19.3±2.3 kg/m^2, 1.66±1.28; $p<0.05$), respectively. After the first year of age, BMI values in patients with biallelic *LEP*, *LEPR*, and *MC4R* variants reached a plateau that lasted until five years of age. In patients with biallelic *POMC* variants, BMI and BMI SDS increased up to two years of age (27.1±7.0 kg/m^2, 5.23±2.29), followed by BMI stabilization. Body length at birth was similar in all patient groups. However, patients with biallelic *MC4R* variants had significantly greater length SDS values (2.27±1.57) than patients with biallelic *LEP* (0.47±1.34, $p<0.05$) and *LEPR* variants (0.55±1.58, $p<0.05$) at the age of six months, which remained greater until the age of five years.

Conclusion: In this large multicenter cohort study of patients with monogenic obesity, early childhood BMI development is characterized by a steep increase in the first year of life (biallelic *LEP*, *LEPR* and *MC4R* variants) or in the first two years of life (biallelic *POMC* variants), followed by a plateau. In contrast to patients with other forms of monogenic obesity, patients with biallelic *MC4R* variants exhibited accelerated growth from six months onwards.

FC3.2

Analysis of ligand- and mutation-dependent signaling of the melanocortin 4 receptor (MC4R): an example of the relevance of differential signaling (bias signaling)

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Introduction: The melanocortin 4 receptor (MC4R) is a G protein coupled receptor (GPCR) and plays a pivotal role in the central regulation of body weight in the hypothalamus. In the context of the leptin-melanocortin signaling pathway, the MC4R is activated by the endogenous ligands a- and b-MSH (melanocyte-stimulating hormone). This leads to the feeling of satiety and to a reduction in food intake. Mutations within the genes leptin, leptin receptor (LEPR), pro-opiomelanocortin (POMC) and MC4R lead to a functional impairment of the leptin-melanocortin signaling pathway and thus to hyperphagia and the development of early-onset obesity. Recently, the MC4R agonist setmelanotide was approved as a drug therapy for patients with homozygous mutations in the LEPR and POMC genes. Initial studies indicate that the effect of setmelanotide is particularly due to a change in MC4R signaling (differential signaling). For this reason, the aim of this investigations was to determine the extent to which ligands such as setmelanotide and mutations in the MC4R gene alter the signaling profile of the MC4R.

Methods: 10 MC4R mutations associated with the development of obesity were investigated in vitro in HEK293 cells. After transfection and expression of wild-type MC4R and MC4R mutations, four different signaling pathways (Gs, Gq/11, ERK, G12/13), b-arrestin2 recruitment, as well as surface expression were examined after stimulation with three different ligands (a-MSH, b-MSH, setmelanotide). Additionally, the mutations were structurally characterized based on the cryo-electron microscopic (cyro-EM) structure of MC4R.

Results: The investigated MC4R mutations affected the signaling profile of the MC4R in different ways. Also, stimulation with certain ligands led to a change in differential signaling. We were able to show that a mutated and therefore disturbed MC4R signaling pathway could be restored after stimulation with specific ligands. These observations can be explained by changes in the MC4R structure.

Conclusion: The results indicate the importance of differential signaling of the MC4R. On the one hand, this is relevant for the therapy of patients with monogenic obesity. Additionally, this mechanism can also be used to identify patients with certain mutations in the MC4R who would benefit from drug therapy with an MC4R agonist. Moreover, a detailed knowledge of MC4R signaling enables the optimization of drug intervention strategies.

FC3.3

Frequency of Obesity-Related Gene Variants in a European Population With Early-Onset, Severe Obesity

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Background: Patients with genetic variants in the melanocortin-4 receptor (MC4R) pathway may present with early-onset, severe obesity and hyperphagia. Increasing awareness of genetic testing could improve diagnosis of rare genetic causes of obesity and identify patients who might benefit from targeted therapy; however, such testing has been limited. Moreover, the frequency of specific genetic variants in this population is currently unknown. The Rare Obesity Advanced Diagnosis™ (ROAD) genetic testing program aims to enhance access to genetic testing for patients with suspected rare genetic causes of obesity. Here, we used ROAD data to assess the frequency of selected rare variants in individuals with early-onset, severe obesity.

Methods: Individuals with early-onset, severe obesity were sequenced as part of the ROAD genetic testing program. The panel included 79 genes and 1 chromosomal region that have well-established associations with obesity and the MC4R pathway. Eligible individuals had severe obesity (defined as ≥97th percentile of body mass index [BMI] for age in those aged ≤18 years or BMI ≥40 kg/m^2 in those aged ≥19 years), were an immediate family member of selected previously tested patients, or showed clinical symptoms that suggested Bardet-Biedl syndrome.

Results: Overall, 2,253 individuals were sequenced in Spain (n=1,020), Italy (n=508), Ireland (n=216), Turkey (n=178), Israel (n=189), the United Kingdom (n=138), and Germany (n=4), of whom 1,208 (54%) were aged <18 years. The mean (standard deviation [SD]) BMI Z score of individuals aged ≤18 years was 3.40 (0.93), the mean (SD) BMI of individuals aged >18 years was 44.2 kg/m^2 (8.48), and the mean (SD) age of obesity onset for all individuals was 6.9 years (8.5). Genetic variants that have been indicated for treatment in Europe with the MC4R agonist setmelanotide or that are being investigated for setmelanotide efficacy in clinical trials were identified in 46 (2.0%) and 661 (29.3%) individuals, respectively. An additional 481 (21.3%) individuals had variants that might support a diagnosis of genetic obesity but are neither currently indicated for setmelanotide treatment nor being investigated for setmelanotide efficacy in clinical trials. Genetic variants were not identified in 1065 (47.3%) individuals.

Conclusions: In this cohort of individuals with early-onset, severe obesity, ~35% carried potentially actionable variants. Genetic testing of patients with early-onset, severe obesity may be an important component of understanding the etiology of these patients' disease and could potentially affect the course of care for these patients.

FC3.4

A Novel Mutation in DYRK1B Associated With Abdominal Obesity Metabolic Syndrome 3 (AOMS3)

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Background: Dual-specificity tyrosine phosphorylation-regulated kinase 1B (*DYRK1B*) is a nutrient-sensing protein that suppresses the RAS–RAF–MEK pathway and is known to have a role in glucose uptake and glycolysis. The expression of *DYRK1B* increases during adipogenic differentiation suggesting an important role in adipogenesis. Mutations in *DYRK1B* have been described in three Iranian families and five Caucasian patients with Abdominal Obesity Metabolic Syndrome 3 (AOMS3). We report the youngest patient with phenotypic features of AOMS3 associated with a novel de-novo missense variant of the *DYRK1B*.

Case Presentation: A 13-years-old developmentally normal boy started to gain weight at the age of 4 years. He was a product of full-term uneventful pregnancy with a birth weight of 2.6kg, born to non-consanguineous parents. He had no significant neonatal history and in the family history his father had type 2 diabetes. He was tall (Height +2.39 SD, MPH: 180 cm) and obese (BMI +2.46 SD, mainly central) with marked acanthosis nigricans. He had a mild elevated blood pressure (147/90 mmHg) that was conservatively managed. He had an elevated HBA1c (6.1%), impaired fasting glucose (6.3 mmol/L), normal C peptide (6.81 ng/ml [0.70-11.20]) and insulin level (308 pmol/L [20-571]), negative type 1 diabetes antibody profile, elevated liver enzymes (ALT 191 IU/L [12-26], AST 65 IU/L [18-38], GTT 40 IU/L [6-15]) with normal thyroid function and lipid profile. On ultrasonographical examination, the liver was enlarged with marked fatty infiltration. His obesity was originally thought to be related to life style and he was managed with life-style modification. However, Targeted Exome Sequencing revealed a novel heterozygous missense variant c.1522C>T, (Pro508Serine) in the *DYRK1B* gene. Three in-silico prediction tools (cadd, sift, and mutation taster) suggest that this variant will have a deleterious effect on the encoded protein and thus is likely to be pathogenic. He was managed with metformin and dietary advise and had a stable glycemic profile but with minimal weight reduction.

Conclusion: This is the youngest patient with a novel variant in the *DYRK1B* gene associated with AOMS3. As mutations in *DYRK1B* gene are associated with early onset coronary artery disease, severe hypertension and frank type 2 diabetes in adults, the early identification of these patients will allow screening for the development of coronary artery disease and timely intervention in terms of management. Functional analysis of novel variants in *DYRK1B* will provide further insights into the molecular mechanisms of metabolic syndrome.

FC3.5

Early corneal nerve loss in children with obesity and type 2 diabetes

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Background: Childhood obesity is highly prevalent in the MENA region and may be associated with sub-clinical neuropathy.

Methods: Children with obesity with normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and Type 2 diabetes Mellitus (T2DM) and healthy controls (HC) underwent body composition analysis, assessment of vibration perception threshold (VPT), monofilament sensitivity and corneal confocal microscopy (CCM) to quantify corneal nerve fiber density (CNFD), branch density (CNBD), and length (CNFL).

Results: Sixty-nine children with obesity (NGT (n=40), IGT (n=13) and T2DM (n=16)) aged 14.0±2.9 years were compared to 20 healthy controls (HC). There was no difference in VPT or monofilament sensitivity between groups. There was no difference in CNFD, CNBD or CNFL between obese children with NGT or obese children with IGT compared to HC and obese children with IGT compared to obese children with NGT. CNBD (34.4(32.3-43.8) vs. 48.9(43.8-66.3), P=0.04) was significantly lower in obese children compared to healthy controls. Children with hidden obesity (high % body fat and low muscle mass) had a significantly lower CNFD (27.8±7.4 vs. 32.8±5.6, P=0.05) with no change in CNBD and CNFL compared to solidly built children. CNFL was non-significantly lower (18.0±4.2 vs. 20.5±4.5, P=0.094) in obese children with T2DM compared to HC and obese children with T2DM had lower CNFD (26.8±6 vs. 30.4±7.5, P=0.067) and CNFL (18±4.2 vs. 21.3±5.8, P=0.027) compared to obese children with NGT.

Conclusion: Children with hidden obesity and especially obese children with T2DM have evidence of early corneal nerve loss, indicative of sub-clinical neuropathy.

FC3.6

Impact of Setmelanotide on Future Metabolic Syndrome Risk in Pediatric Patients With Bardet-Biedl Syndrome

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Background: Children with metabolic syndrome carry an increased risk for development of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) in adulthood. Patients with rare syndromic obesity, such as Bardet-Biedl syndrome (BBS), experience early-onset, severe obesity, which may convey an increased risk for developing obesity-related comorbidities and metabolic syndrome later in life. In clinical trials, treatment with the melanocortin-4 receptor agonist setmelanotide led to significant weight and hunger reductions in patients with BBS, along with improvements in metabolic parameters. To better understand the effect of setmelanotide on future risk of metabolic syndrome development, we evaluated the effect of 1 year of setmelanotide treatment in pediatric patients with BBS using a metabolic syndrome score (MetS-Z-BMI), a measure where high scores indicate increased long-term risk of metabolic syndrome comorbidities. A 1.0-point increase in MetS-Z-BMI score in childhood increases the odds of future CVD and T2DM by 9.8 and 2.7, respectively.

Methods: Metabolic parameters from a Phase 3 trial of patients with BBS (NCT03746522) were evaluated. MetS-Z-BMI score changes after 1 year of setmelanotide were assessed. MetS-Z-BMI outcomes were analyzed in the overall and <18-year (pediatric) age groups. Patients were classified based on weight outcomes as being clinical responders to setmelanotide (ie, patients ≥18 years old achieving ≥10% weight loss or patients <18 years old achieving ≥0.3-point BMI Z score reduction) or nonresponders at Week 52.

Results: Twenty-two patients were evaluated (59% female, 10-44 years old). Pediatric patients with BBS achieving a clinically meaningful reduction in weight with setmelanotide (n=9) demonstrated a reduction in mean (SD) MetS-Z-BMI score after 52 weeks of treatment (−0.38 [0.53]). By contrast, pediatric patients without weight response to setmelanotide showed an increase in mean (SD) MetS-Z-BMI score after 52 weeks (n=4; +0.42 [0.38]). Clinical response to setmelanotide in the overall population (n=16) was also associated with a reduced mean (SD) MetS-Z-BMI score after 52 weeks (−0.54 [0.56]). This change in score compares favorably to an increased score in patients who were nonresponders after 52 weeks of treatment (n=6; +0.17 [0.50]), a between-group difference of −0.71 (P=0.0129).

Conclusions: Setmelanotide treatment response is associated with reductions in metabolic syndrome severity score in pediatric patients with BBS, which are associated with reduced risk of metabolic syndrome, CVD, and T2DM. These data support the broad benefits of setmelanotide beyond weight loss and hunger reduction, thus supporting early initiation of treatment for potentially reducing future risk of CVD and T2DM.

Growth and syndromes (to include Turner syndrome)

FC4.1

Heterozygous Null Mutations in FLNB as a Cause of apparent isolated Short Stature in Chinese Children

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Background: FLNB encodes filamin B (FLNB), a protein expressed in human growth plate chondrocytes, building the cytoskeleton that gives structure to cells and allows them to change shape and move. Biallelic loss-of-function mutations in FLNB result in spondylocarpotarsal synostosis (SCT; OMIM: 272460), while heterozygous null mutations related isolated short stature (ISS) have not been well described previously.

Objective: Describe the clinical characteristics of four unrelated ISS families with novel FLNB heterozygous null mutations.

Design and Participants: We performed whole exome sequencing in an ISS cohort of 189 unrelated patients, and found heterozygous FLNB null mutations in four patients. Detailed genotyping and phenotyping were analyzed in the members of these four families. We confirmed these four mutations by Sanger sequencing, and further verified the pathogenicity of the two splicing variants via splicing assays.

Results: The four probands mainly presented with short stature, short arm span, brachydactyly, and relatively large head. They all had delayed bone age. By whole exon sequencing (WES), we successfully identified the genetic cause of short stature in these four patients: two with splicing mutations c.5888-2A>C (p.?) and c.5110-1G>A (p.?), one with a frameshift mutation (c.2905delA (p.R969Gfs*11)), and one with a nonsense mutation (c.6637G>T (p.E2213*)). The pathogenicity of the two splicing variants was further confirmed by splicing assays.

Conclusions: Heterozygous null mutations of FLNB lead to apparent ISS characterized by short stature with short arm span and relatively large head. FLNB related short stature may not be a rare cause of ISS in the Chinese children.

FC4.2

Genetic and phenotypic features of children with familial tall stature

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Introduction: Familial tall stature (FTS) is defined as height taller than +2 SD in a subject growing within his/her midparental height (MPH) with no apparent dysmorphic features. FTS is routinely not an indication for genetic investigation. However, some subtle dysmorphic features of various genetic disorders might be missed justifying the need for further investigation.

Aims: To elucidate the genetic cause of FTS and to reevaluate the syndromic features via detailed anthropometric examination.

Methods: Tall children with height > +2 SD, absence of intellectual disorder, no apparent dysmorphic features (those identified by routine endocrinological examination), absence of endocrine disease, unknown genetic cause of tall stature and taller parent's height > +2 SD, who were referred to our outpatient clinic from September 2020 to March 2023, were enrolled to the study. In total, 29 children (17 girls) with FTS were enrolled in the study. Their median height was 3.07 SD (IQR 2.64 - 3.67 SD) and their age was 13 years (9 - 16 years). All subjects underwent routine examination by pediatric endocrinologist followed by detailed anthropometric examination. DNA samples were examined cytogenetically (karyotype and FISH) and via next-generation sequencing panel of 788 genes related to growth. The results were evaluated using American College of Medical Genetics and Genomics guidelines.

Results: We elucidated the genetic cause of tall stature in 10/29 (34.4%) children (genes NSD1 [2], FGFR3 [1], SUZ12 [2], PPP2R5D, SHOX duplication [2] and sex chromosome trisomy [2]). Moreover, by four subjects we found 4 variants of uncertain significance in genes FGFR1, FGFR3, TCF20, FBN2. Detailed anthropometric examination revealed subtle syndromic features in 6/10 subjects with positive genetic finding such as arachnodactyly (SUZ12), mild facial stigmatization (SHOX duplication), positive thumb and wrist sign and dolichocephaly (FGFR3), dolichocephaly and macrocephaly (NSD1), macrocephaly, positive thumb and wrist sign (PPP2R5D), dolichocephaly and high palate (NSD1).

Conclusion: Genetic causes traditionally associated with syndromic tall stature can be also found in children with FTS. Subtle syndromic features can be identified in these children by detailed anthropometric examination.

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FC4.3

Pathogenic variants in *GHSR* cause short stature and growth hormone neurosecretory dysfunction; results from a large case series

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Introduction: Ghrelin binds to its receptor GHSR1A, encoded by *GHSR*, on somatotrophs of the pituitary. Growth hormone (GH) secretion is enhanced by ghrelin binding as well as the receptor's constitutive activity. Results from *in vitro* experiments, knock-out mice, and GWAS suggest that heterozygous loss-of-function of *GHSR* may be associated with short stature, but observations in case studies are equivocal. We aimed to better characterize the phenotype, evaluate *in vitro* GHSR function, and assess the response to rhGH treatment.

Methods: This case series includes 18 patients with suspected *GHSR* haploinsufficiency. *In vitro* variant pathogenicity was studied using transfection of mutated *GHSR* in HEK293 cells. We assessed cell-surface expression, and used a luciferase assay to measure serum response element-mediated transcriptional activity in the basal state and after stimulation with ghrelin.

Results: Patients (6F, 12M, 2-12 years) had a birthweight of -0.2±1.4 SDS and birth length of -0.7±1.4 SDS. Height at inclusion was -2.7±0.6 SDS, with normal sitting height/height ratio and an average BMI of -0.8±1.0 SDS. Mean serum IGF-I was -1.5±0.5 and IGFBP-3 was -1.2±0.7 SDS. The stimulated GH response was 11.7-32.7 µg/L. In two patients, a low-dose IGF-I generation test (0.025 mg/kg rhGH for seven days, n=2) showed a significant IGF-I increase of 1.2-1.3 SDS. On rhGH treatment (n=4), height gain after 1 and 2 years was +0.6-1.5 SDS and +1.4-1.6 SDS. Ten different rare *GHSR* variants with ACMG class 3, 4 or 5 were identified (six novel). So far, we have analysed six variants *in vitro*, showing absence of constitutive activity in five (p.Arg141Pro, p.Ala204Glu, p.Arg107Glyfs*31, p.Trp193*, and p.Ala271Pro) as well as decreased response to ghrelin in two (Ala204Glu, Arg107Glyfs*31), and normal constitutive activity and increased response to ghrelin (Phe279Leu) in one. The latter patient (untreated) had shown the highest stimulated GH response (32.7 µg/L).

Conclusion: This is the first study to combine phenotypical, functional and rhGH response data in a large (n=18) group of short children with suspected *GHSR* haploinsufficiency. Overall, these children appear to have proportionate short stature, low-normal serum IGF-I and IGFBP-3 levels and a normal stimulated GH response. The 1- and 2-year growth responses to rhGH treatment in four patients appear similar to those in GH-deficient children, supporting the hypothesis that *GHSR* haploinsufficiency is associated with decreased spontaneous GH secretion. Long-term follow-up of rhGH treatment is needed to establish its efficacy in terms of adult height.

FC4.4

Growth failure in aggrecan haploinsufficiency is due to a decrease in growth plate matrix volume and hypertrophic cell size

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Background: Heterozygous loss-of-function mutations in the aggrecan gene (ACAN) cause autosomal dominant short stature with advanced bone age, early-onset osteoarthritis and intervertebral disc disease (SSOAOD; OMIM#165800). ACAN mutations is a relatively common finding in idiopathic short stature (ISS) and has been reported to be the cause of growth failure in approximately 2% of children with ISS. However, the underlying cellular and molecular mechanisms by which ACAN mutations cause growth failure in SSOAOD have not been elucidated.

Objective: To investigate the underlying cellular and molecular mechanisms of growth failure using a mouse model of SSOAOD.

Methods: Cartilage matrix deficiency mouse (Acan^{cmd}) has a naturally occurring 7 bp micro-deletion in aggrecan gene. Heterozygous Acan^{cmd} and wild-type (WT) male and female mice were assessed for skeletal and body growth at 1,3,6,12 and 24 weeks of age. Histomorphometric analysis was performed on Masson-Trichrome stained proximal tibial and distal femoral growth plates. Cell proliferation was assessed by EdU incorporation. Quantification of percentage matrix area was performed using Image J. Single-cell RNA sequencing was carried out on chondrocytes isolated from 18 day old WT and Acan^{cmd} female mice according to 3' gene expression protocol (10X Genomics).

Results: Heterozygous Acan^{cmd} mice were born at a normal size and similar to humans with SSOAOD but showed decreased postnatal growth resulting in a gradually worsening dwarfism with reduced total body length and tibial and femoral lengths ($p<0.0001$). In the growth plates, chondrocytes were found to be more tightly packed with reduced matrix area ($p<0.0001$) and increased column density in Acan^{cmd} mice compared to WT mice. Growth plate height ($p<0.0001$), heights of the individual zones ($p<0.001$), the number of resting zone chondrocytes ($p<0.01$), proliferative cells per column ($p<0.0001$), and the size of terminal hypertrophic chondrocytes ($p<0.001$) were slightly reduced in both male and female Acan^{cmd} mice, especially at 1 week of age. Interestingly, chondrocyte proliferation was similar in Acan^{cmd} and WT mice at all time-points assessed ($p=0.90$). Female Acan^{cmd} mice exhibited a more pronounced phenotype than male mice.

Conclusions: Similar to children with heterozygous ACAN mutations, heterozygous Acan^{cmd} mice exhibit a growth pattern with postnatal growth failure resulting in adult short stature. The growth failure is primarily caused by decreased matrix production and hypertrophic cell size, whereas chondrocyte proliferation is normal. Single-cell RNA sequencing of growth plate chondrocytes is ongoing and will identify the underlying pathogenic mechanisms and might also identify compensatory mechanisms limiting the effects of aggrecan haploinsufficiency.

FC4.5

From thalidomide embryopathy to genetic defects of the upper limb, internal organs, cerebral midline, and pituitary: The phenotypic spectrum of *SALL4*

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Introduction: In 1950s - 1960s, the thalidomide disaster resulted in congenital malformations in more than 10,000 children. Derivative of thalidomide interferes with early embryonic transcriptional regulation due to selective degradation of SALL4 protein and thus, thalidomide embryopathy phenocopies pathogenic variants of the *SALL4* gene. Their phenotypes range from phocomelia, reduced radial ray, to defects of the heart, kidneys, eye, and cerebral midline. *SALL4*, together with *GLI3*, downregulate the SHH signaling pathway that is essential for pituitary development and function.

We report on a family with a *SALL4* pathogenic variant leading to vertical transmission of radial hypoplasia, kidney dystopia, and short stature due to growth hormone deficiency (GHD).

Clinical Case: Our proband was born at 39th GW small for gestational age (BW 2550 g/BL 47 cm, both≤-2.0 SDS). He had bilateral asymmetrical radial ray malformation (consisting of radial hypoplasia, ulnar flexure, and bilateral aplasia of the thumb), an ectopically placed lower canine and pelvic kidney dystopia, but no cardiac malformations, clubfoot, ocular coloboma or Duane anomaly. He was examined for progressive growth failure at the age of 3.9 years, where his IGF-1 was 68 ug/l (-1.0 SDS), and growth hormone (GH) after stimulation 6.2 ug/l. Other pituitary hormones and brain CT were normal. GH therapy was started at 6.5 years when his height was 109 cm (-2.8 SDS), and he experienced catch-up growth as expected in GHD. Puberty started spontaneously and progressed normally. At age 13 his height was 158.7 cm (-0.2 SDS).

His mother's and father's heights are 152.3 cm (-2.4 SDS) and 177.8 cm (-0.4 SDS) respectively. His father has a milder malformation of the forearm. The affected paternal grandfather (height 164 cm; -2.3 SDS) has a radial ray defect with missing opposition of the thumb. The family reports a similar phenotype in the paternal grandfather's mother and sister. IGF-1 in proband's mother was 153 ug/l (-0.3 SDS) and in paternal grandfather 69 ug/l (-1.9 SDS), which is supportive of GHD.

Whole exome sequencing revealed a nonsense variant in the *SALL4* gene c.1717C>T (p.Arg573Ter) in the proband, his father, and paternal grandfather.

Conclusion: This is the first case demonstrating a patient with a congenital upper limb defect based on a pathogenic variant of the *SALL4* gene where an isolated GHD was detected and has been successfully treated with GH. Thus, *SALL4* joins the candidate gene list for monogenic syndromic pituitary insufficiency.

FC4.6

Persistence of Growth Promoting Effects in Infants and Toddlers with Achondroplasia: Results in Children Aged Over 2 Years Old from a Phase II Extension Study with Vosoritide

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Introduction: Vosoritide increases growth in children with achondroplasia aged 5–18 years (Savarirayan et al, Genet Med, 2021). We recently reported results from a phase 2, randomized, double-blind, placebo-controlled study (111-206) in young children with achondroplasia aged 3 months–5 years Here we present results from an open-label extension study (111-208) spanning up to 4 years of treatment in the children aged 2-5 years at study start.

Methods: After a 1 year placebo-controlled study with vosoritide at 15 mg/kg body weight (111-206), participants transitioned to open-label treatment (ongoing study 111-208). Results were analysed by age cohort at treatment start (>2 years cohort reported herein). Primary objectives were evaluation of safety and tolerability, and change in height z-score. Height z-scores were referenced to CDC average stature growth charts. Comparative cross-sectional analyses were performed for each year of follow-up based on available data using two independent external controls: (1) observational/placebo data from study 111-901 (Savarirayan et al, Genet Med, 2022) and placebo data from 111-301 (Savarirayan et al, Lancet, 2020) and 111-206 vosoritide trials, and (2) external CLARITY natural history dataset (Hoover-Fong et al, Orphanet, 2021). Changes in upper:lower body segment ratio are expressed in relation to findings from observational/placebo controls.

Results: 34 participants started vosoritide treatment in study 111-206 or 111-208 between ages 2-5 years (56% male, 44% female, mean (SD) age 42.3 (10.11) months). Vosoritide remained well-tolerated with no change in adverse event profile and no discontinuations due to treatment-related adverse events. Changes in height z-score over time in participants are shown in the table.

After 4 years, treated children demonstrated greater height gain compared to observational/placebo controls (LS mean change 6.27cm [95% CI 2.98-9.56]) and to matched untreated children from CLARITY (LS mean change 7.77 cm [95% CI 5.14, 10.40]). Compared to observational/placebo controls, improvement in upper:lower body segment ratio was seen after 4 years (LS mean change 0.10 [95% CI -0.19, 0.00]).

Conclusions: Vosoritide was well tolerated and maintained positive effects on linear growth over time. Upper:lower body segment ratio improved over time.

	Treated versus untreated (Observational/Placebo Control)		Treated versus CLARITY	
	Mean height z-score change	**95% CI**	**Mean height z-score change**	**95% CI**
Year 1 (n=34)	+0.24	-0.08, 0.56	+0.40	0.21, 0.59
Year 2 (n=30)	+0.33	-0.01, 0.66	+0.58	0.34, 0.82
Year 3 (n=22)	+0.55	0.17, 0.93	+0.80	0.48, 1.12
Year 4 (n=9)	+1.10	0.46, 1.74	+1.42	0.91, 1.93

Diabetes and insulin 1

FC5.1

Diabetes mellitus and gender incongruence: Worse metabolic control in type 1 and higher mental health issue rates in type 1 and 2 diabetes – a DPV registry study

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Background: The condition when a person's gender identity does not match the gender assigned at birth is called gender incongruence (GI). GI numbers increased tremendously over the last decade. Diabetes mellitus – type 1 and type 2 – is a severe and lifelong disease. GI combined with diabetes may potentiate the burden for affected people.

Objective: The study aimed to characterize people with GI and diabetes from an extensive standardized registry, the Prospective Diabetes Follow-up Registry (DPV), and to identify potential metabolic and psychological burdens.

Methods: We compared demographic and clinical registry data of persons with type 1 or type 2 diabetes and GI to those without GI. To ensure similar baseline characteristics, we used propensity score matching with a ratio of 1:9 for people with type 1 and 1:5 with type 2 diabetes. Age, diabetes duration and treatment year served as covariates.

Results: The unmatched study population comprised 157’866 people with type 1 diabetes and 452’643 with type 2 diabetes; sixty-six persons had a documented gender incongruence, 43 with type 1 diabetes and 23 with type 2 diabetes. We matched those with n= 258 type 1 diabetes and n=138 type 2 persons. HbA1c values were higher in persons with type 1 diabetes and GI than without GI ($p <0.05$) - despite a comparable rate of CGM/FGM devices and insulin pump use - whereas the type 2 group showed no difference. Blood pressure was similar in all groups, as were lipid parameters in the type 1 group, but GI people with type 2 diabetes had lower LDL-cholesterol levels. The depression rate was significantly higher in GI people than in non-GI-people: 23.3% versus 3.9% in type 1 and 39.1% versus 6.5% in type 2 ($p<0.0001$, respectively). Anxiety was significantly more common in type 1 with GI ($p<0.05$), as was suicidality in type 2 with GI ($p<0.001$).

Conclusion: People with GI and type 1 diabetes show worse metabolic control than those without GI. Mental health issues are frequent in all people with diabetes and GI. We think that GI people need screening for distress, special attention, counselling and the best care to shoulder their additional burden.

FC5.2

Nailfold capillaroscopy: An alternative non-invasive tool for evaluating microvascular involvement in children with type 1 diabetes

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Background: Type 1 diabetes (T1D) is characterized by chronic hyperglycemia and microvascular complications like retinopathy, nephropathy, and neuropathy in long term. Nailfold video capillaroscopy (NVC) is a non-invasive method used to examine the microcirculation in the skin. In this study, we aimed to evaluate the microvascular structure in T1D with NVC, observe capillaroscopic alterations, and reveal the relationship of capillaroscopic abnormalities with glycemic control.

Methods: In this cross-sectional study, 40 patients (F/M:19/21) followed for at least 6 months with the diagnosis of T1D and 40 age- and sex-matched healthy controls were included. Demographic data, clinical findings, and laboratory characteristics of the patients were obtained from the patient files. All patients underwent NVC to evaluate morphological and structural changes in the vessels, and findings were compared with healthy peers. Except for the thumbs, all fingers were examined four times from each finger, with a total of 32 images taken from each child.

Results: The median age of the diabetic group was 16.5 (IQR: 11.1-18) years, and the median age of the healthy controls was 15 (IQR: 12-17) years, and the control and patient groups were similar in terms of age and gender ($p>0.05$). The median diabetes duration of the patients was 75 (IQR: 34.5-125) months, and the mean insulin dose was 0.97±0.3 U/kg/day. On physical examination, mean weight SDS was -0.5±1.3; height SDS was -0.4±1.1; and BMI SDS was -0.4±1.3. Fifteen percent of the patients (n=6) was prepubertal. The mean HbA1c value of the last 1 year was 8.9±1.9%. Microalbuminuria, retinopathy, and neuropathy was present in 33.3% (n=13), 7.5% (n=3), and 5% (n=2) of the patients, respectively. When capillary morphology was evaluated, frequency of major abnormalities was higher ($p<0.001$) in children with T1D compared to healthy controls. Children with T1D showed significantly more capillary cross ($p<0.001$), enlarged capillary ($p<0.001$), bushy capillary ($p=0.03$), bizarre capillary ($p<0.001$), microhemorrhage ($p=0.007$), and neoangiogenesis ($p<0.001$). In addition, capillary density ($p=0.01$) was significantly lower in the patient group while intercapillary distance ($p<0.001$) was significantly longer compared with healthy volunteers. Lower capillary density and wider capillary loops were associated with higher HbA1c values (r:-0.32, $p=0.04$; r:-0.35, $p=0.02$).

Conclusion: Besides significant capillaroscopic alterations, a pattern of enlarged capillaries and low density in patients with poor glycemic control were detected, thus NVC appears to be a simple and non-invasive tool for assessing early microvascular involvement in T1D.

FC5.3

How feasible is it to meet the Time in Tight Range (TITR) target with Automatic Insulin Delivery (AID)?: 2128-day real-world data from a single center

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Introduction: With the development and use of automated insulin delivery (AID) technologies like Advanced Hybrid Closed Loop (AHCL or Minimed 780G) system, it becomes possible to achieve tighter glycemic control. A new parameter called “Time in Tight Range” (TITR, 70-140 mg/dL) has been proposed to evaluate glycemic control in the latest consensus on the use of continuous glucose monitoring (CGM) data in diabetes research. This study aims to assess the effect of the AHCL system use on TITR.

Methods: 2128-day CGM and pump reports of 56 children who used AID-AHCL and had at least 14 days of sensor data available between January 2021 and March 2023 were evaluated retrospectively. The CGM data were analyzed in terms of the rates of TIR >70% and >80% and TITR >50% and >60%.The glycemic parameters were evaluated separately as nighttime (00.00-06.00) and daytime (06.00-00.00).

Results: Of the participants, 59% were female, the mean age was 12.2±3.5 years, the mean duration of diabetes was 5.5±5 years, and the mean duration of AHCL use was 0.9±0.56 years. Both mean TIR and mean TITR were significantly higher at nighttime than at daytime (87.5±8.4% vs 78.8±8% & 68.2±13.4 vs 57.5±8.7% p1 <0.001, p2 <0.001). TITR had a strong positive correlation with TIR (r: 0.902, p<0.001) and a negative correlation with HbA1c (r: -0.755, p: <0.001). The rates of TIR >70% and >80% were 93% and 52%, respectively, while the rates of TITR >50% and >60% were 87% and 52%, respectively. The cut-off level for TITR in estimating an HbA1c value of <6.5% was determined to be 62%, with a sensitivity of 80% and specificity of 81%. There was no statistically significant difference between those with and without the rate of TITR >60% in terms of hypoglycemia (TBR <70mg/dl and TBR <54mg/dl; p1:0.084, p2:0.298). Those with autocorrection rate >30% had higher basal insulin percentage (41.2±3.8% vs 35±5.5%, p<0.001) and lower TIR and TITR (75.6±8.6% vs 82.6±6.1% & 53.8±7.5% vs 62.1±7.5%; p1: 0.008, p2: 0.002).

Conclusion: It is possible to meet the CGM consensus targets and recommended TITR target, as a tighter glycemic control parameter, without an increase in the hypoglycemia rate with the use of AID. A target of >50% for TITR seems realistic. Having better TIR and TITR values during nighttime and in those with an autocorrection rate <30% indicates the effect of postprandial hyperglycemia in diabetes management.

FC5.4

Changes of intestinal flora in children with type 1 diabetes mellitus and its related immune mechanism

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Keywords: Type 1 diabetes mellitus; Intestinal flora; metagenomic sequencing; cytokines; Autoimmunity

Objective: This study aims to verify the effect of intestinal microbiota diversity on the disease development of T1DM mice model, and to explore the mechanism of intestinal microbiota in the development of type 1 diabetes mediated by related cytokines.

Method: T1DM mouse model was established and different gut bacterial humoral transplants were performed. Differential strains were validated and screened using high-throughput cytokine chip technology, and differential proteins and enriched immune related signaling pathways were screened. The levels of key cytokines in the signaling pathway were detected using ELISA technology, and correlation and regression analysis were performed with the differential strains.

Result: The differences between T1DM and non T1DM intestinal cultures were validated using a mouse model, and different cultures of Klebsiella_grimontii, Absiella_dolichum and Bifidobacterium_longum were screened. High throughput cytokine detection showed elevated levels of pro-inflammatory factors in the IL-17 signaling pathway, with Absiella_dolichum, Bifidobacterium_longum and cytokine IL-17A levels are negatively correlated, while Klebsiella_grimontii strains showed a positive correlation.

Conclusion: The change of Gut microbiota may further promote the occurrence and development of T1DM by over activating IL-17 pathway.

FC5.5

Sleep Characteristics, Glycemic Control, and Endothelial Function in Adolescents and Young Adults with Type 1 Diabetes

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Background: Poor glycemic control in type 1 diabetes (T1D) is linked to cardiovascular complications. Sleep duration and quality have been shown to be related to glycemic control, glucose variability, and endothelial dysfunction in adults with T1D. This study aimed to evaluate the relationship between sleep characteristics, glycemic control, glucose patterns, and endothelial function in adolescents and young adults with T1D.

Method: Thirty subjects with T1D for at least one year, aged 13-25 years, and without chronic complications were enrolled (mean age 18.7±3.4 years, HbA1C 7.6±1.3%). Glycemic patterns and glucose variability indices were assessed using a real-time continuous glucose monitoring (CGM). Sleep characteristics were monitored using wrist-worn actigraphy, along with CGM, for 5-7 days. The Pittsburgh Sleep Quality Index (PSQI) questionnaire was completed to assess subjective sleep quality. Flow-mediated dilatation (FMD) was performed to assess endothelial function at the brachial artery.

Results: Reduced FMD was associated with poor sleep quality in T1D subjects without metabolic syndrome (r = 0.426, P = 0.034). Subjects with poor sleep quality (PSQI score > 5) had significantly lower %FMD than in those with PSQI score ≤ 5 (4.6±3.7% vs. 7.6±3%, P = 0.03). HbA1C levels were correlated with sleep efficiency (r = -0.399, P = 0.039) and sleep duration variability (r = 0.395, P = 0.042). Variability in bedtime and mid-sleep time were associated with insulin resistance, as determined by low estimated glucose disposable rate (eGDR) (r = -0.545, P = 0.003; r = -0.467, P = 0.014).

Conclusion: Sleep efficiency and variability are associated with glycemic control. Sleep quality is linked to endothelial function in adolescents and young adults with T1D. These findings highlight the importance of promoting healthy sleep habits in the management of T1D across the lifespan.

FC5.6

Post-Hypoglycemic Hyperglycemia Are Highly Relevant Markers For Stratification Of Glycemic Variability and Remission Status Of Pediatric Patients With New-Onset Type 1 Diabetes

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Aims: Recently, our team introduced the concept of post-hypoglycemic hyperglycemia (PHH) in the context that recovery of hypoglycemia impacts cardiovascular risk. GLUREDIA study aimed to evaluate whether PHH parameters correlated with glycemic homeostasis during the first year after type 1 diabetes onset and helped to distinguish pediatric patients undergoing partial remission or not.

Methods: In the GLUREDIA study, longitudinal values of clinical parameters, continuous glucose monitoring metrics and residual beta-cell secretion from children with new-onset type 1 diabetes were analyzed for one year. PHH is defined as any hypoglycemia followed within two hours by hyperglycemia. PHH parameters were calculated using an in-house built algorithm. Cross-sectional correlations between PHH parameters (i.e., PHH frequency, PHH duration, PHHAUC) and glycemic homeostasis markers were performed using adjusted mixed-effects models.

Results: PHH parameters were strong markers to differentiate remitters from non-remitters (all $p < 0.001$), the most sensitive being PHH/Hyperglycemia duration ratio (cut-off < 0.02, sensibility: 86%, specificity: 68%). Among those, PHHAUC correlated with clinical parameters and continuous glucose monitoring metrics and inversely correlated with residual beta-cell secretion (all $R2 > 0.22$, $p < 0.001$). Furthermore, combination of PHH parameters identified three groups of patients that might benefit from distinct therapeutic management. Finally, patient classification into four glucotypes, as previously described, independently validated PHH parameters as reliable markers of glycemic homeostasis and improved the segregation of patients with intermediate values of IDAA1C and CPEPEST.

Conclusion: PHH parameters are new minimal-invasive and easily assessed markers of partial remission and glycemic homeostasis during the first year of type 1 diabetes that allow patient-specific therapeutic management.

Pituitary, neuroendocrinology and puberty 1

FC6.1

Methylome analysis in idiopathic central precocious puberty girls

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Background: Although the transition from the pre-pubertal condition to puberty occurs physiologically within a bounded age range, recent data indicate a central role for epigenetics in the regulation of several genes that could mediate an alteration of pubertal onset. Moreover, changes occurring during this developmental stage have often been associated with susceptibility to a wide range of diseases in later life. To identify changes in DNA methylation profile associated with the timing of human puberty, we compared genome-wide DNA methylation patterns of three different groups of girls: with central precocious puberty (CPP), prepubertal, pubertal girls.

Methods: Infinium Methylation EPIC BeadChip technology was used to obtain genome wide DNA methylation levels. We focused our studies on peripheral blood leukocytes from 20 female patients with idiopathic central precocious puberty (CPP) and 30 healthy girls (15 pre- and 15 pubertal). MKRN3 gene screening was performed in all girls with CPP without detecting significant mutations.

Results: Analysing methylation changes associated with normal puberty in healthy pre- and pubertal girls, we identified 1006 differentially methylated CpG sites (DM-CpGs), most of which (86%) were hypermethylated in pre-pubertal controls. Some of these DM-CpGs reside in genes associated with the age of menarche or transcription factors involved in the process of pubertal development. Analysis of methylome changes in CPP patients showed 65% and 55% hypomethylated CpG sites compared with pre-pubertal and pubertal controls, respectively. Interestingly, our results revealed the presence of 38 differentially methylated genes encoding for zinc-finger-proteins (ZNF), 84% of which were shared by at least two groups of tested subjects. Functional analysis of the all DM-CpG detected for the three groups revealed significant networks enriched for neuronal signaling (semaphorin and gustation pathways), estrogen signalling, breast and ovarian cancer signalling or metabolism (sirtuin).

Conclusion: The different methylation profiles of girls in normal and precocious puberty suggest that the dysregulation of the pubertal process in humans is associated with specific epigenetic changes. Our data confirm a role of ZNF genes in pubertal time control. Finally, we suggest that epigenetic control of pubertal onset affects genes involved in signalling pathways that determine the migration and function of GnRH neurons and the occurrence of metabolic and neoplastic diseases that may be associated with CPP in later life.

FC6.2

The role of body composition and appetite-regulating hormones in idiopathic central precocious puberty and their changes during GnRH analogue therapy

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Aim: This study aimed to compare the levels of appetite-regulating hormones (ghrelin, leptin, peptide-YY (PYY), neuropeptide-Y (NPY)) in girls with idiopathic central precocious puberty (ICPP) before treatment with prepubertal girls, and to evaluate changes in these hormone levels and body composition during leuprolide acetate (LA) treatment.

Methods: This prospective, cross-sectional study included girls with ICPP, isolated premature thelarche (IPT), and prepubertal healthy controls. Anthropometric measurements, body composition analysis, and hormone levels were measured at admission and were repeated at 6 and 12 months in the ICPP group receiving LA treatment.

Results: Age, body mass index (BMI), fat ratio were similar in the ICPP (n=20), IPT (n=28) and control (n=21) groups (p=0.135, p=0.738 and p=0.707, respectively). There was no difference between the groups in any of the appetite-regulating hormone levels. A significant correlation of leptin was found with BMI SD and fat ratio in the whole study group (p<0.001 r=0.606, p<0.001 r=0.640, respectively). In the follow-up of the ICPP group, the thelarche stage regressed in all cases with treatment, and LH was suppressed in the GnRHa test. Although BMI SDs did not change significantly in the first 6 months (p=0.407), the fat ratios showed a significant increase. While no significant change was found in ghrelin levels during the treatment, a significant increase in leptin levels and a significant decrease in PYY and NPY levels were detected between 0-6 months.

Conclusion: The similarity in hormone levels between groups suggests that these hormones are associated with adipose tissue, independently of puberty. However, changes in hormone levels during LA treatment suggest that these hormones play important roles in the onset and regulation of puberty. Possible mechanisms will be discussed.

	ICPP	IPT	Control	p*	ICPP 6th month	ICPP 12th month	p**
Ghrelin(ng/mL)	8.10(4.12-13.97)	8.66(3.54-14.37)	7.91(2.01-13.42)	0.511	7.37(2.81-11.90)	7.54(4.10-16.56)	0.216
Leptin(ng/mL)	2.79(0.40-13.40)	2.95(0.45-24.07)	3.85(0.16-14.67)	0.639	4.85(0.91-17.87)	5.67(0.90-17.72)	0.022***
Peptid YY(pg/mL)	46.23(9.74-161.27)	56.07 (17.60-136.83)	55.11 (27.36-124.63)	0.414	32.05 (3.58-110.19)	32.48(5.02-63.36)	<0.001***
Neuropeptid Y (pg/mL)	2644.93 (692.18-14349.27)	3065.63 (484.56-17803.11)	2621.91(252.89-11339.69)	0.466	1991.42 (330.48-7999.09)	1322.13(585.12-4325.23)	<0.001***
BMI SD	1.00±0.86	1.05±1.12	0.79±1.43	0.738	1.06±0.96	1.15±0.93	0.407
Fat ratio (%)	25.81±6.05	26.73±7.34	25.16±5.99	0.712	27.94±5.07	29.17±6.35	<0.001***

*Kruskal Wallis/One-way ANOVA (among ICPP-IPT-control)
**Friedman test/Repeated measures ANOVA (among ICPP-ICPP 6th month-ICPP 12th month)
***Significant between 0-6 months and 0-12 months.

FC6.3

Is the 24-hour urinary gonadotropin assay an effective diagnostic tool in central precocious puberty? A retrospective study of threshold setting and validation in two cohorts

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Background and Aims: Central Precocious Puberty (CPP) caused by the early activation of the hypothalamic-pituitary-gonadal axis is a rare affection that occurs in 0.2% in girls. Clinical signs are suggestive and LHRH-test could be sometimes difficult to use and not always contributive. Gonadotropin assay in twenty-four hours-urinary collection could be an interesting option. The present work intended to evaluate the diagnostic interest of 24-hour urinary gonadotropin assay (FSHU, LHU) in the early pubertal onset in girls.

Methods: Urinary samples of >4 year old girls were addressed in Hormonology laboratory of Lyon University Hospital from October 2012 to July 2015 with puberty stage data for urinary FSH and LH dosages (setting cohort). We excluded incomplete urine collection, uncertain puberty stages, and interfering endocrine diseases further diagnosed (congenital adrenal hyperplasia, peripheral puberty onset, syndromic pathologies …). Distribution of values regarding Tanner stages were analyzed to propose thresholds to confirm puberty onset. We tested thus established cut-offs values in a second monocentric cohort of girls (validation cohort) consulting in Lyon University Hospital, from January 2021 to December 2022, who met the following criteria: (1) addressed for suspicion of precocious puberty; (2) ≤8 year old; (3) had pelvic ultrasonography (US) when stage of breast development was S2 or more. Pelvic US classified patients with estrogenic signs of uterine impregnation (S2+US+) or without (S2+US-). Other exclusion criteria were identical than in the setting cohort. FSH and LH were always measured with Abbott Laboratories® reagents (FSH: ref. 7K75. LH: ref. 2P40) on Architect i2000.

Results and Perspectives: Final numbers of included urine samples were 632 (455 girls) and 43 (33 girls) in setting and validation cohorts respectively. FSHU and LHU were significantly different in the setting cohort regarding Tanner stage ($p<0.0001$). Areas under ROC curves were 0,709 (0,662-0,755), 0,767 (0,725-0,809) and 0,753 (0,710-0,796) for FSHU, LHU and LHU/FSHU ratio respectively. Best thresholds were chosen using Youden's Index and minimum sensitivity of 90% for FSHU and minimum specificity of 90% for LHU. In the validation cohort, combined positive FSHU (>1.1U/24h) and LHU (>0.08U/24h) detected S2+US+ girls with 83% prognostic value. Urines under one or the other threshold (FSHU<1.1U/24h or LHU<0.08U/24h) detected S1 and S2+US- girls with 93.5% prognostic value. These results deserves large-scale reproduction in greater cohorts, but show the usefulness of urinary gonadotropins for girls presenting with CPP suspicion as it is simple, non-invasive and overcomes the limits of circadian variations.

FC6.4

Sleeptime-excreted total urinary luteinizing hormone concentrations reveal that the onset of central puberty occurs at around the same time in boys and girls: a longitudinal study

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Objectives: We designed a longitudinal study to investigate the association between central pubertal activation with age at the appearance of clinical signs of puberty. We, therefore, assessed nocturnal gonadotropin secretion which can be detected in the form of total luteinizing hormone (LH) immunoreactivity in the daytime- and sleeptime-excreted urine.

Methods: Thirty healthy volunteers (17 boys and 13 girls, aged 3.4–15.2 yr and 4.3-14.3 yr respectively at the beginning of the study) were included in the study. Male and female subjects were followed for an average of 15 visits during 5.5 and 5.8 years on average, respectively. In each visit, subjects provided 24-hour urine samples divided into sleeptime and waketime portions according to the participant's sleep-and-wake rhythm. Total urinary LH (U-LH) concentrations were measured in duplicate by Delfia® IFMA (Wallac), which has been designed specifically to detect intact LH as well as the beta-subunit and its core fragment, but not the human chorionic gonadotropin.

Results: The initial increases in sleeptime-excreted total U-LH concentrations over the cut-off value of 0.6 IU/L occurred at around the same time (around 9.75 years of age) in both sexes. The mean time span from the age at which sleeptime total U-LH concentration first exceeded the 0.6 IU/L level to observing pubertal stage 2 was 1.5 yr in boys and 0.3 yr in girls.

Conclusions: Findings in our population with a limited sample size suggest that the timing of central pubertal activation is a sex-independent phenomenon, which can be observed by monitoring the nighttime total LH concentrations in sleeptime-excreted urine samples. The lag time from central pubertal activation of gonadotropin secretion to the clinical onset of puberty is significantly longer in boys.

FC6.5

Clinical characteristics of 213 children with early pubertal development complicated with pineal cyst

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Background: Previous studies have speculated that melatonin secreted by the pineal gland plays a role in the regulation of puberty, and pineal cyst may affect its secretory function ,thus causing early pubertal development. However, there are few studies on early pubertal development with pineal cyst and its clinical features are not clear. This study aims to explore its clinical features and the relationship with cyst size to further improve the understanding of this disease.

Methods: The clinical, laboratory and imaging findings of children with early pubertal development complicated with pineal cyst admitted to the Children's Hospital Affiliated to Zhengzhou University from January 2017 to February 2023 were retrospectively analyzed. According to the size of cysts, girls were divided into three groups(< 6mm, 6-10mm, >10mm), the difference in clinical characteristics was compared to explore the relationship between the size of pineal cysts and the development process of puberty.

Results: From January 2017 to February 2023, the incidence of pineal cyst in children with early pubertal development who underwent MRI examination of pituitary gland was 6.30% (478/7582), and the incidence of pineal cyst in children aged 7-9 years was the highest (348/478,72.80%). Among them, 213 children who met the screening criteria and had complete clinical data were included in the study. There were 203 girls (203/213,95.31%) and 10 boys (10/213,4.69%), which were consistent with the gender characteristics of early pubertal development. The height is higher than the average level of children of the same age, the bone age is mostly advanced, and the BMI is overweight or obese, which is in line with the clinical characteristics of early pubertal development. All children had no symptoms of cyst occupying. However, the proportion of rapidly progressing puberty, sex hormone levels and gonad size were further increased with the increase of cysts, with statistical significance ($P < 0.05$ for all). It is suggested that pineal cyst is closely related to precocious puberty, especially rapid progression precocious puberty.

Conclusion: The pineal cyst may promote the process of puberty development, leading to early pubertal development in patients. The most common age of visit was 7-9 years, and the cyst size was associated with the progression of puberty. It is a kind of central nervous system disease which can not be ignored in secondary central precocious puberty. Therefore, routine MRI examination of pituitary gland is recommended for all children with rapidly progressing puberty.

FC6.6

Serum Kisspeptin and DLK1 levels as a tool for diagnosis and monitoring of central precocious puberty treatment in Thai girls

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Background: Kisspeptin and Delta-like 1 homolog (DLK1) are neuropeptides that regulate pubertal timing by activating and inhibiting the hypothalamic-pituitary-gonadal axis; consequently, measuring these biomarkers could potentially distinguish central precocious puberty (CPP) from premature thelarche (PT) girls and monitor CPP treatment.

Objectives: To compare baseline serum kisspeptin and DLK1 levels in girls with CPP at diagnosis with age-matched PT girls and after CPP treatment.

Methods: From November 2009 to July 2022, a cross-sectional study was conducted in Pediatric Endocrinology Clinic of King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. CPP and PT were defined as girls with breast onset before the age of eight years and peak LH levels of ≥ 6 IU/L and < 6 IU/L after the GnRH stimulation test, respectively. Serum Kisspeptin and DLK1 levels were measured by ELISA at baseline in both groups and 6 months after GnRH analogue treatment in the CPP group. Wilcoxon rank sum test and Chi-square test were used to compare continuous and categorial data between CPP and PT. Serum Kisspeptin and DLK1 levels in CPP were compared using the Wilcoxon sign rank test before and after treatment.

Results: Of the 48 participants included in the study, 24 are CPP girls (mean age 7.7 ± 0.7 years) and 24 are PT girls (mean age 7.4 ± 0.8 years). CPP girls were significant taller (132.6 ± 7.6 cm vs. 126.4 ± 6.7 cm, $p<0.05$) and had more advance bone age than PT girls [1.08 (0.08-2.03) years vs. 0.11 (-0.84-0.71) years, $p<0.05$]. In response to GnRH stimulation test, the CPP group had significantly higher basal LH, FSH and estradiol levels, basal LH/FSH ratio, peak LH levels, and peak LH/FSH ratio than PT group ($p<0.05$). Baseline serum Kisspeptin levels in CPP and PT group were 50.5 (38.2-77) and 49.5 (39.7-67.6) pg/mL, respectively ($p=0.89$), while baseline serum DLK1 levels were 6.5 (5.9-7.5) and 6 (4.4-14.4) ng/dL, respectively ($p=0.68$). After six months of treatment in CPP group, median serum kisspeptin levels were lower than baseline [46.4 (37.1-60) pg/mL, $p=0.002$], although median serum DLK1 levels were higher than baseline [7 (6.7-8.9) ng/mL, $p=0.002$].

Conclusion: Baseline serum Kisspeptin and DLK1 levels cannot be used to differentiate CPP from PT in Thai girls; however, significant changes in serum Kisspeptin and DLK1 levels are observed after CPP treatment. More studies are required to elucidate the clinical use of these biomarkers as a monitoring tool for CPP treatment.

Sex differentiation, gonads and gynaecology or sex endocrinology

FC7.1

Polygenic scores for testosterone and SHBG are associated with hormone levels in male infants

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Background: The male Hypothalamic-Pituitary-Gonadal (HPG) axis undergoes a transient activity phase during the first months of life with surging serum concentrations of reproductive hormones. Theoretically, the hormonal surge could represent a passive postnatal feedback to the withdrawal from the high sex steroid levels in pregnancy. However, we believe that minipuberty rather represents an active, tightly genetically-regulated biological process. We therefore set out to evaluate whether polygenic scores (PGS) that have been found to predict serum testosterone and SHBG in adult men are also operational in male infancy.

Objective: We investigate PGS of total testosterone (T) and Sex hormone-binding globulin (SHBG) and their impact on sex hormone levels in a deeply phenotyped cohort of male newborns.

Participants & Methods: In a prospective, longitudinal cohort (The COPENHAGEN Minipuberty Study, 2016-2018) we followed 233 healthy, term, singleton newborns (119 boys) from birth onwards with six repeated clinical examinations including blood sampling during a one-year follow-up. Genotyping was performed in 109 boys using a customized Illumina GSA array including HRC imputation, and PGS for SHBG and total testosterone were calculated based data on >200.000 men (Ruth et al. 2020). Linear regression analyses were performed to examine the associations between PGS and the mean age-specific hormone values (mean standard deviation score, SDS) based on longitudinal follow-up throughout the first year of life.

Results: We observed significant associations between T-PGSadult on the one side and mean T-SDSinfancy, mean SHBG-SDSinfancy and mean LH-SDSinfancy on the other side (p = 0.04, 0.003 and 0.02, respectively). SHBG-PGSadult was significantly associated with SHBG-SDSinfancy (p < 0.001) explaining around 19% of the phenotypic variation of SHBG levels in male newborns ($r^2 = 0.19$).

Conclusion: We provide evidence that the genetic architecture underlying circulating testosterone and SHBG levels in adult life are already operational in infancy, which may suggest that minipuberty is a genetically regulated biological process that determine adult reproductive function.

FC7.2

Mapping the transcriptomic landscape of early human fetal ovary development through a clinically-focused lens

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Introduction: Ovary development was once considered a largely passive process. RNA sequencing (RNAseq) approaches have allowed us to begin to characterise ovary development in previously unparalleled detail, revealing the process to be complex and, still, little understood. A challenge is synthesising and using these data to advance our understanding of clinical disease. Through a clinically-focused lens, we elucidate novel aspects of the transcriptional landscape of the human fetal ovary across a critical period in early development.

Methods: We combined bulk RNA-seq (n=47)(19 ovaries, 20 testes, 8 control tissues between Carnegie Stage (CS) 22/23 and 15/16 weeks post conception (wpc); single nuclei RNA sequencing (snRNAseq) (n=2; 12wpc; 10,291 cells)(10X Genomics); microfocus computed tomography (microCT; n=6); and macroscopic specimen examination (n=27 samples) to map gene expression and morphological change of early human fetal ovary development.

Results: Fetal ovary growth curves demonstrated that the ovary grows substantially in size during fetal development, with the increase in weight and length most marked from 17wpc. MicroCT shows that fetal ovaries move progressively anterolaterally within the abdomen between 12 and 19wpc. Bulk RNAseq revealed more differentially expressed genes (DEGs) in the fetal ovary compared to the testes at all developmental stages examined, most marked at meiosis (15/16wpc: n=1229 ovary DEGs; 632 testes DEGs; log2FC>2, p.adj<0.05). The fetal ovary is enriched for a distinct subset of transcription factors, including known (*FOXL2, LIN28A*), novel (*ZIC1*), and emerging ovary genes (*DMRT2C, DMRTB1, MAEL*) which localise to oogonia populations on snRNAseq analysis. Gene enrichment analysis of ovary DEGs revealed processes related to neurotransmitter signalling, neuroendocrine networks, and neural development; specific genes of interest included NPY, GABAergic genes (e.g., *GABRG1*), NAV3, and TAC1, localising to ovarian surface epithelial (OSE) snRNAseq populations. By overlapping ovary-specific DEGs at 15/16wpc with highly expressed genes from oogonia snRNAseq populations, new meiosis candidate genes were identified, including STRIP2, GBX1, TEX30, and NUP210L. Genes associated with mitochondrial metabolism were also highly expressed in the meiotic fetal ovary, including *SLC25A31*, *OTUD6A*, and *DMN1L*, localising to oogonia snRNAseq populations.

Conclusion: This work expands our knowledge of early human fetal ovary development. The ovary undergoes significant morphological change within a narrow time window.The ovary has a distinct transcriptomic signature and novel gene networks and signalling pathways are described. Genes important to early fetal ovary development are also important for later ovary function; these data will guide gene discovery in primary ovarian insufficiency and differences of sex development.

FC7.3

ROS scavengers may improve genital skin healing in boys with hypospadias

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Introduction: Hypospadias is often associated with reduced testosterone synthesis or action. High rates of complications are reported with surgical repair of hypospadias, including wound dehiscence. Boys with hypospadias have previously been demonstrated to have increased reactive oxygen species (ROS) compared to healthy controls and there is a known link between male hypogonadism and oxidative stress. It is not clear what effect ROS has on wound healing in boys with hypospadias.

Aims: To identify if cell migration and proliferation in genital skin are altered in boys with hypospadias, and whether this can be altered by antioxidants.

Methods: Genital skin (GS) samples were collected from boys undergoing hypospadias repair (cases) or routine circumcision (controls) for GS fibroblast culture. Cells were seeded at a density of 100,000 cells/well using a haemocytometer and grown until 80% confluence. A sterile pipette tip was used to scratch a wound. Cells were imaged using an EVOS XL Core microscope immediately after the wound was made and 48 hours later, in the presence/absence of ROS scavengers, N-acetylcysteine (NAC) or Tempol. Cell migration was determined using ImageJ software. Cell proliferation was measured using a commercial Cell Count Kit-8 (Abcam, UK).

Results: Twenty four cases (median age (range) 1.8 (1.2, 6.3) years) and 28 controls (median age 1.6 (1.2, 6.1) years) were recruited. Of the boys with hypospadias, 14 (58%) had distal hypospadias, 9 (38%) had proximal hypospadias and 1 (4%) had midshaft hypospadias. The median External Masculinisation Score of cases was 10 (3, 11). There were no statistically significant differences in endocrine biochemistry between the 2 groups at the time of surgery. Genetic testing had been performed in all proximal hypospadias cases, with no variants identified. Boys with hypospadias had impaired cell migration with reduced % wound closure at 48 hours (2.0 fold, $p<0.0001$) and reduced cell proliferation (1.3 fold, $p=0.01$). External Masculinisation Score was positively correlated with % wound closure ($r=0.5$, $p<0.0001$) and cell proliferation ($r=0.3$, $p=0.002$). There were no statistically significant correlations between birthweight, gestation at birth or endocrine biochemistry. Exposure to both NAC and Tempol improved wound closure (1.9 fold, $p=0.01$, and 1.5 fold, $p=0.02$ respectively) and cell proliferation (1.5 fold, $p=0.02$ and 1.4 fold, $p=0.05$ respectively).

Conclusions: There is an association between wound healing and virilisation of the external genitalia in boys. ROS scavengers improve cell migration and proliferation in boys with hypospadias and could represent a therapeutic solution for reducing surgical complications.

FC7.4

The effect of common genetic variants in *CYP19A1* on serum Estradiol to Testosterone Ratio in healthy Danish children and adolescents

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The *CYP19A1* gene encodes the enzyme aromatase, which converts testosterone (T) to estradiol (E2). In adults, single nucleotide polymorphisms (SNPs) in *CYP19A1* are associated with circulating estradiol (E2) concentrations and bone mineral density. Thus, we hypothesize that the ratio between circulating E2 and T in healthy boys and girls is affected by the *CYP19A1* genotype.

Aim: To describe E2/T ratio in healthy boys and girls in relation to age, and to evaluate the influence of *CYP19A1* variation on E2/T ratio.

Methods: In total, 1068 healthy children (643 girls), aged 6 to 19 (median age: 12.5 years), were included. Sex steroid concentrations were determined using LC-MS/MS, and reference ranges were calculated using GAMLSS allowing sex- and age specific SDS calculation. In 35.9 % (179) of boys, E2 concentrations were below LOD of 4.04 pmol/L; E2 was assigned 0,5 x detection limit of E2. Three common *CYP19A1* SNPs previously reported to affect E2 levels were selected and evaluated by quantitative endpoint PCR: rs727479, rs2899472 (both intronic), and rs10046 (3'UTR).

Results: The E2/T ratio correlated positively with age in girls (Spearman rank $r = 0.63$, $p<0.01$) and negatively with age in boys (Spearman rank $r = -0.68$, $p<0.01$). The correlation between E2/T and BMI was significantly positive in girls and negative in boys. Distribution of rs727479, rs2899472 and rs10046 are shown in Table 1.

Overall, in sex specific analyses, no associations were seen between *CYP19A1* genotypes and SDS T, E2 and E2/T ratio, respectively. However, in girls, the rs2899472 genotype was associated with a significant difference in E2/T SD levels, with AA carriers having the highest levels (median: 0.10 (AA), -0.07 (CA) and -0.26 (CC); p=0.04). In boys, *CYP19A1* SNPs did not affect circulating levels of T, E2 or E2/T ratio.

Conclusion: E2/T-ratio (SDS) and BMI correlated positively in girls and negatively in boys. In girls, but not in boys, an increased number of A-alleles in the rs2899472 A>C SNP was associated with significantly higher E2/T-ratio.

Table 1. *CYP19A1* SNPs in 1068 Danish boys and girls

rs727479	**CC**	**CA**	**AA**	***total***
n (%)	422 (36.2)	518 (44.5)	125 (10.7)	1065
rs2899472	**CC**	**CA**	**AA**	
n (%)	93 (8.0)	403 (34.6)	568 (48.8)	1064
rs10046	**CC**	**TC**	**TT**	
n (%)	262 (22.5)	554 (47.6)	252 (21.6)	1068

FC7.5

SGPL1 deficiency, a cause of 46XY DSD and adrenal insufficiency, impairs lipid metabolism and steroidogenesis in Leydig cells

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Loss of function mutations in *SGPL1* (sphingosine-1-phosphate lyase) give rise to a multisystemic syndrome with predominating features of primary adrenal insufficiency (PAI) and steroid resistant nephrotic syndrome. Retrospective analysis of our patient cohort and the wider literature also demonstrated primary gonadal insufficiency in a third of male patients with microphallus and bilateral cryptorchidism (all with concomitant adrenal disease and high mortality in infancy). Mortality is high in the condition overall (50% in childhood), with pubertal delay yet to be reported in surviving male patients. SGPL1 carries out irreversible breakdown of sphingosine-1-phosphate (S1P) and deficiency leads to accumulation of S1P and upstream sphingolipid intermediates, that are bioactive signalling molecules with roles in various cellular processes.

We developed an *in vitro* model to study the impact of SGPL1 deficiency on gonadal steroidogenesis by generating CRISPR-engineered knock-out (KO) of *Sgpl1* in the MA10 immortalised Leydig cell line, validated by Sanger sequencing and western blotting demonstrating loss of SGPL1 expression.

In response to forskolin stimulation, KO cell lines produced significantly reduced levels of progesterone when compared to wild type (WT). This was associated with decreased steroidogenic enzyme STAR and CYP11A1 protein expression, both in unstimulated and forskolin stimulated conditions in the KO lines. MTT assays also demonstrated reduced cell proliferation in the KO Leydig cells. Transcriptomic analysis highlighted dysregulation of genes in cholesterol and wider lipid metabolism in addition to steroid biosynthesis providing further insight into possible underlying mechanisms of disease.

Given current findings, SGPL1 deficiency should be considered in the differential diagnosis of 46XY infants with differences in sex development (DSD) and PAI. SGPL1 deficiency impairs lipid metabolism and steroidogenesis in Leydig cells and clinicians need to consider evolving gonadal disease in affected patients

FC7.6

GnRHa response patterns of testis expressed genes in cryptorchid boys

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Introduction: Most testis expressed (TEX) genes are testis-specific and evolutionarily conserved and several studies have reported important roles of TEX11,TEX12,TEX14,TEX15 and TEX 101 in mammalian fertility. Retrotransposons are thought to be critical for the evolution of mammalian genomes. TEX19 functions in the post-translational regulation of L1 retrotransposons, which are involved in maintaining trans-generational genome stability. In boys with cryptorchidism, prepubertal hypogonadotropic hypogonadism alters expression of ASZ1, PIWIL, and CFTR. The abrogated expression of these gene leads to abnormal activation of transposons and ultimately, infertility. Here, we report TEX expression profiles in testicular biopsies from cryptorchid boys.

Patients and Methods: We sampled testicular biopsies from bilateral cryptorchid boys for histological and transcriptome analyses using the RiboMinus Gold/TrueSeq (Illumina) RNA-Sequencing protocol. Lacking Ad spermatogonia distinguished high infertility risk (HIR) from low infertility risk (LIR) patients. HIR patients were randomized for treatment either with surgery and GnRHa or surgery only.

Results: 10 TEX genes were expressed at lower levels in samples from HIR patients as compared to low infertility risk controls (Table 1). Following GnRHa treatment, we identified three TEX genes, TEX19, involved in retrotransposon control, TEX35 in Leydig cell development and TEX38 important for spermatogenesis, that showed increased expression signals (Table 1).

Conclusion: We report novel testicular TEX expression profiles in cryptorchid patients, and their response to GnRHa treatment. We found that curative GnRHa treatment stimulates TEX19 expression, which might contribute to silencing of retrotransposons. Our data are consistent with TEX11's previous association with azoospermia.

Table 1. TEX gene expression profiles in testicular cells. RNA-Seq data are indicated for biopsies from high/low infertility risk patients (HIR/LIR) and samples with/without GnRH treatment. RNA levels (reads per kilobase and million, RPKM), log2 fold-changes (log2FC) and false discovery rates (FDR)are given; not significant (n.s.).

Gene	HIR/LIR (RPKM)	log2FC / FDR	-/+ GnRHa treatment (RPKM)	log2FC / FDR
TEX9	2.08/2.80	-0.46/0.04	n.s.	n.s.
TEX10	12.47/16.05	-0.30/0.01	13.1/11.6	-0.77/0.001
TEX11	0.23/1.15	-2.25/0.0002	n.s.	n.s.
TEX13B	0.06/0.44	-2.85/0.001	n.d.	n.d.
TEX14	0.93/2.60	-1.53/0.0004	n.s.	n.s.
TEX15	4.8/13.45	-1.58/0.0004	5.28/5.75	-0.84/0.001
TEX30	2.58/5.9	-1.27/0.0008	3.3/3.54	-0.64/0.051
TEX37	0.2/2.78	-3.64/0.0000	n.s.	n.s.
TEX41	0.64/1.64	-0.85/0.024	n.s.	n.s.
TEX101	0.24/0.87	-1.75/0.001	n.s	n.s.
TEX19	n.s.	n.s.	0.11/0.80	+2.16/0.007
TEX35	n.s.	n.s.	0.16/0.67	+1.14/0.083
TEX38	n.s.	n.s.	0.19/1.38	+1.83/0.02

Fat, metabolism and obesity 2

FC8.1

Aberrant expression of agouti signaling protein (ASIP) as a new cause of monogenic severe childhood obesity

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Here we identified and characterized a heterozygous tandem duplication at the *ASIP* (agouti-signaling protein) gene locus causing ubiquitous, ectopic *ASIP* expression in a female index patient with extreme childhood obesity.

In patient-derived adipose tissue samples, we observed pronounced differentiation of stroma-vascular fraction (SVF) cells into adipocytes in the patient compared to normal control cells. We further found reduced mitochondrial maximum respiration, spare capacity, and proton leak in the patient's SVF cells as proxies for reduced energy expenditure. By transcriptome screen, we identified overexpression of one single gene, *ASIP*. We found and functionally confirmed a chromosomal rearrangement at the *ASIP* locus, that places *ASIP* under control of the ubiquitously active itchy E3 ubiquitin protein ligase (ITCH) promoter.

The patient's phenotype of early-onset obesity, overgrowth, red hair, and hyperinsulinemia is concordant with that of mutant, so called agouti mice ubiquitously expressing the homolog nonagouti. Physiologically, ASIP antagonises the melanocortin 1 receptor (MC1R) in the skin. Due to its homology to the hypothalamic regulator of eating behaviour agouti-related protein (AgRP), we hypothesize that ectopic ASIP similarly influences eating behaviour via repressing melanocyte-stimulating hormone-mediated activation of MC4R and that the mutation might therefore represent a novel monogenic cause for severe childhood obesity. We show that the tandem duplication results in the ectopic generation of ASIP in patient-derived native stroma-vascular fraction (SVF) cells, adipocytes and blood cells as well as in induced pluripotent stem cells (iPSCs) generated from SVF cells of the patient, thus indicating ubiquitous ectopic *ASIP* expression. This overexpression persisted after differentiation of iPSCs into the three germ layers, mesoderm, ectoderm and endoderm, and after differentiation into hypothalamic-like neurons. Furthermore, we observed that ASIP causes a reduction of MC4R activity *in vitro* supporting the hypothesis that the obesity phenotype of our patient is caused by ectopic ASIP acting at the MC4R in the hypothalamus.

Since the type of mutation escapes standard genetic screening algorithms, we rescreened the Leipzig childhood obesity cohort of 1745 patients and identified four additional patients with the identical mutation, ectopic *ASIP* expression and a similar phenotype.

Taken together, our data indicate that ubiquitous ectopic ASIP expression is likely a monogenic cause of human obesity and might be potentially treatable with melanocortin 4 receptor agonists.

FC8.2

Frequency of MC4R Pathway Variants in a European Cohort of Individuals With Early-Onset Severe Obesity

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The melanocortin-4 receptor (MC4R) pathway is critical for the regulation of hunger, energy balance, and weight regulation.

Individuals who carry variants in MC4R pathway genes may present with early-onset severe obesity and hyperphagia. Historically, genetic testing in individuals with severe obesity has been limited. The Rare Obesity Advanced Diagnosis™ genetic testing program aims to enhance access to genetic testing for European individuals with suspected rare genetic causes of obesity.

Genes from individuals with early-onset (<5 years of age) severe obesity (defined as ≥97th percentile of body mass index [BMI] for age in those ≤18 years old or BMI ≥40 kg/m^2 in those >18 years old) were sequenced. We evaluated a subset of genes that encode proteins in the MC4R pathway (POMC, PCSK1, LEPR, NCOA1, SH2B1, MC4R, MC3R, CPE, LEP, KSR2, SIM1) and are associated with genetic obesity. Variants were classified as pathogenic/likely pathogenic/variants of unknown significance (P/LP/VUS) according to American College of Medical Genetics criteria. The VUS category was further divided into suspected pathogenic (SP), uncertain, or suspected benign (SB) based on available evidence. A non-rare variant (PCSK1 p.N221D) that has been suggested to predispose carriers to obesity was included and is therefore categorized as "risk."

Among 2,253 individuals, 6.0%, 20.7%, 26.9%, and 46.4% were aged <6, 6-12, 12-18, and >18 years, respectively, and the mean age of obesity onset was 6.9 years. Overall, 20.4% of individuals carried ≥1 variant in the 11 studied genes; 5.0% had a P/LP/VUS-SP variant and 15.4% had a VUS-uncertain/VUS-SB/risk variant. The variant frequency for genes with demonstrated responsiveness to the MC4R agonist setmelanotide (POMC, PCSK1, LEPR, NCOA1, SH2B1) was 15.7%, which included 7.3% of individuals with the PCSK1 p.N221D variant. When stratified by age, 30.4% (41/135), 20.1% (94/467), 19.5% (118/606), and 19.7% (206/1045) of individuals aged <6, 6-12, 12-18, and >18 years, respectively, carried ≥1 of the 11 studied MC4R pathway variants.

In our large European-based cohort of individuals with early-onset severe obesity, 20.4% carried a variant in ≥1 of the 11 studied MC4R pathway-related genes. Ongoing clinical trials EMANATE (NCT05093634) and DAYBREAK (NCT04963231) are currently assessing the effect of setmelanotide in individuals with variants in a subset of these genes. Genetic testing of individuals with severe obesity may therefore be an important part of clinical care at any age to improve understanding of their disease etiology and identify those who may benefit from novel therapies.

FC8.3

Impact of growth hormone therapy on body mass index in childhood-onset craniopharyngioma: a multicenter Italian study in 117 patients

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Background: Patients with childhood-onset craniopharyngioma (CO-CP) present long-term outcomes, including growth hormone (GH) deficiency and obesity. Currently, data on the effects of GH therapy (GHT) on the body mass index (BMI) in CP are inconclusive. Aims of the study were to evaluate BMI over time and its determinants in a large cohort of CO-CP patients treated with GH therapy (GHT).

Methods: A multicenter retrospective study conducted by the Italian growth working group of the Italian Society of Pediatric Endocrinology involved 117 CO-CP subjects treated with GHT, followed between 2000 and 2018. Seventy-five underwent

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transcranial-TC, and 34 transsphenoidal-TNS surgery. Height SDS, BMI SDS, Tanner stage, GHT start (GHS) date, GH dose were collected at the time of CF diagnosis (n=78), 4-6 months after surgery (n=95), GHS (n=112), pubertal induction/start (n=78) and final height (FH,n=46). Forty-six patients presented a CF relapse.

Results: GHT improved height (p<0.0001) from GHS to FH, while BMI SDS only slightly decreased (p=0.23). Overall, BMI steeply increased after surgery (from 0.8±1.7 to 1.7±1.6SDS; +0.8SDS, p<0.0001) and decreased from GHS up to puberty (-0,36SDS,p<0.0001). No gender differences were observed. The TC group displayed a higher BMI SDS than the TNS surgery group already at CF diagnosis, after surgery and at GHS (all p<0.01); at FH a borderline difference persisted (p=0.08). Age at GHS was 10.7±4.1 yrs, at puberty 13.3±1.6 yrs. GHT was initiated at a mean dose of 4.9±2.3 mcg/m2/week; within 6 mts after surgery in 15 (12.8%), 12 mts in 26 (22.2%), 24 mts in 36 (30.8%) and >24 mts in 40 (34.2%). The latter group showed higher BMI SDS than patients that started earlier (p<0.01); BMI differences persisted up to FH. BMI SDS at FH was predicted by BMI SDS at GHS (coeff 0.93,p<0,0001) and negatively by GHT duration (coeff 0.132,p=0.03), but not by GHT dose (R2 0.611). Twenty-six patients (58,7%) relapsed before and 19 (41,3%) after GHS (p=0.49).

Conclusions: We demonstrated in our large cohort of CO-CP that GHT improved height and slightly BMI SDS at the time of puberty but not at FH; however, most patients started GHT later than 6 mts after surgery. TNS surgery, a longer GHT duration and a lower BMI at GH start seem associated to a lower BMI over time. The actual dose does not increase the risk of CP recurrence; studies are needed to evaluate the impact of different GH doses on BMI.

FC8.4

Irs1 expression in peripheral blood associates with obesity and cardiovascular risk parameters in school-age girls

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Background and Aim: IRS1 (Insulin Receptor Substrate 1) is involved in the insulin signalling pathway and abnormalities thereof have been related to metabolic disorders and obesity. In obese subjects, insulin resistance has been associated with changes in IRS1 expression in peripheral in blood. Sex-based differences in cardiovascular disease are well established. Previous results from our group disclosed the association between IRS1 placental methylation with obesity parameters in school-age children. Here, we aimed to analyse IRS1 expression in peripheral blood from the same children and to study its association with obesity and cardiovascular risk parameters in boys and girls.

Methodology: The study population consisted of 94 subjects (46 girls and 48 boys; age 6.1 ± 0.9) from a prenatal cohort of healthy children who were followed up from birth to school age. Clinical data were obtained from all subjects at 1, 3, 6, and 12 months [weight, height, ponderal index (PI)] and at 6 years of age [weight, height, body mass index (BMI), waist circumference, hip circumference]. Biochemical data (insulin, HOMA-IR) and body composition (fat mass, visceral fat) were also assessed at 6 years of age. IRS1 expression was analysed in total peripheral blood samples by RT-qPCR. Associations between IRS1 blood expression and the studied parameters were analysed in all subjects and in subgroups thereof according to sex.

Results: Early postnatal growth (weight and PI at 1, 3, 6, and 12 months) was positively associated with IRS1 expression in peripheral blood (r from 0.216 to 0.316; all p <0.05) in all subjects, but the associations were stronger in girls (r from 0.309 to 0.469; all p <0.05). In addition, in girls, positive associations were observed at 6 years of age between IRS1 blood expression and obesity and cardiovascular risk parameters (weight, BMI, waist circumference, waist/hip ratio, waist/height ratio, fat mass, visceral fat, insulin and HOMA-IR index; r from 0.332 to 0.470; all p <0.01) that were not observed in boys. All the observed associations were independent for potential confounding variables in multivariate analyses.

Conclusions: Higher postnatal weight gain early in life is associated to higher IRS1 blood expression in school-age children. In school-age girls, higher IRS1 blood expression is further related to several obesity and cardiovascular risk parameters. Our results suggest that IRS1 could be a potential blood biomarker of cardiovascular risk in healthy school-age girls.

FC8.5

Impact of Setmelanotide on Metabolic Syndrome Risk in Pediatric Patients With POMC and LEPR Deficiency

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Background: Patients with rare monogenic obesity caused by biallelic variants of genes such as proopiomelanocortin (POMC; including variants in PCSK1) or leptin receptor (LEPR) deficiency, experience hyperphagia (a pathologic, insatiable hunger) and early-onset, severe obesity. This suggests potential increased risk over time of obesity-related comorbidities, including metabolic syndrome, a cluster of conditions associated with increased risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). In Phase 3 trials, treatment with the melanocortin-4 receptor agonist setmelanotide resulted in significant weight and hunger reductions in patients with POMC or LEPR deficiency; treatment also demonstrated an effect on several parameters of metabolic syndrome. To quantify the effect of setmelanotide on metabolic syndrome risk, we evaluated the effect of 1 year of setmelanotide in pediatric patients on metabolic syndrome severity score based on body mass index (MetS-Z-BMI score), a practical measurement that positively correlates with long-term risk of T2DM and CVD. Each MetS-Z-BMI score 1.0-point increase in childhood increases the odds of future CVD and T2DM by 9.8 and 2.7, respectively.

Methods: Metabolic parameters from Phase 3 trials of patients with POMC (NCT02896192) or LEPR (NCT03287960) deficiency were used to calculate MetS-Z-BMI score change after 1 year of setmelanotide treatment. MetS-Z-BMI score change was evaluated in the <18-year-old (pediatric) and overall age groups. Pediatric patients were classified based on weight outcomes, and clinical responders to setmelanotide were defined as having ≥0.3-point BMI Z score reduction after 52 weeks.

Results: Nine pediatric patients were evaluated (56% female, 11-17 years old). Pediatric patients with POMC or LEPR deficiency who were responders (n=8) achieved a highly relevant reduction in mean (SD) MetS-Z-BMI score after 52 weeks of treatment (−1.18 [0.72]); 1 pediatric patient with LEPR deficiency who did not achieve the clinical response threshold after 52 weeks of treatment demonstrated a BMI Z score reduction of −0.1 and MetS-Z-BMI reduction of −0.34.

Conclusions: One year of setmelanotide treatment is associated with reductions in MetS-Z-BMI score in pediatric patients with POMC or LEPR deficiency that have been associated with reduced risk of developing metabolic syndrome, CVD, and T2DM. These data support the broad benefits of setmelanotide beyond weight loss alone and suggest early initiation of treatment may lead to reduction in future risk of T2DM and CVD.

FC8.6

Liraglutide treatment in adolescents with extreme obesity - Effects on weight loss in the first 9 months under real-life conditions

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Introduction: The Glucagon-like Peptide(GLP1)-analogue liraglutide is the first drug approved for the treatment of obesity in adolescents in Europe. While clinically relevant effects of liraglutide treatment in adolescents with obesity had been shown in a phase III study, there are no reports about the use under real-life conditions in these patients.

Our aim was to report the effect of treatment with liraglutide on body weight loss in a cohort of adolescents with extreme obesity, including also patients with genetic obesity.

Methods: Data from n=13 patients (n=9 female) for whom liraglutide treatment was initiated after unsuccessful multidisciplinary lifestyle intervention were retrospectively analyzed (age T0:16.2±4.3 years; BMI-SDS T0:3.4±0.7). Dosing started at 0.6mg and was increased up to max 3.0mg. Molecular genetic testing of relevant obesity genes was performed initially. Anthropometric parameters (body height (m), body weight (kg)) were collected at T0 (baseline), T1 (3 months), T2 (6 months) and T3 (9 months) after treatment start. Changes in percentage body weight (Δ%BW) and BMI-SDS (ΔBMI-SDS) were evaluated.

Results: Molecular genetic abnormalities were diagnosed in n=5 patients (MC4R:c.253A>G (hom) +MC4R:c.802T>C (hom); POMC:c.641A>G (het); proximal microdeletion syndrome 16p11.2 (n=2); NTRK2:c.446C>T (het)). The mean reduction in %BW T0-T1 after 3 months was -4.8±3.1%. The mean reduction in BMI-SDS T0-T1 was -0.17±0.19. In three patients, gratifying weight reduction was already achieved after three months with a dosage of only 1.2 or 1.8mg/d (range ΔBW T0-T1:4.8 to 9.6%). Patients with genetic causes of obesity also achieved a %BW reduction of >5% in the first 3 months. Mean %BW reduction was -8.2±4.3% (ΔBMI-SDS T0-T2:-0.29±0.20) and -9.5±7.3%

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(ΔBMI-SDS T0-T3:-0.34±0.31) after 6 and 9 months of liraglutide treatment. Side effects such as nausea, vomiting, stomach pain and obstipation were reported in five patients during the gradual dose escalation. No side effects were reported after six months of treatment. The patients reported a significant reduction of their hunger feelings and asked for continuation of liraglutide treatment.

Conclusion: This case series of adolescents with extreme obesity, including also adolescents with genetic obesity, shows that treatment with liraglutide up to 3.0mg results in clinically significant weight loss in the first 9 months under real-life conditions. For their first time in life, the patients achieved a clinically significant weight loss.

Diabetes and insulin 2

FC9.1

Reference values for the insulin response to glucose challenge enable the early detection of emerging (pre)diabetes in children and young adults with obesity

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Background: The course of type 2 diabetes is more severe among children with obesity than among adults. Therefore, children at high risk for glycemic deterioration should be detected early enough to guide preventive (and interventional) clinical management.

Methods: We established age- and puberty-specific reference values for 7 different indexes addressing the insulin response during oral glucose tolerance testing upon 459 healthy participants (1127 observations) aged 6 – 30 years. Based on those cut-offs, we determined the prevalence of insulin resistance and its longitudinal stability in a cohort of 1484 children with obesity (2207 observations). Furthermore, we assessed the predictive value of insulin resistance regarding the onset of (pre)diabetes by survival analyses.

Results: Insulin resistance was already present in half of the children with obesity at preschool age (6-8 years), peaked during puberty and still remained high during early adulthood resulting in two thirds of pathological values among subjects with obesity aged 18-30 years. Indexes of insulin resistance/ hyperinsulinemia outside the reference range had an 80-83% risk to remain pathological during subsequent confirmative testing and hence are more stable than established markers of glucose metabolism (2 hour glucose: 36,4%, fasting glucose: 54%, HbA1c: 34,4%). Children with insulin resistance were four times more likely to develop (pre)diabetes within 12 years of follow-up than those without (hazard ratio (HR) for ISI-Matsuda 3.94 (95% CI 1.98 - 7.88); HR for AUC-insulin 3.33 (95% CI 1.73 - 6.40)).

Conclusions: The herein provided reference values facilitate the evaluation of insulin resistance both in a clinical and epidemiological context. Children with obesity and insulin resistance should be monitored carefully and treated rigorously, as they are four times more likely to develop (pre)diabetes than those without.

FC9.2

Characterization of pediatric patients with type 2 diabetes and trends in their pharmaceutical management 2000-2022 in German-speaking countries: Analysis based on the DPV registry

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Introduction: The prevalence of pediatric type 2 diabetes (T2D) increased over the last 2 decades, related to the rise in obesity. Meanwhile, treatment options for T2D have evolved considerably. Therefore, we analyzed changes in treatment approaches for pediatric T2D over two decades.

Material and Methods: Patients with T2D from 321 pediatric diabetes centers (Austria 24, Switzerland 2, Luxemburg 1, Germany 290) were recorded in the multicenter German Diabetes Prospective Follow-up Registry DPV, diagnosed younger than 18 years and with a medical follow-up between 2000 and 2022.

Statistical analysis was performed using the Wilcoxon rank sum test for continuous and Chi-square test for qualitative variables with adjustment for multiple testing (Bonferroni step-down). For longitudinal observations, adjusted regression models were used.

Results: 2554 patients with T2D fulfilled the inclusion criteria, with mean age 15.9 years, HbA1c 7.8% and BMI-SDS 2.0 (German KiGGS data), 42% were male and 22% were non-Caucasian. At diagnosis, boys were older (14.36 vs 13.78 years, $P<0.001$) and more severely obese (2.04 vs 1.97 BMI-SDS, $P = 0.014$). During the first 12 weeks, male patients were more frequently started on insulin (16.6% vs 9.2%, $P<0.001$) but the rate of continuous insulin therapy tended to be lower (26.2% vs 28.2%, ns). When comparing different T2D age groups at diagnosis (A: 6-11 ys, n=456; B: 12-18 ys, n=2098), older patients were more often treated exclusively by oral antidiabetic drugs (OAD) and/or GLP-1 analogues (GLP1a) (49.8% vs 34.2%; $P<0.001$) whereas younger patients tended to be treated more frequently with a combination of insulin and OAD (23.5% vs 18.6%; $P=0.12$) or exclusively with insulin (11.2% vs 7.2%; $P=0.03$). Over the last 22 years, we observe a significant increase of BMI SDS ($P<0.001$) and age ($P<0.001$) at diagnosis. Regarding patient management, fewer patients were treated with lifestyle intervention alone ($P<0.001$) or insulin monotherapy ($P<0.001$), whereas treatment with a combination of insulin and OAD/GLP1a ($P<0.001$) and OAD/GLP1a monotherapy ($P<0.001$) increased. Currently Metformin is the most commonly used agent (64%) in pediatric T2D (increase in prescriptions since 2001), followed by insulin (27%) and GLP1a (6%, increase in prescriptions since 2018). Mean HbA1c levels under therapy remained stable ($P=0.58$).

Conclusions: While HbA1c levels in pediatric T2D remained stable throughout the past 22 years, patients became more severely obese and older at diagnosis. Pharmacological therapy has changed significantly from lifestyle intervention alone or insulin monotherapy to an increasing use of OAD/GLP1a (alone or in combination with insulin).

FC9.3

A novel case of hypoglycaemia secondary to a pro-insulin processing disorder

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Background: Hypoglycaemia in patients with a high concentration of insulin and low concentration of C-peptide can be secondary to administration of exogenous insulin. This often results in safeguarding measures, with significant consequences for the patient and family. We report a novel case of a patient with symptomatic hypoglycaemia. Initial results suggested high insulin and low C-peptide levels, but subsequent testing revealed a pro-insulin processing disorder.

Case Report: This female patient was born at term in good condition. At 12 hours of age she had postnatal collapse with hypothermia, seizures and apnoeas. MRI showed subdural haemorrhages and brain and spinal infarcts. She developed severe cerebral palsy, cortical blindness and had global developmental delay. She had severe early onset obesity and multi-drug resistant epilepsy.

At 3 years of age she was started on a ketogenic diet, and was found to have episodes of hypoglycaemia. Results from a hypoglycaemia screen demonstrated hyperinsulinaemia (128 pmol/L), with C-peptide below reportable range (<94 pmol/L). This led to concerns about exogenous insulin administration and she was admitted into hospital.

While in a hospital setting she was found to have high insulin immunoreactivity using the Iso-Insulin ELISA, in contrast to a lower insulin result generated using an alternative immunoassay (DiaSorin LIAISON XL), with samples taken when her blood glucose was 3 mmol/l.

The C-peptide levels using the Mercodia ELISA was below reportable range as before, however C-peptide measured using an alternative immunoassay (DiaSorin LIAISON XL) was higher. In-house measurement of proinsulin and split 32,33 proinsulin were markedly above their respective upper reference limits, with a high proinsulin/insulin molar ratio, suggesting a proinsulin processing disorder. Information provided by the assay manufacturers reported substantial cross-reactivity of proinsulin in the Iso-Insulin ELISA and the LIAISON XL C-peptide immunoassay but not in the Mercodia C-peptide ELISA or the LIAISON XL insulin immunoassay

Conclusion: The laboratory investigation of this patient was complicated by the high proinsulin (and 31,32 proinsulin), causing a positive bias in insulin immunoassay but not C-peptide immunoassay (Mercodia), artefactually skewing the insulin/C-peptide molar ratio upwards. This case highlights a novel condition that

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generated initial high insulin and low C-peptide results that was not due to exogenous insulin administration. In complex cases, repeating testing whilst the patient is in a place of safety may help to elucidate if there is a possibility of an alternative mechanism of action, and use of different immunoassays may be required.

FC9.4

The high proportion of INS-MODY in Chinese children with MODY

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Background: The incidence rate of maturity onset diabetes of the young (MODY) and the proportion of different types of MODY will be different in different countries and races. GCK, HNF1A, and HNF4A are the three most common types of MODY, but the occurrence of other rare MODY subtypes in Chinese children is unknown. Therefore, studying the case group of MODY in Chinese children can help deepen understanding of MODY, early identification, and precise treatment.

Methods: From January 2015 to December 2022, patients with persistent hyperglycemia who were suspected of having monogenic diabetes or diabetes syndrome were recruited and next-generation sequencing (NGS) was performed at Shanghai Children's Medical Center. Clinical and laboratory characteristics of the patients were recorded. Target panel sequencing and whole-exome sequencing were performed. Candidate variants were verified by Sanger sequencing and other methods as needed. Variant pathogenicity was further evaluated according to the American College of Medical Genetics and Genomics guideline.

Results: A total of 175 children underwent genetic testing. MODY related pathogenic or likely pathogenic gene variants were found among 30 patients. Combined with clinical features, MODY was diagnosed. Among them, 11 patients were diagnosed as GCK-MODY (36.7%), 6 patients were INS-MODY (20%), 5 patients were HNF1A-MODY (16.7%), 5 patients were ABCC8-MODY (16.7%), 2 patients were HNF1B-MODY (6.7%), and 1 patient was HNF4A-MODY (3.3%). There were 2 shift variants, 7 splice site variants, and the rest were missense variants. 7 variants were newly discovered which were not included in databases such as HGMD and gnomAD. 6 patients of INS-MODY were diagnosed as type 1 diabetes for the first time, and diabetes related antibodies were negative in 4 patients. The fluctuation range of glycosylated hemoglobin was 8.3-15.3%, and the fluctuation range of fasting C-peptide level was 0.05-0.67nmol/L in patients with INS-MODY.

Conclusion: GCK-MODY is still the most common type of MODY in Chinese children, while INS-MODY accounts for a relatively high proportion of MODY in Chinese children. Clinical awareness of this type of MODY needs to be improved.

FC9.5

A case of NARS1 deficiency resulting in diabetes mellitus with liver cirrhosis and pancreatic atrophy

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Background: Aminoacyl tRNA synthetases (ARSs) are enzymes that bind amino acids to tRNAs, and many of their genetic variants are known to be pathogenic. Asparaginyl Aminoacyl tRNA synthetase (NARS1) deficiency was first reported as a cause of microcephaly in 2020. NARS1 deficiency is characterized by microcephaly, psychomotor retardation, epilepsy, congenital abnormalities of the limbs and skeleton, and a peculiar facial appearance. However, there have been no reports of diabetes mellitus complicated with resulting from gradually progressive liver cirrhosis and pancreatic atrophy in patients with NARS1. We report a case of NARS1 deficiency with diabetes mellitus associated with liver cirrhosis and pancreatic atrophy.

Case Report: The patient was a 12-year-old Japanese boy born 37 weeks and one day after conception, weighing 1,884 g. He was treated with tube feeding due to poor weight gain. Liver dysfunction appeared at the age of one year. In addition, intrahepatic nodules, uncontrolled hypertriglyceridemia, hypoproteinemia, and intractable diarrhea were also observed since infancy. A liver biopsy was performed, but no neoplastic lesions were found. Although examination for inborn errors of metabolism was also performed, no abnormality was found. Liver damage progressed over time, and liver cirrhosis developed at school age. After Nissen surgery for gastroesophageal reflux at age four, hypoglycemia with insulin excess due to dumping syndrome was observed. It was difficult to control despite enteral nutritional support, oral diazoxide, and continuous subcutaneous octreotide injection, but we stopped octreotide injection due to severe gastrointestinal symptoms. Transient postprandial hyperglycemia associated with infection was observed from age seven and worsened over time, and his HbA1c increased to 7.5% at 12 years and pancreatic atrophy was found. His HbA1c quickly improved to normal after introducing insulin for postprandial hyperglycemia. Comprehensive genetic analysis identified a compound heterozygous mutation in NARS1, leading to the diagnosis of NARS1 deficiency.

Conclusion: This is the first report of NARS1 deficiency with liver cirrhosis and pancreatic atrophy resulting in diabetes mellitus.

FC9.6

Puberty and Gonadal function in Wolfram Syndrome: A retrospective single centre study

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Background: Wolfram Syndrome (WS) is a rare progressive neurodegenerative disorder characterised by early-onset diabetes and optic atrophy as well as a variable spectrum of other clinical features. It is caused by mutations in the WFS1 gene. There is currently limited published literature on pubertal progression and gonadal function in WS.

Aims: To review the gonadal function and pubertal progression of a cohort of adolescent and young adult patients seen within a single national service for Wolfram Syndrome

Methods: Retrospective case review of all CYPD with WS who had completed puberty, seen in a single paediatric centre with classical WS mutations. Electronic records were assessed for documented testicular volumes, age of menarche and menstrual irregularities as well as gonadotrophin, testosterone and oestrodiol levels.

Results: 25 patients (16-23 years) were assessed (12M: 13F).

In males, there was evidence of hypogonadism in 5 (41.7%) with both hypogonadotrophic and hypergonadatrophic hypogonadism seen (n=2 and n= 3 respectively). All 5 patients had evidence of low Inhibin B levels. In males with normal testosterone and gonadatrophin levels (n=7), no evidence of low inhibin B was seen. In addition, 3 (25%) male patients had erectile dysfunction (ED) documented (not associated with hypogonadism but all had bladder dysfunction). 3 (25%) required testosterone replacement to complete puberty.

In females, 1 (7.6%) showed evidence of hypogonadotrophic hypogonadism with primary amenorrhoea. There was evidence of menstrual irregularities in 53.8% (n=7). Bladder dysfunction was common in both males and females with > 75% (9M and 10F).

Conclusions: In this contemporary young adult UK cohort we demonstrate a significant number of pubertal abnormalities in both males and females. Over half of females reported menstrual irregularities despite a normal puberty. This may cause particular issues in young women with sensory deficits. In young men, almost half showed evidence of hypogonadism on completion of puberty with a smaller number needing testosterone replacement into adulthood. The proportion of young males with ED is also high although may be related to both diabetes and bladder dysfunction requiring intermittent catheterization. We show that there is a wider phenotypic spectrum of gonadal abnormalities as well as a very high proportion of bladder dysfunction in young adulthood than previously suspected in WS. Young people with Wolfram syndrome should have a full pubertal assessment and that of gonadal function as a baseline, with hormone replacement and psychosexual counselling as necessary.

Fetal, neonatal endocrinology and metabolism (to include hypoglycaemia) & Multisystem endocrine disorders

FC10.1

Dasiglucagon safety in paediatric participants with CHI

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Background: Congenital hyperinsulinism (CHI) is a rare disorder, which causes persistent and severe hypoglycaemia in infants and children. CHI can be treated with glucagon, but long-term use is challenging owing to its instability in aqueous solution. Dasiglucagon, a stable glucagon analogue designed for long-term use as a subcutaneous continuous infusion, is in clinical development. Here, we present dasiglucagon safety results in participants treated for up to 8 weeks from 2 completed trials.

Methods: Trial 17103 (NCT04172441) included neonates and infants with CHI aged 7–364 days. In Part 1 (P1), participants were randomized to receive dasiglucagon or placebo (48 hours each) in a double-blind, crossover design. In open-label Part 2 (P2), all participants received dasiglucagon for 21 days. Open-label trial 17109 (NCT03777176) included children with CHI aged 3 months to 12 years. In P1 participants were randomized to receive standard of care (SOC) or dasiglucagon+SOC for 4 weeks. In P2 all participants received dasiglucagon+SOC for 4 weeks. Safety analysis comprised treated participants.

Results: In trials 17103 (n=12) and 17109 (n=32) respectively, participants' median age was 1.3 months and 4.3 years; 83.3% and 50.0% were male. Most participants had not had a pancreatectomy (17103: 91.7%; 17109: 65.6%).

The table summarizes safety results. In both trials, most treatment-emergent adverse events (TEAEs) were mild. Hemodynamic events were infrequent; no clinically relevant abnormalities were observed for blood pressure and heart rate. Necrolytic migratory erythema (NME) was confirmed in 2 participants.

Table 1.

	17103 (N=12)	**17109 (N=32)**
Participants completing trial, n (%)	12 (100.0)	32 (100.0)
Participants with TEAEs, n (%)	Dasiglucagon (n=12): 3 (25.0)	Dasiglucagon+SOC (n=16): 14 (87.5)
P1	Placebo (n=12): 7 (58.3)	SOC (n=16): 8 (50.0)
P2	10 (83.3)	24 (75.0)
Most common TEAEs, n (%)		
Vomiting	3 (25.0)	7 (21.9)
Eczema	0	6 (18.9)
Papular rash	3 (25.0)	0
Anaemia	3 (25.0)	0
Serious TEAEs, n (%)		
P1	0	Dasiglucagon+SOC (n=16): 2 (12.5)[b] SOC (n=16): 1 (6.3)[c]
P2	1 (8.3)[a]	2 (6.3)[d]
Discontinuation due to TEAEs, n (%)		
P1	0	0
P2	0	1 (3.1)[e]
NME, n (%)		
P1	0	0
P2	0	2 (6.3)

[a]Acute respiratory failure; [b]vascular device infection, localised infection; [c]hypoglycemia; [d]folliculitis, H1N1 influenza, hyperglycemia; [e]hyperglycemia

Conclusions: Dasiglucagon was well tolerated over 8 weeks, with a good and expected safety profile, confirming known class effects; no new safety concerns were identified. A trial investigating dasiglucagon's long-term safety profile is ongoing.

FC10.2

Immune profile response to rituximab in ROHHAD syndrome

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Background: Rapid-onset obesity with hypoventilation, hypothalamic dysfunction, autonomic dysregulation (ROHHAD) is a rare syndrome associated with high morbidity and mortality presenting with rapid onset of obesity in early childhood. An immune-inflammatory aetiology has been postulated; however, the immune profile is not well described.

Case Report: We report the case of a five-year-old female who presented in respiratory arrest after 6-months of rapid weight gain with central hypoventilation, central diabetes insipidus, growth hormone deficiency and hyperprolactinaemia fulfilling criteria for a diagnosis of ROHHAD. With no proven treatment for ROHHAD, two courses of the monoclonal antibody rituximab (750 g/m^2) were given four weeks apart to target any underlying immune dysregulation.

A cytokine profile was analysed before and after treatment including measuring tumour necrosis factor (TNF), interleukin-6 (IL-6), interleukin-1b (IL-1b) and interleukin-1 (IL-10) levels in response to stimulation by lipopolysaccharide (LPS) and anti-cluster of differentiation 3 (anti-CD3) with interleukin-2 (IL-2). Each of these pro-inflammatory molecules (TNF, IL-6 and IL-1b) have been heavily implicated in the development of obesity-related metabolic dysfunction, with IL-10 being metabolically protective.

Results: Our cytokine profile demonstrated a highly inflammatory state (table 1), with significantly raised TNF, IL-6 and IL-1b levels and low IL-10 levels in response to stimulation by both LPS and anti-CD3/IL-2. A repeat profile six months after rituximab therapy demonstrated a reduction in TNF of nearly a third, near halving of IL-6, two third's reduction in IL-1b and a threefold increase in IL-10 on LPS stimulation compared to pre-rituximab. On anti-CD3/IL-2 stimulation a small reduction in TNF, a reduction in IL-6 of a quarter and a greater than threefold increase in IL-10 was noted. Significant weight loss was observed (2.13 BMI-SDS reduction) in the 12 months following rituximab therapy.

Table 1. Cytokine profile pre- and post-treatment with rituximab (pg/ml)

	TNF		**IL-6**		**Il-1b**		**IL-10**	
Stimulus	Pre	Post	Pre	Post	Pre	Post	Pre	Post
LPS	2150.7	1491.6	17522.2	9723	5300.2	2000.8	586.9	1775.4
aCD3 + IL2	1269.6	1158.1	865.1	639.5	579.7	620.9	278.3	961.2

Discussion: We describe a highly inflammatory immune profile in this patient with ROHHAD with elevated TNF, IL-6 and IL-1b, and low IL-10, suggestive of both myeloid and T-cell lineage involvement. This suggests an immune-inflammatory pathology driving metabolic dysfunction and potentially other aspects of the condition. We demonstrate significant improvements in the inflammatory phenotype following rituximab therapy with potential clinical benefit. Further characterisation of the immune profile and response to immunomodulation in ROHHAD warrants exploration.

FC10.3

ROHHAD syndrome, thrombotic risk and endothelial damage: a single center experience

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Background: ROHHAD/ROHHADNET syndrome (rapid-onset obesity with hypothalamic dysfunction, central hypoventilation, autonomic dysregulation with or without neural tumor - NET) – has been reported in association with cerebral venous thrombosis events, as reported also in central hypoventilation syndrome. It is not clear whether thrombotic risk represents a cause or a consequence of hypoventilation and hypothalamic dysfunction. Aim of our study was to characterize thrombotic risk and endothelial damage in ROHHAD/ROHHADNET patients.

Patients and Methods: We analyzed clinical, biochemical and EndoPAT® data from 14 patients with ROHHAD syndrome (4M, 10F), followed at a single centre (Pediatric Endocrinology Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy). ROHHAD diagnosis was based on the presence of at least 3 of the following criteria: early, rapid-onset obesity, central hypoventilation, neural tumor, hypothalamic/pituitary disorders, and autonomic dysfunction, after excluding other forms of syndromic obesity. Biochemical data and thrombotic risk profile included levels of PT(%), PTT(sec), Fibrinogen(mg/100mL), Factor VIII(%), von Willebrand's factor(%), Antithrombin(%), Protein C(%), Protein S(%), D-Dimer(mg/L), Homocysteine(micromol/L). EndoPAT® was performed in order to obtain reactive hyperemia index (RHI, n.v. >1.67). Oxygen desaturation index (ODI) during sleep was detected by means of nocturnal transcutaneous saturimetry at the time of blood sampling.

Results: Among 14 ROHHAD patients, one presented cerebral venous thrombosis at 3 years of age. EndoPAT® study performed in 6 patients from the original cohort (2M, 4F) displayed a pathologic RHI level was in 4 of them (66.7%). No significant difference was found in thrombotic risk parameters between ROHHAD patients with or without GHD, central adrenal insufficiency, central hypothyroidism, neural tumor, water/electrolyte defects. A strong negative correlation was found between PT and RHI (r=-0.600) and between fibrinogen and RHI (-0,657). No correlation was found between coagulation parameters and blood sodium levels. A strong negative correlation was found between antithrombin levels and ODI (r=-0.721) while no correlation was found between ODI and the other biochemical parameters. A strong positive correlation was found between von Willebrand's factor and BMI SDS (r=0.709) and between protein C and BMI (r=0.828).

Conclusions: Our preliminary results indicate that endothelial damage (shown by lower RHI) might be related to altered coagulation profile in ROHHAD/ROHHADNET patients. Furthermore, BMI and sleep-related respiratory disorders are to be considered as risk factors for thrombotic disorders in these patients. We suggest that thrombotic risk and endothelial damage should undergo careful evaluation in this rare, life-threatening condition.

FC10.4

A Novel Mutation in RAI1 Gene in a Patient with Clinical Diagnosis of Rapid-Onset Obesity with Hypothalamic Dysregulation, Hypoventilation, and Autonomic Dysregulation (ROHHAD) Syndrome with Overlapping Symptoms of Smith Magenis Syndrome (SMS)

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Background: Pathologic mutations in RAI1 gene (typically microdeletions) cause SMS. Patients have characteristic physical appearance, developmental delay, sleep disturbances, and obesity; without hypothalamic dysfunction. Thaker et al published a case of a child with clinical diagnosis of ROHHAD with a mutation in the RAI1 gene (c.3265C>T: p.R1089X) found by whole exome sequencing. He had a physical appearance consistent with SMS and sleep cycle disturbances. 83% of ROHHAD patients require mechanical ventilation for hypoventilation within 5 years of rapid weight gain.

Case Description: We describe a 7 year old girl with accelerated weight gain since 4.5 months of age, hypotonia, motor and speech delays. Notable dysmorphic features of deep set eyes, midface hypoplasia, flattened nasal bridge, and brachycephaly, features seen in SMS. At age 6 she presented with hypernatremia (Na 206 mMol/L) and respiratory failure due to pneumonia. She was ultimately diagnosed with diabetes insipidus based on urine studies and supported by absent pituitary bright spot on MRI and was started on DDAvP. Sleep study showed severe mixed sleep apnea (OAHI 28/hr, CAI of 158/hr, no hypoventilation). She was started on BiPAP with increased needs. One year later returned with severe hyperglycemia (1135mg/dL), new onset of Diabetes Mellitus, HbA1c 9.6%, and Islet cell autoimmune antibodies negative. Other hormonal evaluation showed growth hormone deficiency with low IGF-1 [44ng/mL (55-238)] and IGFBP3 [1.66 mg/L (2.02-5.52)]. She was started on GH therapy. A clinical diagnosis of ROHHAD was made based on rapid weight trend, sleep apnea, and worsening hypothalamic dysfunction such as hypopituitarism.

Results: A genetic obesity panel resulted with a heterozygous variant of currently classified as of uncertain significance (VUS) in the RAI1 gene (c.604C>T,p.Pro202Ser).

Conclusions: This is the second reported case of a patient with a missense mutation in the RAI1 gene with clinical features of both ROHAHD syndrome and SMS. The two cases shared similar clinical course. Both developed obesity prior to age 2 and have a missense mutation rather than microdeletions. The hypoventilation has progressed slowly. The original patient underwent tracheostomy at age 10; our proband has yet not developed hypoventilation. The ability to accurately diagnose ROHHAD syndrome is crucial as it will lead to appropriate surveillance and management. As comprehensive genetic testing becomes more readily available, we will continue to establish a genetic basis for rare syndromes such as ROHHAD and SMS.

FC10.5

MCM4 deficiency causing Natural Killer and Glucocorticoid Deficiency with DNA repair defect (AR-NKGCD) - a large cases series from the Irish Traveller population

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A new condition, unique to Irish Travellers, was first described clinically as autosomal recessive natural killer and glucocorticoid deficiency (AR-NKGCD) ORPHA:75391 in 2008 and was attributed to recessive founder variant in MCM4/PRKDC gene in 2012. Irish Travellers are an indigenous endogamous population numbering ~40,000 in the Republic of Ireland.

AR-NKGCD is characterised by short stature, glucocorticoid and natural killer cell deficiency and is a disorder of DNA repair. Since first described, through monitoring cases our knowledge and experience of the condition has grown as more cases have been confirmed.

Objectives: To review the clinical presentation, diagnostic workup, and outcomes of known patients with AR-NKGCD attending our centre over the past 10 years. We compiled data from available medical, laboratory, genetic and radiology records on patients attending paediatric endocrinology and immunology services.

Results: Sequencing analysis of intron 1 of the MCM4/PRKDC gene in all patients (n=15) revealed the known homozygous variant c71-2A>G p.(Phe24Argfs). Those children for whom data was available (n=7), were all small for gestational age, birth weight between 0.4th-2nd centiles. Further endocrine data are outlined in Table 1.

Most children (n=14) had mild dysmorphic features. Feeding difficulties, failure to thrive (n=14) and recurrent infections such as respiratory tract (n=8) and herpes simplex labialis (n=6), were observed in infancy and young childhood. Tiredness (n=5), hyperpigmentation (n=8) and mild development delay (n=4) were also observed.

All 15 had severe NK cell deficiency (NK cells represented just 0.1-4% of the peripheral blood lymphocytes). Nine patients (60%) required corticosteroid replacement (hydrocortisone doses range 9-15mg/m2), in others only emergency treatment was recommended. Mineralocorticoid secretion was not impaired. A serious adrenal crisis following infection occurred in two patients. Two patients developed haemophagocytic lymphohistiocytosis (HLH), one of which died.

Conclusions: AR-NKGCD is a rare disorder affecting children from the Irish Traveller population with a variable phenotype. They have an increased risk of primary adrenal insufficiency, adrenal crisis, infection, malignancies and premature death. Input from endocrinology and immunology specialists is required.

Clinical characteristic	*n= (%)	Description
Short stature	14 (93%)	93% < 9th centile 60% < 2nd centile
Low weight	12 (80%)	80% < 9th centile 60% < 2nd centile
Bone age delay	7 (100%)	median delay 2 years
Low morning cortisol (< 100nmol/L)	7 (50%)	at diagnosis
Raised adrenocorticotropic hormone (ACTH)	10 (83%)	at diagnosis

*n= number of patients where data on that variable was available

FC10.6

Placental mest gene expression is associated with postnatal growth and obesity

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Introduction and Aims: *MEST* (Mesoderm-specific transcript), a candidate gene for Silver-Russell syndrome, is a paternally expressed imprinted gene that positively regulates foetal growth. *MEST* has also been shown to promote adipose tissue expansion in conditions of positive energy balance.

In this context, our objective was to study the possible relationship between placental *MEST* gene expression and postnatal growth and obesity parameters in otherwise healthy newborns.

Subjects and Methods: The study population consisted of 109 pregnant women and their newborns who were followed from birth until six years of age. All mothers and newborns were healthy, all with term pregnancies and infants' weights appropriate for gestational age. The study population was divided into two groups according to birth weight of the offspring [newborns with higher birth weight (N=58) and newborns with lower birth weight (N=51), according to the 50th percentile of the studied population]. *MEST* gene expression was assessed by RT-PCR in placenta samples. Associations of placental *MEST* expression and various growth and obesity parameters in the offspring during the first year of life and at six years of age [weight, height, body mass index (BMI), fat and lean mass, among others] were assessed.

Results: Placental *MEST* expression did not show significant associations with the examined parameters in the offspring when the subjects were studied together as a whole. Nevertheless, associations were elicited when analysing separately the two groups of newborns with either higher or lower birth weight.

In the group of higher birth weight (>50th percentile), *MEST* expression in the placenta was positively associated with weight-SDS, BMI-SDS and fat mass at six years of age (all $\beta \geq 0.42$, $p \leq 0.006$), while in the group with lower birth weight (<50th percentile), *MEST* expression was negatively associated with weight-SDS at 12 months of age, and with weight-SDS, height-SDS, fat mass and lean mass at 6 years of age (all $\beta \leq -0.31$, $p<0.05$ to $p<0.001$). All these independent associations were derived from linear regression models adjusting for possible confounding variables (maternal smoking, maternal pre-gestational BMI, age and sex of the offspring).

Conclusion: *MEST* expression in the placenta associates with various parameters of growth and obesity in newborns followed from birth until 6 years of age. Our results suggest that *MEST* expression may have a prevalent role in postnatal growth and adiposity that is dependent on the previous growth of the infant, likely reflecting a condition of either positive or negative energy balance.

GH and IGFs

FC11.1

GH replacement therapy with once-weekly somapacitan in children with GH deficiency is effective and well-tolerated: 2-year results from REAL4

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Daily subcutaneous (s.c.) injections of growth hormone (GH) to treat GH deficiency (GHD) in children is burdensome for both patients and caregivers. Somapacitan (Novo Nordisk) is a long-acting reversible albumin-binding human GH derivative in development for once-weekly s.c. administration in children with GHD, and aims to overcome the treatment burden of daily injections.

REAL4 is a multi-national, randomised, open labelled phase 3 trial with a 52-week main phase followed by a single-group three-year extension (NCT03811535). During the main phase, 132 patients received once-weekly 0.16 mg/kg/week somapacitan with another 68 receiving daily GH (0.034 mg/kg/day Norditropin®, Novo Nordisk). Following 52-weeks, patients receiving somapacitan continued treatment (soma/soma group) and patients receiving daily GH were switched to somapacitan (switch group). In year two, 194 patients (127 and 67 for soma/soma and switch groups, respectively) completed 104-weeks of treatment, with results presented here.

Height velocity (HV) was similar between groups during the 2-year period with HV at week 104 being 8.7 vs. 8.4 cm/year for the switch and soma/soma groups, respectively. Other height-related assessments supported these findings. For example, a continuous increase in HSDS was observed with measurements for the switch and soma/soma groups being -3.47 and -2.99 at week 0, -2.09 and -1.78 at week 52, and -1.47 and -1.23 at week 104, respectively. IGF-I SDS increased in both groups (observed mean IGF-I SDS at week 104 was -0.25 and -0.27 for the switch and soma/soma groups, respectively) with mean IGF-I SDS within normal range (-2 to +2) during the study. PK/PD modelling suggests similar mean average IGF-I levels over the weekly dosing interval for both groups in year 2.

Somapacitan was well tolerated, with no safety or local tolerability issues identified. A low number of patients reported injection-site reactions in the second year, with no injection-site pain reported.

Patient preference questionnaires were responded to by 50 caregivers of patients in the switch group. Almost all (90%) preferred somapacitan with none preferring daily GH. The top reason given for this preference was the frequency of injections. Of the 45 caregivers who preferred somapacitan, 35 (77.8%) believed they would be more adherent to treatment with somapacitan rather than daily GH.

In conclusion, once-weekly somapacitan, for 2 years, or for 1 year after switching from daily GH, was efficacious and well-tolerated. A preference for somapacitan was reported in those who switched from daily GH.

FC11.2

Clinical characteristics of heterozygous *ACAN* gene variants and longer-term response to growth hormone treatment: real-world data

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Background: Heterozygous pathogenic variants in the *ACAN* gene underlie disproportionate short stature with characteristically accelerated bone age (BA) maturation and/or osteochondritis dissecans (OD)/early-onset osteoarthritis (OA).

Objective: To describe the phenotypic spectrum and assess the response and safety of growth hormone (GH) treatment in children with a heterozygous pathogenic *ACAN* variant.

Patients: Thirty-six (23 boys, 13 girls) short statured children with pathogenic *ACAN* variants and treated for ≥1 year with GH (1.4 mg/m2/day) were identified in the Dutch National Registry of GH treatment in children.

Results: We identified 25 different pathogenic *ACAN* variants located throughout the gene in 36 children and adolescents. Twenty-two subjects were prepubertal, 14 subjects were pubertal. Median (IQR) height SDS at start of GH treatment was -2.6 SDS (-3.2 to -2.2). Characteristic features such as disproportion, advanced BA, OD/early-onset OA and dysmorphic features like midface hypoplasia and brachydactyly were present, but in ~20% of children no specific clinical or dysmorphic features were reported. After 3 years of GH treatment, height gain SDS in prepubertal children was 1.0 SDS (0.9 to 1.4, P <0.01). In pubertal children height SDS remained stable, which is in contrast to the significant loss in height SDS that is typically observed in untreated, pubertal *ACAN* patients. Ten children reached adult height: 4 subjects reached an adult height ≥-2 SDS and in 5 subjects adult height SDS had improved in comparison to the affected parent. GH treatment was well tolerated without the report of severe adverse events or *ACAN*-related side effects

Conclusion: The phenotype of patients with a heterozygous pathogenic *ACAN* variant is highly variable. Genetic testing for *ACAN* deficiency should be considered in any child with disproportionate short stature, also in the absence of specific dysmorphic features or bone-age advancement. We furthermore show that most *ACAN* patients have a significant response to GH, which is sustained after 3 years of treatment and most likely results in an increased adult height.

FC11.3

Analysis of a large panel of genes in a cohort of patients with severe short stature: detection rate and genotype-phenotype correlations

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Short stature is a frequent reason for referral to pediatric endocrinologists and this phenotype has been associated with a large number of gene variations during the last decades, highlighting its complex and heterogeneous etiology.

We evaluated the detection rate of the analysis of a selected gene panel in a cohort of patients with short stature defined as height below -2 standard deviations (SD).

Overall, 134 patients were included in the study: 73 with GH deficiency (GHD), isolated or associated with other pituitary hormone deficiencies (CPHD), and 61 without GH deficiency (NGHD). A pathological brain MRI was found in 78.9% of patients with CPHD compared to those with isolated GHD (22.9%) ($p<0.0001$). Most patients with GHD had a severe GH deficiency (peak after stimulation < 5 ng/ml). In 14 NGHD patients, *SHOX* deletions or duplications were identified by MLPA analysis. A multigene panel including 77 genes known to be associated with short stature were analysed by Next Generation Sequencing (NGS) in *SHOX*-negative NGHD patients and in all GHD patients. Variants identified in probands were searched in their parents for a better interpretation. Results were statistically evaluated using the Mann-Whitney test or Kruskal Wallis one-way ANOVA test (continuous variables) and the chi-square test or Fisher's exact test (categorical variables); p-values <0.05 were considered statistically significant.

Overall, one or more potentially relevant variants (positive test) were detected in 65.8% of patients studied by NGS. Among GHD patients, 48 (65.8%) tested positive, including 20 cases carrying variants classified as pathogenic (P) or likely pathogenic (LP) according to the American College of Medical Genetics criteria. The detection rate was higher in patients with isolated GHD (73.6%) than those with CPHD (45%) ($p=0.02$) confirming the frequent multifactorial origin of CPHD. Among *SHOX*-negative NGHD patients, 31 (66%) tested positive at the NGS analysis, including 9 cases carrying P/LP variants. Pathogenic variants were inherited from a parent with a similar phenotype in 66.7% of cases ($p=0.001$), revealing the genetic etiology of the familiar short stature.

Our data showed a good detection rate of a custom multi-gene panel sequencing test in a cohort of patients with short stature who underwent deep auxological phenotyping. A genetic cause of the short stature was identified in approximately 27% of our GHD patients and 19% of *SHOX*-negative NGHD patients.

FC11.4

Long-term GH-treatment of children born small for gestational age (SGA) does not result in cerebrovascular abnormalities in adulthood compared to untreated controls

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Background: Increased cerebrovascular morbidity and mortality was reported in adults who were treated with growth hormone (GH) during childhood, including those born SGA, compared to the general population. However, previous studies did not have an appropriate control group of untreated SGA adults which was a major limitation.

Objective: To assess cerebrovascular abnormalities (aneurysms, previous intracerebral hemorrhages and microbleeds) using brain MRI in adults born SGA at 12 years after cessation of childhood GH-treatment (SGA-GH) compared to age-matched untreated control groups.

Methods: We prospectively compared the prevalence of cerebral vascular abnormalities in adults born SGA who were treated with GH during childhood (SGA-GH) and 3 untreated age-matched control groups around age 30 years: born SGA with persistent short stature (SGA-S), born SGA with spontaneous catch-up growth to a normal height (SGA-CU) and born appropriate for gestational age with a normal height (AGA). All brain MRIs were performed between May 2016 – December 2020 on the same 3T MRI system. MRI images were scored by two neuroradiologists who were blinded to patient groupings.

Results: 301 adults were investigated (94 SGA-GH, 42 SGA-S, 69 SGA-CU and 96 AGA adults). Aneurysms were found in 6 adults: 3 (3.6%) SGA-GH, 1 (2.9%) SGA-S and 2 (2.2%) AGA adults, without differences between SGA-GH adults and the 3 control groups. Previous intracerebral hemorrhages were found in 2 SGA-S adults (4.8%). Microbleeds were found in 17 adults: 4 (4.3%) SGA-GH, 4 (9.5%) SGA-S, 3 (4.3%) SGA-CU and 6 (6.3%) AGA adults, also without differences between SGA-GH adults and the 3 untreated control groups.

Conclusion: Long-term GH-treatment during childhood does not increase cerebrovascular abnormalities in SGA-GH adults compared to SGA-S, SGA-CU and AGA adults.

FC11.5

Effective GH Replacement with Once-weekly Somapacitan in Japanese Children with GH Deficiency: 2-year Results from REAL4

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Growth hormone deficiency (GHD) in children results in reduced adult height. Children with GHD typically require daily subcutaneous (s.c.) injections of growth hormone (GH). Daily injections are burdensome for both patients and their caregivers and reduced adherence negatively impacts clinical outcomes. Somapacitan (Novo Nordisk) is a long-acting reversible albumin-binding human GH derivative in development for once-weekly s.c. administration in children with GHD, aiming to overcome the treatment burden of daily injections.

REAL4 is a multi-national, randomized, open labelled phase 3 trial consisting of a 52-week main-phase followed by a single-group three-year extension (NCT03811535). Here we present a sub-analysis of Japanese GHD patients. Thirty patients from Japan were recruited into the study. During the main-phase, 11 received daily GH (0.034 mg/kg/day Norditropin®) and 19 patients received 0.16 mg/kg/week somapacitan. After 52-weeks of treatment, patients in the daily GH group switched to somapacitan (switch group) while patients receiving somapacitan continued treatment (soma/soma group). All patients participated for 104-weeks.

Similar mean annualised height velocity (HV) was observed at week 52 between treatments (9.8 vs. 10.3 cm/year for daily GH and somapacitan, respectively). Similar values for the groups were also observed at week 104 (annualised HV of 7.9 vs. 7.4 cm/year for switch and soma/soma, respectively). Other height-related parameters supported sustained growth, including similar increased Height SDS change from baseline to week 104 (1.54 and 1.39 for switch and soma/soma, respectively). IGF-I SDS increased in both groups (observed mean IGF-I SDS at week 104 was 0.14 and -0.06 for switch and soma/soma groups, respectively) with mean IGF-I SDS being within -2 and +2 during the study.

Somapacitan was well tolerated, with no safety or local tolerability issues identified. No neutralizing anti-somapacitan antibodies were detected. One mild injection site reaction was reported, with no reports of injection site pain.

Patient preference questionnaires were responded to, in week 56, by all caregivers of patients in the switch group. Almost all (91%) preferred somapacitan, to some degree, with none preferring daily GH. The top reason given for this preference was the number of times needing to do injections. Of the 10 caregivers who preferred somapacitan, 6 believed they would be more adherent to somapactian over daily GH.

In conclusion, once-weekly somapacitan showed sustained efficacy and was well-tolerated for 2 years in Japanese patients and a preference for somapacitan was reported in those who switched from daily GH.

FC11.6

Longitudinal analysis of the risk of brain tumour recurrence or progression in relation to the timing of commencement of growth hormone replacement therapy

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Introduction: Growth hormone deficiency (GHD) is the most frequent endocrine deficit in childhood survivors of brain tumours. However, there is insufficient evidence to guide the timing of growth hormone replacement (GHR). At Great Ormond Street Hospital timing is based on clinical need rather than in relation to oncological treatment. Therefore, sufficient variability in GHR timing is available to analyze its effect on tumour progression and recurrence.

Aim: To examine the association between tumour progression or recurrence and time of GHR initiation.

Methods: Retrospective analysis of children with brain tumours on GH replacement from 2000-2023. GHR timing was defined as time from the end of oncological treatment for primary disease or previous progression/recurrence until GH initiation. Adjusted Hazard Ratios (HR) for first and further recurrence/progression were estimated through Cox Regression.

Results: Data from 75 survivors of brain tumours have been analyzed so far. Gliomas (38.7%), embryonal tumours (25.3%), and craniopharyngiomas (24%) were the most frequent diagnosis. Mean follow-up time was 8.96±3.35 years. GHD was diagnosed by glucagon test, GHR was started at a median of 1.3 years (IQR 0.5-2.2) after the end of oncological treatment. During follow-up, 44% of patients presented relapse/progression: 26.7% during GHR (20% with history of recurrence/progression before GHR, 6.7% with first event after GHR); 17.3% had relapses/progressions before GHR only. Initial analysis showed that starting GHR later post-end of treatment was borderline associated with better 5-year progression-free survival (p 0.05; HR 0.671; 95% CI 0.451-0.999). However, multivariate COX-regression analysis showed no significant decrease in the HR (p 0.431; HR 0.865; CI 0.604-1.240) after adjusting for tumour status, previously progressive disease (≥ 1 previous progression/recurrence), and cranial radiotherapy (CR). Residual disease (p 0.046; HR 5.178; CI 1.032-25.981) and history of previous relapses (p 0.043; HR 3.094, CI 1.038-9.221) were associated with an increase in the adjusted HR for further recurrence/progression, and CR with decreased HR (p 0.016; HR 0.325; CI 0.129-0.814). Analysis of patients without relapse/progression pre-GHR showed no significant increase in progression or recurrence-free survival in relation to GHR timing (p 0.349; HR 0.681, CI 0.305-1.522).

Conclusions: No independent association was found between tumour progression/ relapse-free survival and GHR timing when the pre-existing increased risk for tumour progression in patients with residual or previously progressive disease was accounted for. Analysis of the complete cohort of patients is needed to increase the power of the study and drive definitive conclusions.

Thyroid

FC12.1

Graves' disease – are we just delaying the inevitable?

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Background: The incidence of Graves' disease in patients aged <15 years is estimated at 0.9 per 100,000.

Parental anxiety around definitive treatment, timing of this around schooling and clinician confidence in long-term medical treatment often results in prolonged medical management. This audit aimed to assess the rates of remission, timing of definitive treatment and long-term medical management in children managed for Graves' at a UK tertiary centre.

Methods: The electronic medical records at Great Ormond Street Hospital were searched for patients reviewed with a diagnosis of Graves' disease between 2018 and 2022.

Results: 51 patients were identified in this time window (median age at diagnosis: 9.71 [1.95-16.85] years). Nine patients were treated by block and replace (BR) and 42 with dose titration (DT)(5 switched to BR). Two patients required treatment with propylthiouracil (liver toxicity and severe neutropenia on carbimazole respectively); the remainder received carbimazole. 1/18 children remitted after a first trial off therapy (mean treatment duration: 2.75 [1.17-4.75] years). 2/6 remitted after a second trial off (mean treatment duration: 4.42 [3-7] years). 20 children had definitive treatment (18 thyroidectomies, 2 radioactive iodine treatment (RAI) with a further 5 referred for definitive treatment (mean treatment duration: 3.25 [0.33-10] years). 27 patients remain on medical therapy (median treatment duration: 4.25 [0.3-14.4] years). 37 patients received medical treatment exceeding three years. 7 were diagnosed at <5 years (mean treatment duration: 6.7 [3.16-10] years), 3 received definitive treatment and 4 long term medical therapy. 12 were diagnosed at 6-10 years (mean treatment duration: 6.6 [3.46-14.24] years), with 3/12 undergoing definitive management and 1/12 remitting. 8 were diagnosed at 10-15 years (mean treatment duration: 5 [3.25-8.25] years), all remaining on long-term therapy.

Conclusions: The remission rate in paediatric Graves' is estimated to be 20-30% after 3 years. The remission rate is much lower in our group, with the majority of patients remaining on long-term therapy. The practicalities of thyroidectomy and RAI become simpler with age but teenagers may choose to defer this decision during critical school exam years and further prolong medical management. The variable and short-lived nature of remission in this group, alongside evidence suggesting that paediatric thyroidectomy does not negatively impact quality of life, may support earlier definitive treatment, rather than delaying the inevitable. Additionally, thyroxine replacement is safer and requires less monitoring. Further understanding of the young person's wellbeing and quality of life throughout Graves treatment would be valuable.

FC12.2

Thyroid function analysis in 48 patients affected by severe combined immunodeficiency caused by adenosine deaminase deficiency

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Background: Adenosine deaminase (ADA) deficiency is a systemic metabolic disease that primarily affects the immune system and lymphocyte development, causing a severe combined immunodeficiency (ADA-SCID). However, the accumulation of toxic metabolites occurs in other organs and systems. Since most ADA-SCID patients undergo definitive treatment with Gene Therapy (GT) or allogeneic haematopoietic stem cell transplantation (HSCT), preceded by conditioning (either myeloablative or not), endocrinological evaluation becomes fundamental. Currently, no studies in the literature have evaluated thyroid function before and after definitive treatment in ADA-SCID patients. Therefore, our study aims at describing these characteristics in our cohort of patients.

Materials and Methods: We retrospectively analysed data of 48 patients who underwent GT (n=43) or HSCT (n=5) and performed follow-up from 1993 to 2022 in Our Centre; we considered TSH, fT4, fT3, and thyroid autoantibodies (anti-thyroglobulin, anti-thyroperoxidase and anti-TSH receptor). When performed, we also evaluated thyroid ultrasound and brain MRI.

Results: 24/48 patients had normal thyroid function, while 24/48 presented thyroid function tests' alterations. We detected three main categories: subclinical hypothyroidism (5 patients, of whom 1 started treatment with levothyroxine - L-T4), autoimmune hypothyroidism (7 patients, of whom 5 requiring L-T4), and reduced fT4 levels with inappropriately normal TSH values (12 patients, of whom 5 required treatment). In the last group, 3 patients had a small pituitary gland at brain MRI, 1 had both small pituitary gland and thyroid gland at ultrasound and 1 was taking antitubercular medications.

The alterations in thyroid function occurred before definitive treatment in 9 patients (in 4 of them they resolved after definitive treatment, in 4 patients they were persisting after treatment and in 1 patient they were not assessed), while in 15 patients they occurred after treatment, and 4 were autoimmune thyroiditis.

Conclusions: We detected thyroid function alterations in 50% of our patients, 46% of whom required substitutive treatment with L-thyroxine. This underlines the importance of screening thyroid function (TSH and free hormones), autoantibodies, and ultrasound in ADA-SCID patients at diagnosis and of monitoring it during follow-up. This is even more important considering that ADA-SCID is usually diagnosed in the first months of life, when adequate thyroid function is necessary for proper neurological development. Finally, we suggest periodically reassessing thyroid function, especially in patients who started L-thyroxine: it would be helpful, as soon as complete immune reconstitution after GT or HSCT has occurred, to try to stop L-T4 in order to document whether thyroid function has restored.

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FC12.3

Hypothyroidism due to IYD bi-allelic pathogenic variants: clinical description of eight patients

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Introduction: The iodotyrosine deiodinase (IYD) enzyme recycles iodine by deiodinating mono- and di-iodotyrosines. This is crucial for efficient thyroid hormone synthesis. Bi-allelic loss-of-function variants in the *IYD* gene cause hypothyroidism resulting from iodine wasting. It is reported that these patients can be efficiently treated with iodine supplementation rather than with L-thyroxine.

Aim: To describe the phenotypes of patients harboring bi-allelic pathogenic variants in *IYD* gene followed in our Paediatric Endocrinology Clinic.

Results: Eight patients (from 4 consanguineous families of Moroccan origin) were homozygous carriers for a pathogenic variant in *IYD* gene. Their clinical presentation is described in table. All patients presented with a large goiter and severe hypothyroidism with very high thyroglobulin (Tg) plasma level. The goiter subsided with L-thyroxine therapy and iodine supplements. Treatment could be interrupted in 5 patients, while for the 3 others, goiter and hypothyroidism reappeared so that treatment was resumed. Affected individuals in families 2, 3, 4 harbor the same known pathogenic variant (c.658G>A, p.(Ala220Thr) NM_001164694.1) while 3 affected individuals from family 1 harbor a novel missense mutation (c.791C>T, p.(Pro264Leu) NM_203395) considered likely pathogenic based on segregation, correlation with phenotype, and high pathogenicity scores (no genetic analysis for patient 1d). No heterozygous carrier had a thyroid disease history.

Conclusion: Hypothyroidism due to bi-allelic pathogenic variants in IYD gene is characterized by a large goiter, very high thyroglobulin levels and fluctuating thyroid function. No patient was diagnosed in the neonatal period and a majority of patients could be weaned from L-thyroxine after an episode of profound goitrous hypothyroidism. We didn't observed any phenotype–genotype correlation with a wide phenotypic variability within families. We report a novel IYD variant in a consanguineous family with 4 affected individuals.

Table. Clinical description of affected family members

	At diagnosis					L-thyroxine treatment duration (years)	Iodine supplement	Treatment interruption
Family/ patient	**Age (years)**	**TSH (mU/L)**	**Free T4 (pmol/L)**	**Tg (ng/mL)**	**Thyroid volume(ml)**			
1/a	14.2	201	1.29	5524	21.2	7	no	no
1/b	12.5	16	4	232	27	4	no	yes
1/c*	9			-		31	no	yes
1/d$	25	429	<1.3	1396	50	2	no	yes
2	5.7	435	<1.3	2799	21	5	no	no
3	6	464	3.2	3897	46.6	0.1	yes	yes
4/a	13. 2	533	0.6	4514	44.5	6	yes	no
4/b	16.2	362	<1.3	-	131	1.3	yes	yes

* mother of 1a and 1b, having a goiter during childhood, $ brother of 1c

FC12.4

Thyroid hormone resistance due to THRB gene mutations: neonatal manifestations in two cases

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Introduction: Thyroid hormone resistance (THR) is a rare disease (≈ 1/50000) mainly due to thyroid hormone receptor beta gene (*THRB*) mutations, generally identified in late childhood and adulthood. We report 2 atypical cases of neonatal diagnosis of THR.

Case 1: The newborn presented with neonatal respiratory distress due to a voluminous compressive goiter, requiring invasive ventilation. Thyroid function tests (TFT) showed very high TSH and free THs levels (see table). He also presented supra-ventricular tachycardia, managed by adenosine, β-blockers and digoxin. Tiratricol, a T3-analog, reduced TSH levels and decreased goiter size allowing spontaneous ventilation at day 17. Clinical and biological evolution remains satisfactory at the age of 18 months.

Case 2: The patient was referred after positive neonatal screening for congenital hypothyroidism. TFT revealed elevated levels of TSH and THs, and clinical symptoms are detailed in table. Tachycardia was treated with β-blocker and then with α-blocker. High doses of T3 given every other day decreased TSH values with a slight reduction of the goiter, although goiter size increased again upon follow-up.

Genetic Results: Both patients had a de novo heterozygous mutations in the exon 10 of *THRB*, classified as pathogenic according to ACMG criteria, but not previously reported. Given the unusual neonatal presentation, we further evaluated genes involved in thyroid development and function through whole exome sequencing or targeted NGS. In case 1, we found an heterozygous missense mutation in the *TSHR* gene c.1703T>A, p.I568N, inherited from the father. Functional tests confirmed the constitutional activation of the mutated receptor. In case 2, no other pathogenic or likely pathogenic variant was detected.

Conclusion: Neonatal manifestations of THR are very rare and are likely due to genetic or epigenetic events occurring in addition to *THRB* mutations. We have identified a likely such event in the form of an activating *TSHR* mutation. Therapeutic management is challenging.

	Case 1	Case 2
Family history	None	None
Diagnosis circumstances	Neonatal respiratory distress	CH screening result
TFT		
TSH (mUI/L)	73.8	>75
fT4 (pmol/l)	77.1	>77.3
Thyroid size (N<1.53ml)	9.7ml (compressive)	5.1ml
Clinical symptoms	Supra-ventricular tachycardia Premature dental eruption Insufficient weight gain	Tachycardia Brain Ventriculomegaly Hearing loss Insufficient weight gain
***THRB* mutation**	c.1352_1353delinsAA p.F451Stop	c.1301_1301delG p.C434Sfs*9
Second genetic event	*TSHR* c.1703T>A	None identified
Treatment	Tiratricol	T3 every other day
Evolution	Marked reduction in goiter size	Increased goiter size

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FC12.5

Teprotumumab in an adolescent with severe corticosteroid-resistant Graves ophthalmopathy: success but unexpected neurological manifestations

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Moderate to severe Graves ophthalmopathy (GO) is rare in children and most patients have mild GO. This complex inflammatory autoimmune disorder affecting the orbital fat and muscles is linked to circulating TSH receptor antibodies and involves the insulin-like growth factor-I receptor (IGF-IR) on orbital fibroblasts. Severe GO features include proptosis, diplopia and vision loss. Intravenous glucocorticoid pulse therapy is the first line medical treatment for moderate to severe GO but about 30% of patients are corticosteroid resistant. Other medical treatments such as rituximab or tocilizumab have been proposed with limited efficacy. More recently, teprotumumab (TEP), a human IGF-IR inhibitory monoclonal antibody has demonstrated significant efficacy in adult patients with severe GO and is approved in several countries since 2020. Mild to moderate side effects have been described and safety reports are still under investigation.

We described the first pediatric patient with active corticosteroid-resistant GO treated with TEP. Graves' disease occurred at the age of 13 yr. with initially mild GO. After 16 months of treatment with carbimazole, GO became active with conjunctival redness, increased proptosis and diplopia. Intravenous glucocorticoid pulse therapy during 7 weeks (cumulative dose = 6 g) was used and active signs of GO decreased. Six months later, GO became active again and resistant to corticosteroids. He received 5 infusions of TEP (10 then 20mg/kg, 3 weeks apart). TRAb were negative before start of TEP. Redness disappeared after the first infusion, with clinical activity score (CAS) decreasing from 5 to 1 and proptosis significantly decreasing by 5 mm changing GO grade from 3 to 1 (MRI data).

A sudden coma occurred after the 5th infusion and the patient received 3 days of noninvasive artificial ventilation. All investigations were normal and ruled out other causes of impaired consciousness, in particular toxic, infectious or autoimmune. No haplotype of susceptibility to Graves' disease, autoimmune encephalitis or TED was found (HLA). The patient remained with lethargic state associated with dysgeusia and sensory hallucinations for several weeks. After a few months, a spontaneous clinical improvement occurred but concentration issues are still present. TEP was stopped after the occurrence of neurological manifestations and GO has remained stable with a 14 month follow-up.

In conclusion TEP was efficient in an adolescent with severe corticosteroid resistant GO. The role of TEP in the severe neurological manifestations observed cannot be ruled out given the chronology and the safety profile of TEP in adult patients.

FC12.6

TSH screening in premature newborns: a critical appraisal of the value of a second sample

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Introduction: Consensus guidelines (2021) state that a second dry blood spot (DBS) should be considered for newborn screening (NBS) in preterms (delayed TSH rise).

Objective: To evaluate the diagnostic yield of an NBS strategy including a second DBS at 14 days in preterms.

Material and Methods: Retrospective study of 2 cohorts. Cohort 1: live births <37 weeks of gestational age (GA), screened by the ULB NBS Center between January 2019 and December 2022 (digital database available since January 2019); cohort 2: permanent CH born between 1981 and 2019, followed at our Hospital.

Results: See table. Cohort 1: among 6,391 preterms with a median GA of 35.3 (23-36) weeks, six have been diagnosed with CH, all transient. Two out of 6 had a delayed TSH rise. A serum TSH of 33.7 mU/L on day 14 was noted in the twin brother (patient 7) of patient 6.

Cohort 2: among 193 patients with permanent CH, we identified 7 preterms diagnosed between day 4 to 7 of life.

Conclusion: Transient CH was observed in six out of 6,391 preterms and was not detected on the first NBS in two. Permanent CH in preterms occurred in seven out of 193 patients (fewer than expected given that births <37 weeks in Belgium occur in 8% of newborns) and was readily detected on the first NBS sample. More studies are necessary to justify a second DBS at 14 days of life in all preterm newborns.

Table. Characteristics of PRETERM newborns with CH

					1st DBS		2nd DBS	
Patient	**Sex**	**GA (wks)**	**Birth weight (g)**	**Diagnosis**	**Age (days)**	**TSH (mU/L)**	**Age (days)**	**TSH (mU/L)**
Cohort 1:								
1	F	27	500	Transient	3	4.1	31	50.9
2	F	34	2360	Transient	2	3.2	14	37.4
3	M	31	2280	Unknown (neonatal death)	5	459	-	-
4	M	36	3350	Transient*	3	16.5	-	-
5	F	36	2500	Transient*	2	59.7	-	-
6	M	36	2315	Transient	4	16.7	12	15.7
7	M	36	2175	Transient	4	11.2	-	-
Cohort 2:								
8	M	28	700	Orthotopic	4	127	-	-
9	F	35	2700	Lingual	7	55	-	-
10	F	35	2510	Lingual	4	251	-	-
11	F	35	2500	Lingual	4	99.7	-	-
12	F	34	1990	Unknown	5	132	-	-
13	M	34	1910	Lingual	6	247	-	-
14	M	36	3380	Lingual	4	251	-	-

*Iodine overload

Pituitary, neuroendocrinology and puberty 2

FC13.1

Genetic evaluation in children with self-limited pubertal delay discloses new candidate genes

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Introduction: Age at pubertal onset is a markedly inherited trait. The most common cause of pubertal delay, self-limited pubertal delay, is defined by the absence of secondary sexual characteristics after 13 years in girls and 14 years in boys, with progression before age 18. This study aimed to detect novel candidate genes for self-limited pubertal delay.

Methods: Eighty-one patients with confirmed self-limited delayed puberty after retrospective appraisal were evaluated by whole exome sequencing. We prioritized variants with MAF<0.001, classified as loss-of-function (LoF) or missense predicted to be deleterious on *in silico* analysis. Variants of interest were classified by the ACMG/AMP criteria. Genes previously associated with pubertal delay and/or short stature were assessed first. Candidate genes were chosen according to gene function, protein expression, associated phenotypes, GWAS analysis, constraint scores, and clinical plausibility.

Results: Patients had a mean height-SDS at the onset of puberty of -3.0±0.5 (95% had short stature). They reached an adult height-SDS of -1.4±0.8, below their mid-parental target height (-0.8±0.7 SDS, p<0.001) and 40% remained short in adult life. The frequency of a positive family history of pubertal delay was 61%, and 30% of parents had height SDS<-2. We found 28 variants of interest in 23 patients, of which 18 were LoF (stopgain=8, frameshift=5, splicing=5) and 10 were missense. We categorized the genes with variants into three groups. The first one was constituted of genes associated with pubertal delay (*MC3R, LGR4, CCDC141, GHSR*), and all variants were of uncertain significance. The second group comprised genes related to phenotypes that explained short stature but not delayed puberty (*GDF5, ANKRD11, TYMP, KMT2C, NPR2, SHOX, BRAF*). The third group consisted of candidate genes (*INHBB, CDK13, CDK16, STXBP5L, OLIG3, TAOK3, TLN1, MYO18A, TMEM108, TRERF1, MAP3K4, BAG6, DROSHA*), which harbored LoF variants despite a high constraint score (pLI=0.83-1 from gnomAD). Within the third group, *INHBB* was the major candidate because it encodes the beta B subunit of activin and inhibin and was previously linked to late voice-breaking in males in GWAS. In further analysis, we found 5 female carriers of LoF *INHBB* variants in the UKBiobank and a nominal association with later age at menarche (p=0.01).

Conclusions: The high frequency of LoF variants in constrained genes drew attention because it is unusual compared to previously published cohorts. We hypothesize that carriers of deleterious variants in such genes have their reproductive capacity limited from the perspective of evolutionary genetics.

FC13.2

Targeted gene panel screening in 144 congenital hypopituitarism patients, incorporating 135 known and novel genes implicated in hypopituitarism and/or hypothalamo-pituitary development

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Congenital hypopituitarism (CH) is a highly variable disorder affecting 1:3000 - 1:4000 live births, and is characterized by deficiencies in one or more of the 7 pituitary hormones, with growth hormone (GH) being the most frequently-occurring deficiency. It may be associated with a range of syndromic features including visual impairment, midline brain abnormalities and facial clefting. The development of the pituitary gland is closely associated with that of the forebrain and hypothalamus, and involves a cascade of transcription factors and signalling molecules, intrinsic and extrinsic to the developing anterior pituitary, essential for correct hypothalamo-pituitary (HP) development.

We have collected DNA from a cohort of patients with CH and related disorders, followed up at Great Ormond Street Hospital (GOSH) and other national/international centres (n=>1900). Our previous studies have revealed mutations in known causative or novel genes in ~10% of patients, with no aetiology identified in up to 90%.

We have set up a new targeted gene panel, including 135 genes, both known and novel, that have previously been associated with CH or related disorders, or that have been implicated as playing a role in murine or human HP development e.g. *HESX1, GLI2, SOX2/3, LHX3/4* etc. We have incorporated genes from our exome sequencing projects (published and unpublished) e.g. *EIF2S3, RNPC3, MAGEL2*, which has enabled us to analyse mutation frequency in these genes within a larger proportion of our cohort simultaneously. Thereby suggesting candidate genes which may be worth pursuing functionally and may have essential roles in HP development.

We have so far processed 144 patients on the targeted gene panel, and data have been aligned using 3 different pipelines; haplotype, strelka and manta. To date, ~50% of these patients have had their results analysed through variant calling, with 148 variants identified in 70/144 patients so far. These variants have been carefully filtered as potentially pathogenic mutations, contributory or causative of the CH in the patient, and have acceptable frequency rates on control databases including the GnomAD browser. Variants that do not meet our stringent criteria thresholds have been excluded. Variants of unknown significance will be

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functionally tested and genotype-phenotype correlations will be carefully analysed for each patient. Preliminary data suggest an oligogenic basis to many of these cases, with the involvement of multiple genes in the pathogenicity of the disease.

FC13.3

Variants in Methyl-CpG-binding protein 2 (MECP2) are associated with X-Linked Central Precocious Puberty

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Whilst several key genetic contributors to the phenotype of central precocious puberty (CPP) have been recognized, many familial cases remain without clear a genetic aetiology. Causal genetic variants are reported in imprinted genes Makorin ring finger protein 3 (MKRN3) and Delta-like homolog 1 (DLK1), alongside Kisspeptin-1 (KISS1) and (KISSR1), implicating mis-regulation of transcriptional control of the kisspeptin and GnRH neuroendocrine systems in onset of CPP. We recently published a large cohort study identifying CPP associated variants in Methyl-CpG-binding protein 2 (MECP2), a chromatin-associated transcriptional regulator, with known roles in neuronal maturation (Canton et al, Lancet Diabetes and Endocrinology, accepted). MECP2 is encoded by a gene on Xq28, is highly expressed in hypothalamic nuclei (arcuate, suprachiasmatic, and paraventricular) and co-localises with GnRH within GnRH neurons, suggesting a role in puberty onset through regulation of the GnRH neuronal axis.

Loss-of-function mutations in MECP2 are usually associated with Rett syndrome, a severe neurodevelopment disorder characterized by developmental regression and intellectual disability. Interestingly, patients with Rett syndrome loss-of-function variants in MECP2 are reported with precocious puberty. Comparison of the in vitro impact of CPP-associated MECP2 variants in otherwise healthy patients, to those identified in Rett syndrome, may inform about the disparate phenotypes, aiding in differential diagnosis.

We investigated the in vitro impact of 5 CPP associated and 2 Rett syndrome associated MECP2 variants in a GT1-7 mouse neuronal GnRH producing cell line. Immunocytochemistry of MECP2 variant overexpressing GT1-7 identified differential expression of CPP associated and Rett associated MECP2 variants, with lower MECP2 expression in Rett syndrome variants as compared to CPP associated variants. Variation was also observed between CPP MECP2 variants. Western blotting confirmed differential protein expression of overexpressed MECP2 variants of interest compared to wildtype MECP2. Preliminary studies in a GnRH reporter system demonstrated differential ability of MECP2 variants to supress GnRH promoter activity, suggesting a possible regulatory role in the GNRH neuronal network.

Here we present data suggesting that CPP associated variants in MECP2 alter protein expression and localisation within a GnRH neuronal cell line. Mechanisms of action of gene regulation by MECP2 is complex, comprising transcriptional regulation and chromatin compaction, thus further studies are required to determine the molecular basis of MECP2 regulation of key players in GnRH neuroendocrine regulation. Identification of key differences in expression and activity of CPP associated MECP2 variants, compared to those associated with Rett syndrome, can aid in genetic diagnosis and treatment of patients.

FC13.4

Clinical and molecular genetic characteristics of 98 patients with congenital hypopituitarism: A single-center experience

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Background: Congenital hypopituitarism (CH) refers to a deficiency of one or more pituitary hormones resulting from variants in genes encoding transcription factors for pituitary development. CH cases are mostly sporadic but 5-30% can be familial. Genetic etiology is not determined in most cases. The aim of our study was to evaluate the genetic features of CH using different molecular and/or molecular cytogenetic techniques.

Subjects and Methods: The data of 98 patients (34 girls) from 90 unrelated families were evaluated. Next-generation sequencing (NGS), multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) were used. MLPA (Probemix P216 GHD mix-1: *GH1, LHX4, POU1F1, HESX1, PROP1, GHRHR, LHX3*) (MRC Holland Amsterdam, Netherlands) was used. Clinical Exome Sequencing (CES) was performed using SOPHIA Clinical Exome Solution V2 (Boston, USA) via the Illumina Nextseq 550 platform (San Diego, CA, USA). Segregation analyses were performed.

Results: The median age at presentation was 6.6 years (range 7 days – 17.9 years). The mean gestation age was 37.8±2.8 weeks. Birthweight SDS was -0.3±1.4, and the SGA ratio was 12.8%. Consaguinity rate was %48.0. The neonatal jaundice and hypoglycemia ratio was 51.1% and 13.3%, respectively. Micropenis was detected in 19.9%, and cryptorchidism in 27.6%. At admission, height and BMI were -2.9±2.3 SD (target height -1.0±0.9 SD) and -0.3±1.5 SDS, respectively. Pituitary hormone deficiency rates were 95.9% for growth hormone (GH), 75.5% for TSH, 43.0% for ACTH, 34.7% for gonadotropin, 23.5% for prolactin, and 15.3% for AVP, during follow-up. Anomaly (agenesis, hypoplasia, and/or ectopic neurohypophysis) rate was 69.8% in pituitary MRI. Molecular genetic etiology was determined in 21.5% of families. Pathogenic variants were detected in *PROP1*(7 cases from 3 families), *POU1F1* (6 cases from 4 families), *GLI2* (n=2), *FOXA2*(n=2), *LHX3*(n=1), *LHX4*(n=1), and *WDR11*(n=1) genes. In two cases CMA provided a definitive diagnosis (*FOXA2* and *LHX4*) and MLPA *(PROP1)* in three cases. In one case with Cantu syndrome and CH, a previously reported variant in the *KCNJ8* gene was detected. CES revealed pathogenic variants in other genes (*PDE11A, KMT2A, H1-4, HUWE1)* that are not yet associated with CH but have a known association with certain diseases. In one case, further analyses are proceeding on the candidate gene.

Conclusion: The molecular etiology was identified in 21.5% of our cohort. This low rate suggests that there may be many unknown molecular pathways that contribute to the complexity of pituitary development.

FC13.5

Systematic review and meta-analysis of spermatogenesis rates after pubertal induction with gonadotropins in males with hypogonadotropic hypogonadism

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Background: Hypogonadotropic hypogonadism is characterised by inadequate secretion of gonadotropins (luteinising hormone (LH) and follicle-stimulating hormone (FSH)) leading to absent, partial or arrested puberty. In males, classical treatment with testosterone promotes virilisation but does not facilitate testicular growth and spermatogenesis. Conversely, treatment with gonadotropins or gonadotropin-releasing hormone (GnRH) stimulates Sertoli and Leydig cells directly, leading to increased testicular volumes, appropriate serum testosterone concentrations and spermatogenesis. To quantify treatment practices and efficacy, we aimed to systematically review all studies investigating gonadotropin and GnRH therapies for the induction of spermatogenesis in males with hypogonadotropic hypogonadism.

Methods: A systematic review of Medline, EMBASE, Global Health, and PsychInfo databases was conducted in December 2022, with RoB 2.0/ROBINS-I/NHLBI scoring for quality appraisal. Protocol registered on PROSPERO (CRD42022381713). Eligibility criteria: studies since 1990 of patients with hypogonadotropic hypogonadism treated with gonadotropins/GnRH for 6+ months assessing pubertal outcomes including spermatogenesis.

Results: After screening 3,925 abstracts, 106 studies were identified assessing pubertal outcomes (81 observational studies, 19 comparative non-randomised studies, six randomised controlled trials), including 5,283 patients from 21 countries. Of these, 98 evaluated spermatogenesis. Median NIHLBI score for observational studies was 9/12 (interquartile range (IQR) 8-10) and 41.4% of comparative studies had serious risk of bias in at least one domain. The average age of participants was <25 years in 49.1% (n=52) of studies. Studies utilised hCG (n=96, 90.6% of studies), hMG (n=44, 41.5%), FSH (n=38, 35.8%), and 28.3% (n=30) used GnRH. Median reported duration of treatment/follow-up was 18 months (IQR 11.5-24 months).

Meta-analysis of proportions found a pooled proportion of patients achieving spermatogenesis with a random effects model was 40.1% for hCG (95% CI 25.0-56.1%), 84.5% for hCG + FSH (recombinant or urinary) (95% CI 80.2%-88.4%), 75.2% for hCG + hMG (95% CI 66.7-83.0%) and 72.4% for GnRH (95% CI 59.3-84.0%). There was a significant degree of heterogeneity for all treatment modalities except hCG + FSH. The most frequent adverse effects were gynaecomastia, acne and injection site pain/reaction.

Conclusions: There is a growing body of evidence regarding the use of gonadotropins or GnRH for attainment of spermatogenesis in patients with hypogonadotropic hypogonadism and outcomes are promising. We found that hCG + FSH was superior to hCG alone for induction of spermatogenesis. However, there remains substantial heterogeneity across studies in terms of treatment choice, dose, duration, and outcomes assessed, and in particular, randomised studies are needed to inform the development of guidelines for this important patient group.

FC13.6

Effects of Blue Light Exposure and Exposure Duration on Male Rats Puberty Process

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Purpose: Our study aimed to examine the effects of blue light exposure on prepubertal male rats' puberty and testis tissue.

Methods: Eighteen 21-day-old male Sprague Dawley rats were divided into three groups consisting of six rats in each group: Control Group (CG), Blue Light-6 hours (BL-6), and Blue Light-12 hours (BL-12). CG rats were maintained with 12/12-hour light-dark cycles. The rats of BL-6 and BL-12 were exposed to blue light (450–470nm, irradiance level 0.03uW/cm^2) for 6 hours and 12 hours, respectively. Rats were exposed to blue light until the first signs of puberty. The ELISA method was used to analyze the serum concentrations of FSH, LH, testosterone, DHEA-S, leptin, ghrelin, melatonin, glutathione, glutathione peroxidase, and malondialdehyde. Testes were dissected for histomorphological examination.

Results: The medians of the pubertal entry days of the CG, BL-6, and BL-12 were 38th, 30th, and 28th days, respectively *(p: 0.001).* The age of onset of puberty decreased as the duration of blue light exposure increased *(r: -0.97, p<0.001)*. Weight gain (%) was similar between the groups (p>0.05). Leptin concentrations were lower in BL-12 compared to BL-6 *(p: 0.003)*. There was no correlation between weight gain (%) and leptin (p>0.05), although serum leptin concentrations decreased as the onset of puberty progressed earlier *(r: 0.53, p: 0.02)*. Ghrelin concentrations in the groups were similar (p>0.05). The FSH, LH, and testosterone concentrations of all groups were similar (p>0.05). The FSH concentration increased as the LH concentration increased *(r: 0.82, p: 0.001)*. The LH concentration increased as serum testosterone, and DHEAS decreased, respectively *(r:-0.56, p:0.01),(r:-0.55 p:0.01)*. Testicular lengths and weights of the BL groups were smaller compared to CG *(p=0.03),(p=0.04)*. GPx was higher for BL-6 and BL-12 than the CG *(p:0.02, p:0.02)*. Testis tissue was compatible with the pubertal period in all groups. As the blue light exposure time increased, spermatogenesis was suppressed, and capillary dilatation and edema in the testis tissue increased.

Conclusion: In our study, exposure to blue light accelerated the onset of puberty in male rats. When the length of exposure to blue light increased, the onset of puberty occurred earlier. To the best of our knowledge, this study is the first to demonstrate the effects of blue light exposure on male rats' puberty onset. The blue light exposure suppressed spermatogenesis, marked vasodilatation in the interstitial area of the testis, and disrupted the integrity of the basement membrane. These findings intensified with increasing exposure time.

Late Breaking

FC14.1

Sleep health characteristics in children with congenital adrenal hyperplasia

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Introduction: Cortisol secretion is circadian-driven and plays a significant role in sleep quality. In children with congenital adrenal hyperplasia (CAH) hydrocortisone is the preferred treatment. Hydrocortisone has a short half-life producing alternating hyper- and hypocortisolemia, a non-physiologic cortisol profile, likely disrupting sleep. However, minimal literature exists on sleep health in children with CAH.

Objective: A pilot study evaluating sleep health in children with CAH.

Methods: Children ages 3-15 with CAH were recruited from a multidisciplinary CAH center and wore an Actigraph Link accelerometer watch for one week; objective sleep measures (duration, latency, night wakings, and sleep efficiency) were estimated. Children 8-18 years completed the Children's Report of Sleep Patterns (CRSP) questionnaire; parents of children 3-10 years completed the Children's Sleep Habits Questionnaire (CSHQ). This data was compared to published community and clinical samples of same-aged children using linear regression and T-tests.

Results: The sample included 44 children (23 males, mean-age 8.45 years) diagnosed with CAH (25 salt-wasting) on circadian hydrocortisone dosing. Average actigraphy-estimated total sleep time per night was 7.45 hours. None of the children met clinical guidelines for age-specific minimum sleep hours. The average number of night awakenings was highest (average 6 per/hr) between 5-8 hours post hydrocortisone dose, corresponding to elimination of cortisol. Children with CAH had 40.9% more wake time after sleep onset, 38.6% had lower sleep efficiency, and 6.8% had longer sleep latency compared to published healthy controls. Parents of children with CAH (n=30) reported significantly worse CSHQ scores for bedtime resistance, sleep onset delay, and sleep duration versus children with sleep disorders (n=154; p-values<0.05), and for every subscale versus healthy controls (n=469; p-values<0.05) except disordered breathing. There were significant differences (p-values<0.008) in the self-reported CRSP sleep subscales of bedtime worries and restless legs in the 13-18 years age group compared to both community and clinical samples but no differences in the 8-12 age group. However, the 8-12 age group reported increased nighttime awakenings compared to the combined community/clinical sample and worse in the insomnia subscale compared to the community sample, but the differences were not significant.

Conclusion: The objective data showed that children with CAH did not meet recommendations for total sleep time and had more nighttime awakenings compared to peers. With the peak number of awakenings corresponding to when cortisol concentration from the evening hydrocortisone dose was mostly eliminated suggests that impaired circadian secretion of cortisol detrimentally impacts sleep quality.

FC14.2

New Reference Values for Thyroid Volume by Ultrasound in German Children and Adolescents Under Iodine-Sufficient Conditions From a Nationwide Study

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Introduction: Reliable reference values for thyroid ultrasound measurements are essential to effectively guide individual diagnostics and direct health care measures at the population level, such as iodine fortification programs. However, the latest reference values for total thyroid volume (Tvol) provided by the WHO in 2004 are only applicable to the 6 to 12-year-old age group. Moreover, these values are derived from countries with a long history of iodine sufficiency, which doesn't reflect the situation in most European countries, including Germany.

Methods: Data from the baseline assessment of a nationwide study in German children and adolescents (KiGGS) conducted between 2003 and 2006 was used to determine sex-specific reference values for Tvol in thyroid-healthy participants aged 6 to 18 years by age and body surface area (BSA) according to the Lambda-Mu-Sigma (LMS) method.

Results: After exclusion of 5005 participants who did not meet the inclusion criteria, mainly due to missing information, and 994 datasets from three examiners who provided deviant Tvol measurements, data from 5559 participants was available for reference chart construction (girls: 2509 (45.1%)| reference charts according to age - Nmedian: 469.5, Nmin: 398, Nmax: 573 | BSA - Nmedian: 874, Nmin: 62, Nmax: 1061). The data show a continuous increase in Tvol for boys up to the age of 18 years, a pattern also seen in girls, albeit with a slowing trend at advanced ages. Additionally, although girls have larger Tvol during early puberty, this trend reverses later on. This effect is partially mediated by BSA. On average, the 97th percentile is 33.4% and 28.5% higher than the corresponding WHO's reference values for boys and girls, respectively. This is consistent with most other studies in German and European children and adolescents at a similar time of investigation. Notably, the sample used for this study was iodine-sufficient according to WHO criteria.

Conclusions: We present the most recent reference values for Tvol for German children and adolescents under iodine-sufficient conditions. The reference values provided by the WHO are overly conservative for this population, possibly for reasons of long-term iodine supply. Given the methodological strengths of this study - including its representativeness, sample size, and comprehensive information, including laboratory findings - these reference values could potentially be applicable to other European countries with a similar history of iodine supply.

FC14.3

Deconvolution Analysis: GH secretagogue (LUM-201) enhances growth in individuals with moderate idiopathic Pediatric Growth Hormone Deficiency (iPGHD) by enhancing endogenous GH secretion and increasing IGF-1

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An oral GH secretagogue (GHS), LUM-201, stimulates GHSR-1a receptor to enhance endogenous GH pulsatile release. In moderate iPGHD, pulses of GH are found but at reduced levels, resulting in decreased IGF-1 and poor growth. The impact of LUM-201 on GH profiles during treatment of such children has not been reported.

Objective: To characterize GH profiles, defined by deconvolution analysis, based on GH concentration in a time series and its simultaneous clearance, at baseline and after 6 months of therapy with daily oral LUM-201 to illustrate how it affects annualized height velocity (AHV), serum IGF-1 and IGFBP3 in individuals with moderate iPGHD.

Patients & Methods: 15 prepubertal, naive iPGHD subjects were screened with a predictive enrichment marker (PEM) test to assess their acute response to oral LUM-201 (0.8 mg/kg), with a positive test having a peak GH >5 ng/ml with a basal IGF-1 >30 ng/ml. At baseline, subjects (10M:5F) were (mean ± SD) aged 7.9±1.4 years, with IGF-1 SDS -0.82±0.9, and peak GH 7.2±2.2 | ng/mL (clonidine stimulation), consistent with moderate iPGHD.

Deconvolution was performed on serum GH measured every 10 minutes (0800 h to 2000 h). Patients were randomized to receive 1.6 mg/kg/day or 3.2 mg/kg/day of oral LUM-201. GH responses to the PEM test (p=0.9) and the first treatment doses were not different between the groups (34.8±6.6ng/ml for 1.6mg/kg and 38.2±11.2 ng/ml for 3.2mg/kg, p=0.7). The groups were therefore combined for this analysis.

Results: At 6 months GH & IGF parameters, and AHV increased 1.2-2.4 fold: See Table for means (SD).

Conclusions: LUM-201 generated the expected AHV in this iPGHD cohort. LUM-201 enhanced pulsatile GH secretion to similar levels observed in normal growing children, estimated at ~3.5 µg/kg/12h (Albertsson-Wikland et al JCEM 1994); restoring physiological pulsatile GH secretion and IGF-1 were sufficient to support normal growth. LUM-201 in the treatment of moderate iPGHD has the advantages of being taken orally, enhancing endogenous pulsatile GH secretion, and therefore maintaining normal feedback mechanisms, to restore normal growth

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	Baseline	6 Month	t test, p value
GH total*	1.45 (0.89)	2.32 (1.25)	0.013
GH pulsatile*	1.28 (0.83)	1.93 (1.17)	0.035
GH basal *	0.17 (0.11)	0.40 (0.28)	0.008
AHV (cm/year)	4.7 (1.3)	7.6 (1.1)	< 0.00001
IGF-1 (ng/mL)	115.5 (46.6)	205.4 (63.9)	0.0004
IGFBP3 (nmol/L)	139.3 (32.6)	169.0 (30.1)	0.0004
IGF-1:IGFBP3	0.108 (0.031)	0.157 (0.050)	0.0044

*daytime secretion µg/kg body weight per 12hr

FC14.4

Improvement in insulin sensitivity and glucose metabolism in adolescents with obesity treated with once-weekly semaglutide 2.4 mg: a secondary analysis of the STEP TEENS trial

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Obesity in adolescents is associated with increased risk of prediabetes and type 2 diabetes (T2D) and long-term complications in adulthood. Data regarding the effects of anti-obesity medications on glycaemic outcomes in adolescents are sparse. STEP TEENS (NCT04102189), a phase 3a, double-blind, placebo-controlled randomised trial in adolescents 12 to <18 years of age with obesity demonstrated that once-weekly subcutaneous semaglutide 2.4 mg provided a greater percentage reduction in body mass index (BMI) than placebo from baseline to week 68.1

This STEP TEENS secondary analysis investigated the effect of semaglutide 2.4 mg compared to placebo on fasting plasma glucose (FPG), HbA1c, fasting insulin (FI) and homeostatic model assessment for insulin resistance (HOMA-IR) from baseline to week 68. Additionally, this analysis compared measures of glucose metabolism and insulin sensitivity in participants with ≥20% vs <20% reductions in BMI in the semaglutide 2.4 mg treatment arm. Analyses were performed with on-treatment assessments using mixed models for repeated measurements. P-values were not adjusted for multiple comparisons. Participants with T2D (n=8) were excluded.

At week 68, participants receiving semaglutide (n=129) vs placebo (n=64) had greater reductions from baseline in FPG, (−0.22 mmol/L vs −0.02 mmol/L; estimated treatment difference [ETD] [95% confidence interval (CI)]: −0.20 [−0.35, −0.04]; p=0.0117), HbA1c, (−0.36%-points vs −0.14%-points; ETD [95% CI]: −0.22 [−0.30, −0.15]; p<0.0001), FI (−37.00% vs −8.67%; ETD [95% CI]: −31.02 [−42.88, −16.69]; p=0.0001) and HOMA-IR (−38.63% vs −5.84%; ETD [95% CI]: −34.83 [−47.31, −19.38]; p=0.0001). For semaglutide recipients, observed improvements in all endpoints were greater in those who achieved ≥20% vs <20% BMI reduction at week 68 (Table). Results were consistent when stratified by ≥20% (n=49) vs <20% (n=77) weight loss.

Table. Change in glycaemic measures at week 68 among participants receiving semaglutide.

Endpoint	BMI reduction at week 68	
	≥20% (n=53)	<20% (n=73)
FPG mmol/L (mean [SD])	−0.4 (0.4)	−0.1 (0.5)
HbA1c %-points (mean [SD])	−0.5 (0.2)	−0.3 (0.3)
FI percentage change (CV)	−52 (65.3)	−26 (49.3)
HOMA-IR percentage change (CV)	−55 (69.4)	−27 (56.1)

CV, coefficient of variation; SD, standard deviation.

Once-weekly semaglutide 2.4 mg compared to placebo provided significant improvements in glycaemic measures and insulin sensitivity in adolescents with obesity, with greater improvements in semaglutide recipients with ≥20% vs <20% BMI reduction.

Reference: Weghuber D, et al. Once-weekly semaglutide in adolescents with obesity. N Engl J Med. 2022;387:2245–57.

FC14.5

Predicting Average IGF-I Concentration for Once-Weekly Somapacitan in Children with Growth Hormone Deficiency

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Growth hormone (GH) stimulates insulin-like growth factor-I (IGFI) release. IGF-I is the standard biomarker for monitoring GH effects during treatment and to achieve optimal long-term safety, and to a limited extent, monitor efficacy in children with GH deficiency (GHD). The IGF-I profile during treatment with a long-acting GH (LAGH), such as once-weekly somapacitan (Novo Nordisk), differs from the daily GH profile by exhibiting larger peaks and troughs over the dosing interval. Pragmatic guidance on the interpretation of IGF-I concentrations during LAGH therapy is required by prescribing physicians.

We used pharmacokinetic/pharmacodynamic modelling based on data from 186 paediatric patients with GHD treated with 0.16 mg/kg/week somapacitan for 52 weeks in two randomized controlled trials: phase 2 REAL3 (NCT02616562) and phase 3 REAL4 (NCT03811535). IGF-I sampling was performed before first dose, 1-4 days and 4-6 days after dosing and before next dose to determine baseline, estimated maximum, weekly average and minimum IGF-I concentrations, respectively.

A linear relationship was found between somapacitan dose and IGF-I response: a somapacitan dose change of 0.02 mg/kg is expected to result in a change in weekly IGF-I average of 0.32 SDS $[0.28;0.37]_{95\%CI}$. We established linear models between individual estimated steadystate IGF-I concentrations (SDS and ng/ml) at various times after dosing and weekly IGF-I average concentrations (SDS and ng/ml) at steady state (achieved after 1-2 doses). We derived formulas to approximate IGF-I average SDS and absolute concentration (ng/ml) based on IGF-I measurements on different days within the weekly somapacitan dosing interval. The IGF-I measurement closest to the weekly IGF-I average occurs approximately 4 days (97-120h) after dosing. Where practical, measuring IGF-I on day 4 after somapacitan dosing may be optimal to estimate average weekly IGF-I (since no correction needed). We developed a simple calculation table for estimating weekly IGF-I average SDS and absolute concentration (ng/mL) from IGF-I samples taken on any other day after somapacitan dosing to offer flexibility. We approximated the results into a correction parameter for each daily interval (24 hours) for ease of use.

In summary, we characterized the dose-IGFI response of somapacitan in children with GHD. We present a practical guide to support physicians to estimate expected weekly IGFI average concentrations in patients during IGFI monitoring in the clinic.

FC14.6

Understanding the genetic complexity of puberty timing across the allele frequency spectrum

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Background: Pubertal timing varies considerably and has been associated with a range of health outcomes in later life.

Methods: To elucidate the underlying biological mechanisms, we performed multi-ancestry genetic analyses in ~800,000 women.

Results: We identified 1,080 independent common genetic signals associated (at $P<5\times10-8$) with age at menarche. Collectively these loci explained 11% of the trait variance in an independent sample. Women at the top and bottom 1% of a polygenic risk score exhibited a ~11 and ~14-fold higher risk of delayed (menarche >15 years) and precocious (menarche <10 years) pubertal development, respectively, compared to those with median polygenic risk. These common variant analyses were supported by whole exome sequence analysis of ~220,000 women, identifying several genes, including rare loss of function variants in *ZNF483* which abolished the impact of polygenic risk. We implicated 660 genes in the regulation of pubertal development using a combination of in silico variant-to-gene mapping approaches and integration with dynamic gene expression data from mouse embryonic GnRH neurons. This included an uncharacterized G-protein coupled receptor GPR83, which we demonstrate amplifies signaling of MC3R, a key sensor of nutritional status. Finally, we identified several genes, including ovary-expressed genes involved in DNA damage response that co-localize with signals associated with menopause timing, leading us to hypothesize that the ovarian reserve might signal centrally to trigger puberty.

Conclusions: These findings extend our understanding of the biological complexity of puberty timing and highlight body size dependent and independent mechanisms that potentially link reproductive timing to later life disease.

Rapid Free Communications

Adrenals and HPA Axis

RFC1.1

Unfavorable Body Composition in Children with Premature Adrenarche: Implications for Metabolic Health

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Context: Premature adrenarche (PA) could pose an increased risk of obesity and metabolic derangements in adolescence and early adulthood. However, little is known about the body composition of children with PA and its association to the development of adverse metabolic outcomes.

Aim: To describe the body composition of children with PA and explore the interaction between PA and metabolic syndrome components.

Methods: This observational study was conducted in a tertiary center. The study group comprised of 88 children with PA (14 males) and 88 consecutive healthy sex- and age- matched subjects with normal growth and puberty served as their controls. Body composition was measured using bioelectrical impedance analysis (BIA, Tanita MC-780 MA and GMON Professional Software), and muscle-to-fat ratio (MFR) z-scores were calculated. The relationship between parent-offspring MFR was assessed using Spearman correlation. Logistic regression model was applied to determine whether MFR z-scores and metabolic syndrome components were associated with PA. The models were adjusted for sex, socioeconomic position index, family history of metabolic syndrome components, perinatal characteristics, and MFR z-scores.

Results: Subjects with PA had a median age [IQR] of 7.95 years [7.3, 8.7] at BIA and mean HOMA-IR of 2.4 ± 1.3. Subjects with PA had higher median BMI z-scores (0.46 [-0.25, 1.23] vs. -0.06 [-0.92, 0.84], *p*=0.004) and higher median fat percentage (24.9 [21.8, 27.2] vs. 22.3 [20.2, 28.1], *p*=0.012) compared to controls; with no significant differences in MFR z-scores, blood pressure percentiles and lipid profiles between the groups. In the control group, significant correlations between parents' MFR and offspring's MFR z-scores were observed (father-child: r=0.549, *p*=0.015; mother-child: r=0.410, *p*=0.010), no significant correlations were found in the PA group. In the logistic regression models, MFR z-score was not significant, however, subjects with PA had higher odds for family history of metabolic syndrome components OR 2.29 [1.19, 4.42], *p*=0.013; no other significant variables were found.

Conclusions: Our research indicates that pediatric patients with PA exhibit an unfavorable body composition, as evidenced by higher BMI z-scores and fat percentages than healthy matched controls. Additionally, while heritable body composition traits were observed in healthy children, they were not present in those with PA, which suggests that environmental factors play a greater role in this particular group. These findings highlight the importance of early intervention and lifestyle modifications to prevent the development of metabolic complications in children with PA.

RFC1.2

The chimeric *CYP21A1P/CYP21A2* and *TNXA/TNXB* gene deficiencies in patients with Congenital Adrenal Hyperplasia

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Background: Congenital Adrenal Hyperplasia (CAH) is an autosomal recessive disorder with more than 90% of cases caused by defects in the steroid-21 hydroxylase (*CYP21A2*) gene. Such defects are the main cause of 21-hydroxylase enzyme deficiency that affects the biosynthesis of cortisol and aldosterone. The *CYP21A2* gene is part of the RCCX module, which is located on chromosome 6p21.3, in the major histocompatibility complex (MHC) class III region. The RCCX module consists of four genes, *RP*, *C4*, *CYP21*, and *TNX* and can normally be found in two versions in tandem, one consisting of the functional genes *RP2*, *C4B*, *CYP21A2*, and *TNXB* and the second consisting of the corresponding inactive pseudogenes *RP1*, *CYP21A1P*, and *TNXA* and the functional *C4A* gene. The genes in the two versions of RCCX module are highly homologous and events such as unequal crossover during meiosis can occur. These events produce non-functional chimeric genes such as *CYP21A1P/CYP21A2* and *TNXA/TNXB*, which are directly related to CAH and steroid overproduction. To date, nine types of *CYP21P/CYP21A2* chimeras (CH1-CH9) and three types of *TNXA/TNXB* chimeras (CAH-X CH1-CH3) have been described.

Methods: Twenty-four DNA samples from patients previously identified with various genetic defects in the *CYP21A2* gene were selected and re-analyzed for the presence of chimeric genes, using long-range PCR followed by TaqI restriction enzyme digestion, Sanger sequencing, and multiplex ligation-depended probe amplification.

Results: Of the 24 patients, three patients were heterozygous for the CH1 type of chimera, one patient was heterozygous for the CH9 type of chimera and one patient was a compound heterozygous for the CH1 and CH4 type of chimeras. In addition, one patient was found to be heterozygous for the CAH-X CH1 type of chimera, one patient was homozygous for the CAH-X CH1 type of chimera, and one patient was heterozygous for the CAH-X CH2 type of chimera. Interestingly, one patient was identified as heterozygous for the very rare CH4 chimera that lacks the p.Pro30Leu mutation and a second patient was identified as heterozygous for a new type of chimera.

Conclusions: Using the applied methodologies, we successfully identified and characterized the different types of chimeric genes generated by unequal crossover events. Based on our results, the application of improved and more detailed diagnostic methods will help to identify all genetic abnormalities in *CYP21A2* genotyping, therefore, providing more targeted management and genetic counseling for current and future families with CAH.

RFC1.3

The effect of storage and temperature on the stability of steroid hormones in dried blood spots

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Introduction: Monitoring steroid hormone levels of children with endocrine disorders, such as congenital adrenal hyperplasia (CAH) and disorders of sex development (DSD), can be challenging. Dried blood spot (DBS) sampling can be helpful for these patients. DBS sampling is less invasive, easier to sample, and simpler to transport and store compared to venous blood sampling. Additionally, DBS sampling can be done at home at any time of the day, thus improving patient convenience. In order to sample at home and send the DBS to the laboratory, the effect of storage and temperature on the stability of steroid hormones in DBS samples needs to be established.

Methods: DBS from 10 healthy volunteers (5 males, 5 females) were collected and stored per different temperature (-20°C, 4°C, room temperature, 37°C) for 7- and 14-days, and 3- and 6-months (DBS stored at 37^{0}C were kept for maximal 7 weeks). Directly after sampling steroid hormone concentrations of cortisol, cortisone, corticosterone, testosterone, androstenedione, and 17-hydroxyprogesterone were assessed using our in-house LC-MS/MS method and were set at 100% (baseline). Steroid hormone concentrations were considered stable when the median shift stayed within ±10% from baseline.

Results: All steroids in DBS remained within ±10% change from baseline for up to three months when stored at -20^{0}C and 4^{0}C, except for cortisone concentrations which only remained <±10% change up to 14 days. At room temperature steroids remained <±10% change from baseline up to three months, except for androstenedione concentrations which only remained <±10% change up to 7 days, and cortisone concentrations up to 14 days. When stored at 37^{0}C only testosterone concentrations remained <±10% change up to 7 weeks. 17-hydroxyprogesterone and corticosterone concentrations remained <±10% change up to 14 days, while androstenedione and cortisol concentrations only remained <±10% change up to 7 days. Cortisone concentrations already showed >±10% change at day 7 of storage.

Conclusions: In general, the steroid hormones cortisol, cortisone, corticosterone, testosterone, androstenedione, and 17-hydroxyprogesterone remain stable in DBS long enough to be send by regular mail to the diagnostic laboratory. Thus, self-sampling DBS at home could potentially be used for monitoring steroid hormone levels of children with endocrine disorders such as CAH or DSD.

RFC1.4

Lack of NAD(P)$^+$ transhydrogenase activity in patients with primary adrenal insufficiency due to *NNT* mutations

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Background: Mutations in the nicotinamide nucleotide transhydrogenase (*NNT*) gene are a rare cause of primary adrenal insufficiency (PAI), as well as cardiomyopathies and functional impairment of the gonads.

Objective: Despite the description of different *NNT* mutations in homozygosis and compound heterozygosis in PAI patients, it remains to be clarified to which extent the function and expression of the mature protein are compromised.

Design: Blood samples from healthy controls, patients with previous diagnosis of *NNT* mutation-driven PAI (n=5) and their parents were analyzed for NAD(P)$^+$ transhydrogenase (NNT) activity and expression.

Methods: NNT activity was assessed by its reverse reaction assay standardized for digitonin-permeabilized peripheral blood mononuclear cells (PBMC). The enzymatic assay was validated in PBMC samples from a mice model of NNT absence. Additionally, the PBMC samples were evaluated for NNT expression by western blot and RT-qPCR, and for mitochondrial oxygen consumption.

Results: NNT activity was undetectable (<4% of healthy controls) in PBMC samples from patients, independent of the pathogenic genetic variant. In their parents, NNT activity was approximately half of the healthy controls. NNT mature protein expression was lower in patients than in the control groups, while mRNA levels widely varied among genotypes. Moreover, *NNT* mutations did not impair the mitochondrial bioenergetic function in PBMC.

Conclusions: The manifestation of PAI in *NNT*-mutated patients is associated with a complete impairment of NNT activity. Evaluation of NNT activity can be useful to characterize disease-causing *NNT* mutations.

RFC1.5

Clinical and Genetic Characteristics of 42 Chinese Paediatric Patients with X-Linked Adrenal Hypoplasia Congenita

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Background: X-linked adrenal hypoplasia congenita (AHC) is a rare disorder characterized by primary adrenal insufficiency (PAI) and hypogonadotropic hypogonadism (HH), with limited clinical and genetic characterization.

Methods: The clinical, biochemical, genetic, therapeutic, and follow-up data of 42 patients diagnosed with X-linked AHC were retrospectively analysed.

Results: Hyperpigmentation (38/42, 90%), vomiting/diarrhoea (20/42, 48%), failure to thrive (13/42, 31%), and convulsions (7/42, 17%) were the most common symptoms of X-linked AHC at onset. Increased adrenocorticotropic hormone (ACTH) (42/42, 100%) and decreased cortisol (37/42, 88%) were the most common laboratory findings, followed by hyponatremia (32/42, 76%) and hyperkalaemia (29/42, 69%). Thirty-one patients presented with PAI within the first year of life, and 11 presented after three years of age. Three of the thirteen patients over the age of 14 exhibited spontaneous pubertal development, and ten of them experienced delayed puberty due to HH. Six patients receiving human

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chorionic gonadotropin (hCG) therapy exhibited a slight increase in testicular size and had rising testosterone levels (both $P < 0.05$). The testicular volumes of the three patients with pulsatile gonadotropin-releasing hormone (GnRH) therapy were larger than those of the six patients undergoing hCG therapy ($P < 0.05$), and they also exhibited some growth in terms of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone. Of the 42 patients, three had an Xp21 deletion, and 39 had an isolated DAX1 defect. The most common variant, which may be associated with early onset age, was the entire DAX1 deletion (10/42, 23.8%). Fourteen novel DAX1 variants were identified.

Conclusions: This study expands the clinical and genetic spectra of X-linked AHC. Patients with X-linked AHC show a bimodal distribution of the age of onset, with approximately 70% presenting within the first year of life. Compared to hCG therapy, pulsatile GnRH appears to be more effective. The combination of clinical features and molecular tests provides information for an accurate diagnosis.

RFC1.6

Interlaboratory comparison of LC-MS/MS measurements of 11 relevant steroid hormones in 27 DSD patients

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Background: Differences of sex development (DSD) comprise a heterogeneous group of conditions with an atypical sex development. Disorders of steroid biosynthesis are often directly or indirectly involved. For accurate diagnosis, highly specialized laboratory analyses enabling sensitive and specific steroid determinations in low amounts of plasma are required. Within the German ministry of health financed project “DSDCare” (care in compliance with the guidelines for people with variances of sex development (DSD)), we organized an interlaboratory comparison of 11 steroids which are relevant for diagnosing DSD. The interlaboratory comparison was performed among three facilities accredited according to 15189:2014 and using mass-spectrometry based methods.

Methods: We sent aliquots of plasma samples from 27 molecular proven patients with different forms of DSD (aged 2-19 years) to the three laboratories. The following hormones were measured: Progesterone (P), deoxycorticosterone (DOC), corticosterone (B), 17-hydroxy-progesterone (17OHP), 21-deoxycortisol (21S), 11-deoxycortisol (11S), cortisol (F), cortisone (E), androstenedione (A4), testosterone (T), dihydrotestosterone (DHT).

To allow comparisons of steroid profiles between laboratories, multiples of median (MOM) of the specific reference ranges were calculated for the two facilities, who established their own paediatric reference ranges. This was done for 25 cases with congenital adrenal hyperplasia (CAH) (21-hdoxylase-deficiency (21OHD), N=13; 11β-hydroxylase-deficiency (11OHD), N=7; 17α-hydroxylase/17,20-lyase-deficiency (17OHD), N=5)

Results: A comparison of DHT could not be conducted between all three laboratories due to the fact that it was mostly below the limit of quantification. For all other hormones the coefficients of correlation ($r2$) ranged from 0,86 to 0,99, respectively. The MoM patterns for the different forms of CAH were very well comparable between the two laboratories. The 21OHD patients have a mean MoM of 91 for 17OHP, 90 for 21S and 9,5 for P. The 11OHD patients have a mean MoM of 2.7 for 17OHP, 126 for 11S and 23 for DOC. For the 17OHD patients we calculated a mean MoM of 124 for B and 3.3 for P.

Conclusions: We found a very good comparability for ten of the eleven hormones (except DHT) between the three participating LC-MS/MS DSD laboratories. Harmonization using MoM was also well comparable between the two paediatric laboratories, the three forms of CAH show highly comparable MOM patterns. Continuous efforts are required to achieve test standardization and harmonization.

Bone, growth plate and mineral metabolism

RFC2.1

Identification of novel genes including NAV2 associated with isolated tall stature

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Background: Very tall people attract a lot of attention and represent a clinically and genetically heterogenous group of individuals. Identifying the genetic etiology can provide important insights into the molecular mechanisms regulating linear growth.

Methods and Results: We studied a three-generation pedigree with several isolated (non-syndromic) tall members by whole exome sequencing; the tallest man had a height of 211 cm. Six heterozygous gene variants predicted as damaging were shared among the four genetically related tall individuals and not present in a family member with normal height, nor in control individuals. To gain insight into the putative role of these candidate genes in bone growth, we assessed the transcriptome of murine growth plate by microarray and RNA Seq. Two (IFT140, NAV2) of the six genes were well-expressed in the growth plate. Nav2 (p-value 1.91E-62) as well as Ift140 (p-value of 2.98E-06) showed significant downregulation of gene expression between the proliferative and hypertrophic zone,

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suggesting that these genes may be involved in the regulation of chondrocyte proliferation and/or hypertrophic differentiation. IFT140, NAV2 and SCAF11 have also significantly associated with height in GWAS studies. Pathway and network analysis indicated functional connections between IFT140, NAV2 and SCAF11 and previously associated (tall) stature genes. Knockout of the all-trans retinoic acid (ATRA) responsive gene, neuron navigator 2 NAV2, in Xenopus supports its functional role as a growth promotor.

Conclusion: Collectively, our data expand the spectrum of genes with a putative role in tall stature phenotypes and, among other genes, highlight NAV2 as an interesting gene to this phenotype.

RFC2.2

Familial pseudohypoparathyroidism type IB associated with an SVA retrotransposon insertion in the GNAS locus

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Loss of methylation (LOM) at GNAS-A/B:TSS-differentially methylated regions (DMRs) in the GNAS locus is observed in pseudohypoparathyroidism type 1B (PHP1B). Many PHP1B cases are sporadic, but autosomal dominant-PHP1B has a deletion involving NESP55 expressed from the maternal allele or STX16 located upstream of the GNAS locus on the maternal allele. We report the possible first familial PHP1B cases with retrotransposon insertion in the GNAS locus on the maternal allele. To our knowledge, they are the possible first cases with imprinting disorders caused by retrotransposon insertion. The two sibling cases experienced tetany and/or cramps from school-age and had hypocalcemia and an increased serum intact PTH level together with overweight, round face, and normal intellectual levels. Methylation analysis for DMRs in the GNAS locus showed only LOM of the GNAS-A/B:TSS-DMR. Copy number abnormalities at STX16 and the GNAS locus were not detected by array comparative genomic hybridization. Whole-genome sequencing and Sanger sequencing revealed an approximately 1000-bp SVA retrotransposon insertion upstream of the first exon of A/B on the GNAS locus in these siblings. To detect the parental origin of retrotransposon insertion, we conducted long PCR for a region encompassing the retrotransposon insertion using gDNA treated with methylation sensitive restriction endonuclease in these patients. Junction between reference sequence and inserted retrotransposon sequence was detected on the allele having the methylated GNAS-XL:Ex1-TSS-DMR, namely, the maternally inherited allele. Whole-genome methylome analysis by Enzymatic Methyl-Seq in the siblings showed normal methylation status in the region surrounding the insertion site and mild LOM of the GNAS-A/B:TSS-DMR. We conducted transcriptome analysis using mRNA from skin fibroblasts and induced pluripotent stem cells (iPSCs) derived from the siblings and detected no aberrant NESP55 transcripts. Quantitative reverse-transcriptase PCR (qRT-PCR) analysis in skin fibroblasts showed increased A/B expression in the patients and no NESP55 expression, even in a control. qRT-PCR analysis in iPSCs showed decreased NESP55 expression with normal methylation status of the GNAS-NESP:TSS-DMR in the patients. The retrotransposon insertion in the siblings likely caused decreased NESP55 expression that could lead to increased A/B expression via LOM of the GNAS-A/B:TSS-DMR, subsequent reduced Gsα expression, and finally, PHP1B development.

RFC2.3

High incidence of Chiari type I anomalies on MRI in young patients with X-linked hypophosphatemic rickets (XLHR)

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Background: X-linked hypophosphatemic rickets (XLHR) represents the most common form of genetic hypophosphatemia. Even though skull and cranio-vertebral anomalies of potential neurosurgical interest are observed in children with XLHR, their actual incidence and characteristics are not well established. We aimed to analyze the incidence of Chiari type I anomalies in children with XLHR.

Methods and Materials: Our retrospective monocentric study in XLHR patients followed at the French National Reference Center for Rare Diseases of the Calcium and Phosphate Metabolism analysescranial and spinal CT and MRI.

Results: Fifty-six children(35 girls) with XLHR were included. Age at initial MRI was 9.1 ± 3.8 years (range 3 to 19 years).

On sagittal reconstructions, a clear descent of cerebellar tonsils was identified in 32 (57%) of the patients. Among them, 16 patients presented with low-lying tonsils (benign tonsillar ectopia < 5mm) and 16 patients with Chiari I (> 5 mm). Among Chiari I patients, 9 patients (56%) also presented a brainstem descent. Syringomyelia was detected in four patients with a Chiari I > 5 mm.

Four - out of 16 (25%) patients with a Chiari I malformation required neurosurgery, three of which also had syringomyelia.

Previous brain/skull CT scans were available in 32 patients. CT scan was interpreted as normal in three patients who had a Chiari I and in six patients who had low-lying tonsils on MRI.

Follow-up MRIs were available in 39 patients (interval between two MRI 3-8 years). Among the 30 patients who had a normal initial MRI, one patient showed a Chiari I anomaly six years after initial evaluation (not necessitating surgery). The nine patients diagnosed with a Chiari I initially showed no progression on follow-up MRI and none of the patients had neurosurgery.

Conclusion: Our study of 56 young XLHR patients confirms the high incidence of protrusion of the cerebellar tonsils and Chiari I anomalies in this rare disease. In this study based on MRIs the incidence of Chiari I is higher than that observed in our previous study on CT scans, 28.5% vs 16%. Follow-up MRI were reassuring, no progression of Chiari I anomaly was noted and only one patient developed Chiari I anomaly during follow-up.

RFC2.4

Documentation of inactivating PTH/PTHrP Signaling Disorders (Pseudohypoparathyroidism) cases in EuRRECa / EuRR-Bone: a challenging, but worthwhile journey

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Background: A new classification of pseudohypoparathyroidism is available (Thiele et al. 2016, J Endocrinol). The phenotype variability of inactivating PTH/PTHrP Signaling Disorders (iPPSD, former pseudohypoparathyroidism) cases is still very challenging, even for experts. Thus, it is crucial to collect data in a centralized manner for future investigation.

Methods: The EuRRECa/EuRR-Bone registries are the first and only that adopted the new iPPSD nomenclature. In a second phase, the registries iPPSD study group conducted a secondary survey, gathering details on diagnostic procedures, phenotypic and genotypic presentation of the reported cases between 2018 and 2021. The high percentage of responders motivated us to create a condition-specific module that addresses all the medical aspects required for an adequate documentation of iPPSD cases.

Results: During the secondary survey, we obtained feedback on 77 % of the e-REC cases. 76 % had a confirmed diagnosis of iPPSD. PTH (68%) and TSH resistance (64%) were the most common biochemical findings, while majority of genetically confirmed cases presented with a loss of function mutation in the GNAS gene (maternal allele- iPPSD2). Since the secondary survey, due to active promotion of the registry at different scientific events and on social media, the number of reported cases increased substantially in the last three years. At this moment, 75 iPPSD cases (63 pediatric) from 17 countries are documented in e-REC, 46 of the patients having a confirmed iPPSD diagnose (35 children). Twenty-nine cases (19 female) are documented also in the Core-Registry, 52 % having iPPSD2 (PHP type 1A) as diagnosis. 50% of all cases were diagnosed using the combination of clinical, biochemical and genetic data. Four out of 12 patients were diagnosed rather late, after the age of six. Seven patients have at least one medical outcome report in the disease-specific module, increasing the amount of medical information collected in the Core-Registry.

Conclusion: Centralized, high-quality registries, with condition-specific modules are necessary for rare diseases in order to increase the amount of medical information and thus, the statistical power of research studies. An increase in interest regarding active participation in the registry has been observed in the last years, but there is still a need for more detailed data documentation, which can only be reached by increasing the medical information in the core and in the condition-specific module. We strongly believe research in this field will benefit immensely, once awareness within the ESPE community for adding data is reached.

RFC2.5

Growth in young children with X-linked hypophosphatemia treated with burosumab

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Background: Disproportionate short stature is seen in most individuals with X-linked hypophosphatemia (XLH). Vitamin D and phosphate supplementation can improve growth slightly. Burosumab showed minimal improvement of growth in older children. No growth data of XLH children that started burosumab at a very young age, i.e., between 1 and 4 years, are available.

Methods: We included 17 XLH children (11 boys) who started burosumab before the age of 4, treated for at least one year, and 31 treated with vitamin D analogues and phosphate supplements from diagnosis. Two children in the burosumab group additionally received treatment with recombinant human growth hormone, thus their growth was analyzed separately. Auxologic data such as height, weight, BMI and head circumference were analyzed every six months for the first two years of therapy within the two groups. We tested the statistical significance of the differences between timepoints by using a two-tailed t test (SPSS®, IMB version 29).

Results: In the burosumab- treated group, mean± SD for age at therapy baseline was 2.1± 0.7. They were treated conventionally before switching to burosumab for 1.7±0.8 years. Even though they were all eutrophic at birth, height SDS was already lower at burosumab start (mean± SD -0.3±0.7 and -1.4±0.8, respectively, p<0.001). In the burosumab-treated group, we did not see any statistical significant change in height SDS during the first two years of treatment: mean± SD 0.1±0.6 after one yer (p=0.16) and 0.0±0.7 SD after two years (p=0.54). Burosumab did not correct the height deficit during the observation period (still -1.5 SDS difference in height after two years of therapy when compared to birth length SDS, p=0.04). BMI SDS did not significantly change during the first two years of burosumab. In the conventionally treated group, even though therapy was started rather early (1.2±0.8 years old), height SDS decreased by 0.7±0.9 SDS during the first two years of therapy (p<0.001). BMI SDS improved by 0.5±0.9 SDS during the same period (p=0.006).

In conclusion, we present data from the largest and youngest pediatric XLH cohort treated with burosumab over a period of two years. Our data suggest that burosumab does not correct the height deficit during the first years of life, but in contrast to conventional therapy, is not associated with further height loss. In addition, burosumab prevents the excessive weight gain, which is associated with the XLH disease development in children.

RFC2.6

Short term side effects of first bisphosphonate infusion in children with different underlying bone pathologies

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Background: Bisphosphonates act to increase bone mass by inhibition of osteoclastic bone resorption and reduction of bone turnover. Since the successful use of bisphosphonates in children with osteogenesis imperfecta, a broad range of pediatric indications with variable underlying pathomechanism emerged. While the use of bisphosphonates appears to be safe in children, data on risk factors for acute-phase reaction are sparse. A systematic characterization of side effects associated with factors including baseline musculoskeletal pain, mobility and wellbeing has not been performed in pediatric patients to our knowledge.

Materials and Methods: Pediatric patients with commencement of a bisphosphonate treatment have been recruited in 10 centers in the UK, Germany and Austria. A standardized questionnaire including pain, wellbeing, and mobility scoring was completed before therapy onset. Acute-phase effects as reported by the patient / caregiver have been retrieved by a telephone call after the infusion. Data was evaluated by multivariate analysis and linear regression models with correction for age and sex.

Results: 139 children and adolescents (Mean 9.8y, 39% females, 36% Osteogenesis imperfecta) with newly commenced

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bisphosphonate therapy were included. The majority of patients had a history of fractures (64% vertebral, 48% non-vertebral). Zoledronate was used in 83% of cases. The majority of patients (75%) received antipyretics, cholecalciferol and/or calcium supplements as prophylactic treatment.

Febrile episodes have been reported by 45% of patients after the infusion with an average duration of 2.5d. Nausea was noted in 24% of patients with a mean duration of 2.9d. Patients with inflammatory conditions (e.g. CRMO) revealed higher rates ($p=0.045$) and longer duration of fever ($p=0.044$). Prophylactic treatment did neither alter the rate nor the duration of febrile episodes and nausea. Patients with more pain experienced higher rates of febrile episodes ($p<0.05$) with longer duration ($p<0.01$). Vitamin D status or baseline calcium did not alter side-effect frequencies.

Discussion: Acute-phase reactions affect a substantial percentage of pediatric patients with newly commences bisphosphonate treatment. While prophylactic treatment was not associated with lower side effect rates, risk populations including patients with inflammatory disorders or patients with high baseline pain scores might benefit from intensified pain management or modification of the initial bisphosphonate dosage. Knowledge on the risk factors helps to prevent treatment-associated adverse effects and improve acceptance of bisphosphonate use in pediatric bone diseases.

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Fat, metabolism and obesity 1

RFC3.1

Fasting and meal-related zonulin serum levels in a large cohort of obese children and adolescents: a cross sectional study

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Background: due to its recently documented role in intercellular tight junction disassembly, zonulin has emerged as a valuable biological marker to assess the integrity of the intestinal mucosal barrier. Experimental studies have shown an association between intestinal permeability and obesity.

Objectives: aim of this study was to investigate the relationship between serum zonulin levels, both at baseline and postprandial, with body mass index (BMI) and biochemical markers of insulin resistance (IR), insulin sensitivity, β-cell function and cardio-metabolic risk in obese non-diabetic children and adolescents.

Methods: children and adolescents aged 5-16 years with BMI ≥ 2.0 SDS were recruited. Criteria of exclusion from the study were pre-term or post-term birth, genetic or endocrine causes of obesity, chronic diseases, or chronic pharmacological therapies. All the patients underwent complete clinical and biochemical assessment, including oral glucose tolerance test (OGTT) and liver ultrasonography (US). Zonulin serum levels were measured at fasting state, at 60-minute and 120-minute OGTT timepoint. Homeostasis model assessment of insulin resistance (HOMA-IR), β-cell function (HOMA-B), Matsuda-index, Insulinogenic-index, areas under the curves for glucose and insulin were calculated. IR was defined as HOMA-IR >2.5 in prepubertal children and >4 in pubertal youths.

Results: 104 obese patients were enrolled (mean age 11.43 ± 2.66). Impaired fasting glucose was documented in 27.9% and impaired glucose tolerance in 12% of patients. 69.2% patients had insulin resistance. Liver steatosis was diagnosed in 39.4%. Zonulin serum levels significantly increased from baseline to 60-minute and 120-minute OGTT timepoint ($p<0.001$) in the entire study population. Variation in zonulin levels did not differ significantly from those of glucose and insulin curve. We found a positive correlation between BMI SDS and serum zonulin levels at 120-minute OGTT timepoint ($p<0.05$). Multiple linear regression model highlighted a positive association of Zonulin fasting levels with IR and glutamic-oxalacetic transaminase levels ($p<0.05$). No significant differences in zonulin levels were demonstrated for age, sex, pubertal status, glucose, lipid profile and the other obesity-related parameters.

Conclusions: Our results show, for the first time in a pediatric cohort, the meal-related pattern of secretion of serum zonulin, which tends to significantly increase during and at 2-hours postprandial assessment. Even if the underlying mechanisms associating intestinal permeability and obesity have not been fully elucidated yet, our data confirm a close relationship between zonulin concentration and obesity in pediatric population. IR seems to significantly influence zonulin serum levels, thus a central role of IR in this pathway is conceivable.

RFC3.2

Reduced central sensitivity to thyroid hormones in children and adolescents with overweight or obesity and impaired glucose tolerance

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Background: Thyroid hormones (TH) play multiple effects on glucose metabolism. Some recent studies carried out in adult patients suggested an association between altered sensitivity to TH and type 2 diabetes, obesity, and metabolic syndrome. No studies are currently available on the presence of altered sensitivity to the action of TH in youths with prediabetes.

Objective: To evaluate the relationship between sensitivity to TH and impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or glycosylated hemoglobin (HbA1c) ≥ 5.7% in youths with overweight/obesity (OW/OB).

Materials and Methods: This cross-sectional study included 805 Caucasian youths with OW or OB (aged 6-18 years) recruited at seven Italian centers for the care of OW/OB. Inclusion criteria were: TH within the normal range, anti-thyroid antibody negativity, data availability for fasting glucose and insulin, oral glucose tolerance test (OGTT), glycosylated hemoglobin (HbA1c), lipids, blood pressure (BP). Exclusion criteria were: thyroid diseases, subclinical hypothyroidism, genetic or endocrine obesity, diabetes mellitus, chronic diseases, pharmacological treatment. The fT3/fT4 ratio was evaluated to assess peripheral sensitivity, while TSH index (TSHI), Thyrotroph T4 Resistance Index (TT4RI), Thyroid Feedback Quantile-based Index (TFQI) and Parametric TFQI were calculated to assess central sensitivity. Prediabetes was defined as any of the following phenotypes: IGT or IFG or high HbA1c.

Results: Youths with IGT (n=72) showed higher levels of TSH (3.08±0.98 vs 2.68±0.98 mIU/L, P=0.001), TSHI (3.06±0.51 vs 2.85±0.53;P=0.001),TT4RI(46.00±17.87vs38.65±16.27;P<0.0001), TFQI [1.00 (0.97-1.00) vs 1.00 (0.99-1.00)]; P=0.034), PTFQI (0.67±0.20 vs 0.60±0.22;P=0.007) compared to youths without IGT (n=733), independently of centers and age. No differences were observed for fT3/fT4-ratio. The others phenotypes of prediabetes were not associated with altered sensitivity to TH. Odds ratio of IGT rise of 1-7-fold for each increase of 1 mIU/L in TSH (P=0.010), 1 unit in TSH Index (P=0.004), TT4RI (P=0.003) or PTFQI (P=0.018), independently of centers, age, and prepubertal stage (Model 1). This result was confirmed by adjusting the logistic regression model for family history of type 2 diabetes, HOMA-IR, TG/HDL ratio, systolic BP, obesity, IFG and high HbA1c (Model 2).

CONCLUSIONS: IGT was associated with a reduced central sensitivity to TH in youths with OW/OB. Our finding suggests that IGT phenotype, known to be associated with an altered cardiometabolic risk profile, has also been associated with an impaired TH homeostasis in youths with OW/OB.

RFC3.3

Early Corneal Nerve Loss in Children with Melanocortin 4 Receptor (MC4R) Gene Mutation Related Obesity

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Background: Obesity is highly prevalent worldwide, particularly in the MENA region. Whilst simple obesity has a variable genetic and environmental basis, syndromic and non-syndromic monogenic obesity has a strong genetic component. Melanocortin 4 receptor (MC4R) mutations are the commonest cause of monogenic obesity. MC4R also regulates neuropathic pain pathways via JNK signaling after nerve injury.

Methods: Five children with the rare MC4R gene mutations underwent corneal confocal microscopy (CCM) and were compared to healthy controls. Corneal nerve fiber density (CNFD), corneal nerve branch density (CNBD), and corneal nerve fiber length (CNFL) were quantified manually using CCMetrics software.

Results: Children with MC4R gene mutation compared to controls aged 8.43±1.5 vs. 11.6±1.14 years, weighing 76.32±20.54 vs. 44.44±12.09 kg, with 53.46±4.74 % body fat without neuropathic symptoms and normal VPT (3.94±2.22 V) had non-significantly lower CNBD (40.9±20.5 vs. 62.9±20.1, P= 0.344) and CNFL (20.37±2.01 vs. 22.63±4.5, P= 0.334), with no difference in CNFD (29.79±4.0 vs. 30.62±7.0, P= 0.822).

Conclusion: Young children without neuropathic pain and normal vibration perception have evidence of early corneal nerve loss, indicative of sub-clinical neuropathy. Further studies are required to understand how mutations in the MC4R lead to corneal nerve loss.

RFC3.4

Effect of maternal diet and breastfeeding on growth and distribution of adiposity from birth up to 12 months: data from the European LIFE-MILCH project

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The ongoing European LIFE-MILCH project(www.lifemilch.eu), focuses on detecting Endocrine Disrupting Chemicals in mothers, in breast and formula milk and in urine of mothers and infants up to 12 months of age studying relationships with neurodevelopment, growth, distribution of adiposity, pubertal stages to establish a risk assessment model to prepare safety guidelines. In this study we have evaluated the effects of maternal diet during and after pregnancy, and of duration of breastfeeding on longitudinal growth, head circumference, BMI, and skinfold thickness(SFT).

The analyses were carried out on the 254/654 mother-infant dyads enrolled at one site. The mothers were enrolled at 36-40weeks GA, all in good health. Pregnancies were uncomplicated. All women filled questionnaires related to lifestyle and nutritional habits (daily and weekly frequency of intake of cereals, meat, eggs, fruit, vegetables, fatty food and dairy products) at recruitment, 1, 3, and 6 months after delivery. The duration and type of feeding was registered. All anthropometric measurements, bicipital, tricipital, subscapular and supra-iliac SFT were evaluated at 3 and 6 months in the infants. The series included 125 males and 129 females.

After delivery mothers were eating significantly less vegetables, fruit and cereals, and were taking more fat food whereas meat intake was unchanged, and intake of dairy products variable. When breastfeeding stopped, the intake of cereals decreased (p:0.029). The effect of mothers' diet before and after delivery was analysed separately; the average of the frequency of intake of each food category was considered. Whereas at 6 months we did not observe any effect on BMISDS, this was increased at 12 months in the infants of mothers reporting a lower intake of cereals during pregnancy, and a higher intake of dairy products after delivery. BMISDS was higher in those who received formula milk after 3 months of age. Growth velocity was slower in breastfed children. In females, bicipital SFT was greater at 12 months if mothers reported a greater meat and dairy intake during pregnancy, whereas tricipital SFT was smaller if the intake of cereals was less both during and after pregnancy. This was observed also for supra-iliac SFT at 12 months. In males, increased supra-iliac SFT was observed at 6 months when the mothers reported a greater intake of cereals during pregnancy.

In conclusion, maternal nutrition during pregnancy and lactation has effects mostly on weight and distribution of fat in infants. This highlights the need to improve maternal nutrition.

RFC3.5

Multi-omics Reveals molecule target Underlying Adolescent obesity with metabolic syndrome

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Objective: The onset of obesity complicated with metabolic syndrome in children and adolescents is hidden, the mechanism is unknown, and early warning indicators are lacking clinically. This study conducted multi-omics research on children and adolescents with simple obesity and obesity complicated with metabolic syndrome to provide early clinical diagnosis and drug treatment targets for its occurrence and development mechanism.

Methods: We performed proteomics, metabolomics, protein phosphorylation, N-glycosylation and other multi-omics methods are used for detection, and statistical analysis such as differential screening is used.

Results: 1) Serum metabolomics results suggested that MetS (n=40) and Con (n=40) HMDB classification analysis suggested that lyso-paf c-18, 1-heptadecanoyl-sn-glycero-3-phosphocholine, palmitic amide The most obvious down-regulation is 5alpha-androst-16-en-3-one, indoline, 3-dehydroepiandrosterone sulfate and the most obvious up-regulation; OB (n=40) and Con (n=40) HMDB classification analysis suggests that 1-heptadecanoyl-sn-glycero -3-phosphocholine, lyso-paf c-18, and palmitic amide were most significantly down-regulated, and decanoyl-l-carnitine, dodecanoylcarnitine, and eicosapentaenoic acid were most significantly up-regulated.

2) Serum proteomics results suggest that, compared with MetS (n=20) and Con (n=20) differential proteomics, the down-regulation of SHBP, PON3, LSAMP is the most obvious, and the up-regulation of FAH, PRG4, APOL1 is the most obvious; OB (n= 20) Compared with Con (n=20) differential proteomics, the down-regulation of SCG3, SHBG and IGFBP2 was the most obvious, and the up-regulation of COL18A1, FAH and CFD was the most obvious.

3) The omics results of serum 4D Label free protein N glycosylation showed that differential screening of MetS (n=20) and Con (n=20) indicated that A1BG, HYOU1, and C1QA were most significantly up-regulated, and APOC4, SPARCL1, and LAMP1 were most down-regulated obvious. Differential screening between OB (n=20) and Con (n=20) revealed that ORM2, ORM1, and ALPL were most significantly up-regulated, and CFH, LAMP2, and COL1A1 were most significantly down-regulated.

4) The results of serum 4D Label free protein phosphorylation modified omics research showed that GOLM1, ALPL, and TF were most significantly up-regulated, and APOA1, C4BPA, and ITIH4 were most significantly down-regulated.

Conclusion: The results of this study suggest that compared with simple obesity, adolescents with obesity complicated with metabolic syndrome have different differential proteins, which may be used as drug targets for subsequent treatment.

RFC3.6

Glucocorticoid-mediated leptin secretion from human adipocytes is dependent on glucose availability

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Background: Leptin is produced by adipocytes and regulates central hunger and satiety sensation. While the central leptin effects are well understood, little is known about the regulation of peripheral leptin production. Clinical data demonstrate that leptin levels are rapidly declining upon fasting, suggesting that leptin secretion is acutely regulated by nutrient availability. Although it has been previously shown that leptin secretion is under control by glucocorticoids (GC) in human adipocytes, the interplay between nutrients and GC in this context has not been studied.

Our aim was therefore to investigate leptin expression and secretion in response to GC and glucose in a human adipocyte cell model.

Methods: Human SGBS preadipocytes were differentiated into adipocytes for 14 days. The expression of leptin in response to different stimuli were determined by qRT-PCR and Western Blot. Secretion of leptin to the cell culture medium was measured by ELISA after 48 hours. ATP production rates were quantified by quantified using a Seahorse XFe96 bioanalyzer. RNA sequencing was used to investigate transcriptomic changes due to glucose and GC treatment.

Results: As expected, both leptin expression and secretion were strongly enhanced by cortisol (100 nM) treatment (approx. 10-fold and 3.2-fold (111+/-26 vs. 353+/-31 pg/ml) in mature adipocytes. Treatment with different glucose concentrations (0-10 mM) revealed a dose-dependent effect on GC-induced leptin secretion, which peaked at physiological glucose levels (5.5mM). Complete glucose deprivation or inhibition of glycolysis by 2-desoxy-glucose blocked GC-induced leptin expression and secretion, indicating that glucose metabolism is a driver of leptin production. Remarkably, compared to the expression of other known adipokines, leptin was the one most strongly induced by glucose in presence of GC, suggesting a specific influence of glucose on leptin expression under these conditions.

As expected, cellular ATP production was lower in absence of glucose (reduction by approx. 40%), thus we were interested whether leptin secretion by GC and glucose was mediated via common energy sensing pathways. We therefore either activated AMP-dependent protein kinase by AICAR or inhibited mTOR activity using rapamycin. Indeed, both treatments resulted in an inhibition of GC-stimulated leptin expression and secretion, indicating that leptin production is dependent on glycolytic energy supply.

Conclusion: Our data indicate that GC-induced leptin production in human adipocytes is mediated by intracellular glucose availability, suggesting a direct link between glycolytic energy supply and leptin production. These findings may contribute to understand the rapid regulation of leptin levels upon fasting.

Growth and syndromes (to include Turner syndrome)

RFC4.1

Functional networks reveal pathways linking early growth to childhood blood pressure in the Manchester BabyGRO Study

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Background: Many studies have associated being born small for gestational age (SGA) [and by implication having suboptimal fetal growth (SFG)] to childhood cardiometabolic risk markers. However, not all growth-restricted pregnancies result in SGA. In the Manchester BabyGRO study, we focussed on pregnancies at risk of SFG with most babies born AGA, and using transcriptomic and metabolomic data we have identified pathways related to higher child systolic blood pressure (SBP). We aim to use these datasets to define a functionally-related network associated with fetal and child growth that predict higher childhood SBP.

Methods: RNA sequencing (for transcriptomics) and nuclear magnetic resonance (for metabolomics) were performed on fasted blood samples from 25 children, aged three-to-seven years with greater SFG-risk identified in fetal life. Δfetal ([birthweight centile minus 23-week estimated fetal weight centile]/days) and Δchild ([weight centile minus birthweight centile]/years) were calculated. Using rank regression, all genes and then all metabolites were regressed against Δfetal and then Δchild. We used all detected genes and metabolites to form a hypergraph, allowing investigation of complex relationships between all elements. The hypergraph central clusters for Δfetal and Δchild analyses represent subsets of significant genes and metabolites sharing the most correlations, and indicating likely functional relationships. Random forest classification (RFC), was used to establish whether these central clusters could predict the highest quartile of childhood SBP, calculating out of bag (OOB) area under the curve (AUC) and error rate. Gene set enrichment analysis (GSEA) was undertaken using EnrichR.

Results: For Δfetal, the central cluster contained 159 genes and one metabolite, glucose. RFC showed that these predicted the upper quartile of childhood SBP with an OOB AUC of 0.993 and error rate 8.6%. For Δchild, the central cluster contained 180 genes and no metabolites. These predicted the upper quartile of

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childhood SBP with OOB AUC 1.000 and error rate 2.9%. GSEA for Δchild highlighted integrin family cell surface interactions (p=0.002), integrin-mediated cell adhesion (p=0.013), interleukin-2 signalling and vascular wall cell surface interactions (both p=0.010) of central importance.

Conclusion: A functional network predominantly based on genes related to fetal and child growth predicts higher child SBP. This approach has causally implicated integrins, known to regulate endothelial phenotype and facilitate leucocyte homing, as potential mediators linking early growth to childhood BP. The metabolome was not strongly associated, reflecting a need to investigate samples from other tissues and/or select a more sensitive metabolomic technique.

RFC4.2

Molecular genetic diagnosis in children with Idiopathic Short Stature: Single Center Experience

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Introduction: Idiopathic short stature(ISS) refers to children who are short because there is no identifiable defect in the growth hormone (GH)/insulin-like growth factor(IGF) axis and no other endocrine or genetic disorders. The genetic etiology of ISS in children was investigated in this study using targeted next-generation sequencing(NGS).

Method: Eighty patients with short stature of unknown etiology were included in the study. Variants in 23 genes associated with ISS were screened with a panel of targeted NGS.

Results: Aclinical variant was detected in 46% of the patients (Group 1); of these, 6 (7.5%) pathogenic, 12(15%) likelypathogenic, and 19(24.0%) variants of uncertain significance (VUS), and 54%(Group 2) no variant detected. At the time of admission, height SDS of group 1 (-3.1±0.9) was lower than that of group 2 (-2.5±0.66) (p:0.004). While the rate of growth hormone use was76% in group 1, it was 64% in group 2. In addition, the first-year height SDS of group 1 after growth hormone treatment was -2, 7(-3.1/-2), group 2 -2 (-2.48/-1.5) (p:0.01). The final heightS DS of group1 was-2.25(-2.9/-2.1), while it was -1.7 (-2.1/-1) lower than that of group2(p:0, 04). In the first year after treatment, IGF-1SDS was1.56(0.4/4) higher in group1 and0.64(-0.8/1.8) higher than group2 (p:0.018). Characteristics of variants classified as likely pathogenic/pathogenic are summarized in Table1.

Conclusion: TargetedNGS panels can be used successfully to brighten the genetic cause in patients with idiopathic short stature. In patients with mild and heterogeneous clinical findings,the treatment andfollow-up of the cases can be managed more accurately with NGS panels and genetic diagnosis.

Table1. Characteristics of Likely Pathogenic or Pathogenic Variants

Gene	Variant	Zygosity	ACGM	Clinic
FGFR3	c.1620C>A	Het	Pathogenic	Hypochondroplasia
IFT57	c.569T>C	Hom	Likely Pathogenic	Orofasiodigital Syndrome Type8
ANKRD11	c.1372C>T	Het	Pathogenic	KBG Syndrome
COL2A1	c.2356-3C>G	Het	Likely Pathogenic	Spondyloepiphyseal Dysplasia Congenita
TRPV4	c.838G>A	Het	Pathogenic	Spondylometaphyseal Dysplasia, Kozlowski Type
CSGALNACT1	c.1151C>G	Hom	Likely Pathogenic	Mild Skeletal Dysplasia,Joint Looseness,Advanced Bone Age Syndrome
GYS2	c.1451G>C	Hom	Pathogenic	Glycogen Storage Type0
HMGA2	c.30delG	Het	Likely Pathogenic	Silver Russell Syndrome
GHR	c.674A>G	Het	Likely Pathogenic	GH Resistance Tip2
AIRD2	c.5371_5372del	Het	Likely Pathogenic	Coffin Siris Syndrome
PCNT	c.8326C>T	Het	Pathogenic	Microcephalic Osteodysplastic Primordial Dwarfism Type2
GLI2	c.3799C>G	Het	Likely Pathogenic	Culler Jones Syndrome
FGFR2	c.24+2T>G	Het	Likely Pathogenic	Apert Syndrome
ACAN	c.7122C>A	Het	Likely Pathogenic	Advanced Bone Age,Early Osteoarthrosis,Osteochondrosis Syndrome
PROKR2	c.254G>A	Het	Likely Pathogenic	Pituitary Insufficiency
FBN1	c.5351A>G	Het	Likely Pathogenic	Acromicric Dysplasia
FGFR3	c.445+2_445+5del	Het	Likely Pathogenic	Hypochondroplasia
OBSL1	c.1273dupA	Hom	Pathogenic	3M Syndrome

RFC4.3

Aromatase inhibitors: an effective and safe option for height increment in boys with growth hormone deficiency?

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Background: Aromatase inhibitors (AIs) have been suggested to slow down estrogen-dependent skeletal maturation in pubertal boys with short stature. In the literature, few studies evaluate the efficacy and safety of AIs in boys with growth hormone deficiency (GHD).

Objective: To evaluate the auxologic effects and short-term laboratory profiles of combined AI and rhGH therapy in adolescent males with GHD.

Subjects and Methods: Male subjects between the ages of 10 and 16 with GHD from two different centers were included in the study. Patients were divided into two groups: (i) those who only used recombinant human growth hormone (rhGH) therapy for at least 1 year (Group I; G-I) and (ii) those who also used AI therapy (1 mg/day anastrozole or 2.5 mg/day letrozole) along with rhGH for at least 1 year (Group II; G-II).

Results: Forty-one patients (G-I, 46%; G-II, 54%) were included in the study. All of the subjects had isolated idiopathic GHD. At the beginning of the treatment, the chronological ages (CAs) of the patients in the G-I and G-II groups were 11.8 (10.9–13.7) and 12.8 (12.0–14.3) years, respectively. The ratios of bone age (BA)/CA for the two groups were 0.8 (0.8–0.9) and 1.0 (0.9–1.1), respectively ($p<0.001$). The daily dose of rhGH was similar in both groups ($p=0.08$). After the treatment, the median height SD scores of patients in the G-I group increased from -2.6 [(-3.4)-(-2.0)] to -1.8 [-2.1-(-1.3)], while subjects in the G-II group showed an increment from -1.7 [(-2.1)-(-1.1)] to -1.2 [(-1.6)-(-0.8)]. The post-therapy predicted adult height (PAH) significantly increased from baseline in all subjects in the G-I and G-II groups ($p<0.001$; $p<0.001$, respectively). There was no significant change in the ratio of BA/CA post-therapy in the G-I group ($p=0.1$), while there was a small but significant decrease in the G-II group ($p<0.001$). The growth velocities of the patients in the G-I and G-II groups were 9.1 (7.4–10.1) cm/year [1.5 (0.8–5.0) SD score] and 8.7 (7.5–9.9) cm/year [1.1 (0.3–3.1) SD score], respectively ($p=0.6$). While post-therapy serum testosterone concentrations were seen to increase in the G-II group, none of the patients exhibited hematocrit above 50 percent, and the fasting glucose concentrations were normal.

Conclusions: AIs were observed to promote growth potential despite the advanced BA and puberty. AIs could be used as an additional therapy for pubertal boys with GHD.

RFC4.4

Genetic findings in short Turkish children born to consanguineous parents

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Objective: To describe clinical, laboratory and genetic characteristics of 42 short children from 34 consanguineous Turkish families.

Design: Descriptive case series.

Methods: After collecting clinical information, DNA samples were analysed in three European laboratories. In 18 children (12 families) suspected of a genetic defect in the growth hormone (GH)-insulin-like growth factor I (IGF-I) axis (Group 1), a candidate gene approach was performed. In groups 2 (severe microcephalic short stature), 3 (syndromic short stature) and 4 (GH deficiency) an hypothesis-free approach was used (microarray analysis, NGS-based targeted gene panels and whole exome sequencing).

Results: In Group 1, genetic defects were identified in all 12 families: *GH1* (n=1), *GHR* (n=5), *STAT5B* (n=1) and *IGFALS* (n=5). In group 2, genetic defects were detected in 9 out of 10 families. Homozygous *PCNT* mutations (3 novel) were found in five children with MOPD2 from four families. An identical homozygous *SMARCAL1* mutation was found in two children from two families who were not aware of any family connection (but live in the same city) (Schimke immune-osseous dysplasia). One child was homozygous for a novel *WDR4* mutation, consistent with a recently described type of primordial dwarfism. One patient carried a heterozygous *de novo* variant in *SRCAP* (Floating Harbor syndrome) and another was heterozygous for a maternal *GHSR* variant. In nine families in group 3 (syndromic short stature), five genetic defects were identified. One child carried two 17p13.3 microdeletions, containing *YWHAE* and *CRK* but not *PAFAH1B1*. One child was homozygous for a *TTC37* variant (Trichohepatoenteric syndrome 1); two siblings were homozygous for a novel *SCUBE3* mutation; one child was homozygous for a novel *RAB-GAP1* mutation; and one patient had a novel *de novo* heterozygous *NSD2* variant (Rauch-Steindl syndrome). In three children with partial GH deficiency no genetic cause was found. Most genetic defects were homozygous (21/26), one was compound heterozygous and four were heterozygous. Thirteen variants were novel.

Conclusions: For children with consanguineous parents presenting with severe GH deficiency or insensitivity, a candidate approach was successful in all cases. In those with severe microcephalic short stature and other forms of syndromic short stature, the diagnostic yield was 90% and 56%, respectively. In contrast, no genetic cause could be detected in children with partial GH deficiency. In short children suspected for an abnormality of the GH-IGF-I axis or non-isolated short stature, with a family history of consanguinity, genetic testing leads to a high diagnostic yield.

RFC4.5

Real-world safety and effectiveness of vosoritide: Results from an early access program in France

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Introduction: Achondroplasia is the most common skeletal dysplasia, in which the main clinical feature is short stature. Vosoritide, the first specific treatment for achondroplasia; administered as a daily subcutaneous injection, was approved by the European Medicines Agency in August 2021 for patients aged ≥2 years until closure of epiphyses. French Health Authorities granted early access to vosoritide treatment in France on 24 June 2021, which continued until commercialization on 13 December 2022. We report the experience of early access to vosoritide during this period led by six referral centers for constitutional bone diseases (MOC) in France.

Methods: In September 2021, early access to vosoritide was initiated in patients aged ≥5 years with open epiphyses. The national center of MOC network (Necker hospital) and five referral centers evaluated patients for treatment. Patients and families received treatment education and were followed-up at month 1, 3, 6 and every 6 months thereafter. Baseline characteristics, data on treatment compliance, safety and efficacy (height, Z-score using CDC reference population) were collected.

Results: A total of 62 patients were enrolled, of which 57 were able to start early access treatment with vosoritide by Dec 2022. The mean age at treatment initiation was 8.6 years (min-max: 5-13 years) and 52% were male.

The mean exposure to treatment was 277 days (range 32 - 443 days). Among 22 patients (39%) who completed 12 months of treatment, males (n=10) showed a mean (SD) height increase from baseline of 5.8 (1.7) cm with a Z-score improvement of 0.3 (0.28); females (n =12) showed a mean increase of 6.5 (1.3) cm and a Z-score improvement of 0.4 (0.37). After 6 months of treatment (n=36) the mean (SD) annualized growth velocity (AGV) was 5.9 (1.65) cm/year in males (n=20) and 6.5 (2.64) cm/year in females (n=16).

In total, 21 adverse events were reported during the study period. All events were mild and the majority were injection site reactions and vomiting. No serious adverse events were reported. Forty-three missed doses were reported by 14 patients and no patients discontinued vosoritide treatment.

Conclusions: These data from 57 children with achondroplasia who were treated for up to 14.5 months (443 days), indicate that vosoritide under real-world conditions has a safety and effectiveness profile consistent with vosoritide clinical trials. Long term data collection for these patients will continue where possible through the EU Voxzogo Post-Authorisation Safety Study (PASS).

RFC4.6

Results from the PROPEL 2 dose-finding study: oral infigratinib leads to significant increases in height velocity with good tolerability in children with achondroplasia

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Background: Achondroplasia (ACH), the most common short-limbed skeletal dysplasia, is characterized by impaired endochondral ossification resulting from gain-of-function pathogenic variants in the fibroblast growth factor receptor 3 (FGFR3) gene, a negative regulator of endochondral bone growth. People with ACH are at risk for several significant co-morbidities, including brainstem compression due to foramen magnum stenosis, sleep-disordered breathing, chronic otitis media with conductive hearing loss, and symptomatic spinal stenosis. Infigratinib is an oral, selective FGFR1–3 tyrosine kinase inhibitor being investigated for treating children with ACH.

Methods: PROPEL 2 (NCT04265651) is a phase 2 dose-finding, open-label study of infigratinib in children 3–11 years with ACH who participated for ≥6 months in PROPEL (NCT04035811), a non-interventional clinical assessment study. The PROPEL 2 dose-escalation (DE) phase includes 5 ascending dose cohorts ranging from 0.016 mg/kg/day to 0.25 mg/kg/day. Primary endpoints: safety; change from baseline in annualized height velocity (AHV); infigratinib pharmacokinetics.

Results: Children enrolled in PROPEL 2 DE completed ≥6 months of treatment at the assigned dose. Cohorts 1–3 (n=37; 0.016, 0.032, 0.064 mg/kg/day) did not show a significant increase in AHV and these doses were assessed as non-efficacious. Treatment at the cohort 4 dose (0.128 mg/kg/day) resulted in an increase in AHV from baseline of 1.52 cm/year in children ≥5 years old (n=11; p=0.02). Infigratinib at the cohort 5 dose (0.25 mg/kg/day, n=10, month 6) resulted in a significant mean increase from baseline of 3.03 cm/year (p=0.0022). In cohort 5, collagen X marker, a biomarker of endochondrial ossification, showed a median increase of 28% from baseline at month 6 (n=6). Infigratinib was well tolerated with no serious AEs or AEs leading to study discontinuation, with most AEs mild/moderate in severity. At the cohort 5 dose, no grade 3 AEs or treatment-related AEs were reported.

Conclusion: Oral infigratinib in children with ACH, up to 0.25 mg/kg/day, was well tolerated and showed dose-dependent increases in AHV, with a significant mean change from baseline of +3.03 cm/year at the cohort 5 dose. The safety and efficacy of this oral, once-daily dose of infigratinib (0.25 mg/kg/day) will be further explored in a phase 3 randomized controlled study. If these phase 2 data are confirmed, infigratinib could potentially offer children with ACH the first safe and effective oral therapy to improve growth, enhance functionality and decrease medical complications.

Diabetes and insulin 1

RFC5.1

Tear proteomics profile in children and adolescents with type 1 diabetes mellitus

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Background and Purpose: Previous studies have shown differences in serum, plasma, or saliva proteomics profile in patients with type 1 diabetes mellitus (T1DM), compared with healthy controls. The purpose of this prospective study is to identify the tear proteomics profile in children with T1DM that are followed at the

Diabetes Center of the First Department of Pediatrics of the National and Kapodistrian University of Athens, at "Aghia Sophia" Children's Hospital.

Materials and Methods: Fifty-six children and adolescents with T1DM, with a mean age of 11,5 years, without comorbidities and at least one year after T1DM diagnosis, and fifty-six healthy age- and gender- matched children and adolescents, were enrolled in the study. Tear sampling was performed with Schirmer strips and proteins were isolated from 111 tear samples (one was excluded because of no protein detection). Sample preparation was performed using the SP3 protocol and the tryptic peptides were analyzed by LC-MS/MS using high performance liquid chromatography coupled with a Q Exactive HF-X mass spectrometer for the identification and quantification of the tear protein content. The softwares Perseus and Metascape were used for statistics and bioinformatics analyses.

Results: 3302 proteins were identified from all tear samples. Children and adolescents with T1DM showed higher concentrations of immunoglobulins and complement factors and lower expression of proteins S100A8 and S100A9, compared with the control group. Within the T1DM group, differences in protein expression were observed depending on the level of glycemic control. Finally, markers of exosomes were identified in all tear samples.

Conclusions: Tear proteomics profile of children and adolescents with T1DM reveals increased immune response and inflammation processes, even twelve months following T1DM diagnosis compared with the control group. A more exaggerated inflammatory pattern is observed in children with T1DM and bad glycemic control, compared to children with T1DM and good glycemic control. Consequently, tear proteomics could provide biomarkers for early detection of long-term complications in patients with T1DM.

RFC5.2

Comparison of Optical Coherence Tomography Angiography Findings in Children with Type 1 Diabetes Mellitus and Autoimmune Thyroiditis with Healthy Children

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Aim: The study aimed to assess the development of early diabetic retinopathy (DR), one of the microvascular complications, in patients with isolated type 1 diabetes mellitus (DM) (group 1), type 1 DM with a diagnosis of autoimmune thyroiditis (AT) (group 2), and healthy controls (group 3), which were matched for age, sex, number, and body mass index for comparison.

Methods: In this prospective and observational study, group 1 (aged 10–20 years with type 1 DM) and group 2 were followed up for at least 5 years and developed no clinical DR yet. Healthy volunteers were also included. Optical coherence tomography angiography (OCTA) was used to evaluate the foveal avascular zone (FAZ) and parafoveal vascular density (PVD) for the development of early DR among the groups. Patients' OCTA findings were compared with those of healthy volunteers. Obtained data were analyzed using IBM SPSS Statistics for Windows, version 25.0.

Results: The average FAZ and PVD showed a significant difference among the three groups ($p = 0.016$, $p = 0.006$). The mean FAZ was higher in groups 1 and 2 than in group 3 ($p = 0.013$, $p = 0.119$). The mean PVD was lower in groups 1 and 2 than in group 3 ($p = 0.059$, $p = 0.007$). No significant difference was found between group 1 and group 2 in terms of the mean FAZ and PVD ($p = 0.832$, $p = 0.653$). A significant correlation was found between the glycated hemoglobin (HbA1c) level and FAZ and PVD (FAZ; $r = 0.57$ $p < 0.001$, PVD; $r = –0.29$ $p = 0.005$).

Conclusion: In patients with type 1 DM who did not develop clinical DR, OCTA detected an increase in FAZ, which was associated with HbA1c levels. The mean PVD was significantly lower in the group with coexisting AT and type 1 DM than in the control group. These results suggest that coexistence of autoimmune thyroiditis and type 1 DM may contribute to the development of microvascular complications. Thus, studies with larger patient series are required.

This study is underreview process in Journal of Clinical Research in Pediatric Endocrinology.

RFC5.3

3 Screen ICA ELISA–A new tool to identify pre-clinical diabetes in first-degree relatives of patients with type 1 diabetes (pre-d1abetes study)

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Introduction: Overt clinical symptoms of type 1 diabetes (T1D) are often preceded by a pre-clinical stage of varying duration.

Diagnosis of the pre-clinical stage is difficult and is based on the presence of specific islet autoantibodies in the subject's blood.

Objectives: Apparently healthy first-degree relatives of patients with T1D were tested using the 3 Screen ICAELISA (RSR Ltd) for combined testing for autoantibodies to GAD65 (glutamic acid decarboxylase, 65 kDa isoform), ZnT8 (zinc transporter 8), and the islet antigen IA-2. A 3 Screen positives were subsequently tested for individual auto anti bodies. Potentially, approximately 70% of individuals with two or more types of diabetes associated auto anti bodies (including insulin auto anti bodies; IAA) will need insulin treatment over the next 10 years.

Methods: A total of 1227 subjects (age 1–18 years) were recruited from clinical Centers from Białystok (n = 237), Rzeszow (n = 80), Poznan (n = 74), Warsaw IP-CZD (n = 147), Warsaw WUM (n = 42), Opole (n = 106), Wrocław (n = 90), Gdansk (n= 55), Łódź (n= 165), Katowice (n= 46), Krakow (n= 14), Szczecin (n = 20), Bydgoszcz (n = 73), Lublin (n = 42). Serum samples collected by the coordinating clinics were tested by 3-Screen at FIRS Laboratories, RSR Ltd (Cardiff, UK). A 3 Screen positive serum samples were also assayed by GAD65 Ab ELISA, IA-2 Ab ELISA, ZnT8 Ab ELISA and the Insulin Ab RIA (www.rsrltd.com).

Results: Out of 1227 samples n = 105 (8.5%) were 3 Screen positive. Testing in individual autoantibody assays identified 70 children (5.7%) with multiple auto anti bodies who were diagnosed with pre-clinical diabetes. These children were followed-up with a normal glucose tolerance test and glycated hemoglobin determinations.

Conclusions: Early detection of islet autoantibodies by 3 Screen identifies pre-clinical T1D preceding development of carbohydrate abnormalities. This open sup opportunities for the therapeutic interventions in innovative clinical programs. Patient follow up with early education and multidirectional diabetes care should prevent occurrence of ketoacidosis associated with severe clinical manifestations.

RFC5.4

Effect of probiotic on glycemic control in children with type 1 diabetes: A randomized controlled trial

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Background: Studies in animal models and humans with type 1 diabetes mellitus (T1DM) have shown that probiotic supplementation leads to decreased proinflammatory cytokines (responsible for damaging β-cells of the pancreas), improved gut barrier function, and induction of immune tolerance.

Objective: To study the effect of supplementation of probiotics in children with T1DM on glycemic control, insulin total daily dose (TDD) and lipid profile.

Subjects and Methods: A single-centered, double-blinded, and randomized controlled trial was conducted in children (2–12 years) with T1DM (mean diabetes duration: 4.91 ± 2.11 years). Ninety children (45 in each group) were randomized and allocated to control or intervention groups. The intervention group received oral probiotics containing lactobacillus acidophilus La-14 (108 CFU) 0.5 mg once daily for 3 months. Both groups were followed-up for 6 months with assessment of HbA1c, mean blood glucose (MBG), insulin TDD, and lipid profile.

Results: Both groups were well-matched regarding baseline clinical characteristics and laboratory parameters ($p > 0.05$). At 3 months following the intervention, there was a significant decline in MBG (170 vs. 187 mg/dl; p=0.05), and insulin TDD (1.1 vs. 1.4 U/kg/day; p= 0.04). However, there was no significant change in HbA1c % (9.8 vs. 10.2 %; p = 0.2). At 6 months following the intervention, we found a significant decrease in MBG (145 vs. 192 mg/dl; p=0.003), HbA1c % (8 vs. 10.5 %; p=0.002) and a significant decline in insulin TDD (0.9 vs. 1.3 U/kg/day; p= 0.006) in the intervention group when compared with the control group. Serum triglycerides, total cholesterol, and LDL were significantly decreased in the probiotics group than control group (121 vs. 188, 213 vs 318, 113 vs. 149 mg/dl; p=0.001, respectively). Serum HDL was significantly increased in the probiotics group (76 vs. 43 mg/dl; p=0.001).

Conclusion: Probiotics supplementation improved blood glucose levels, glycemic control, and lipid profile. Thus, probiotics could be an effective adjuvant therapy in children with T1DM. However, more studies with an extended intervention period are warranted to assess probiotics' sustained effect over time.

RFC5.5

Syndrome of hypoglycemia unawareness in children with type 1 diabetes: clinical contribution of Clark and Gold questionnaire

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Introduction: For diagnosis of syndrome of hypoglycemia unawareness is used Clarke and/or Gold questionnaire. Frequency of this syndrome in children with type 1 diabetes (T1D) and its association with parameters of metabolic control including the CGM data are not well characterised.

Aims and Methods: The aim of our study was to find the prevalence of this syndrome in children with T1D (age 8-19 years) followed at our department. The positivity of Clarke and/or Gold questionnaire is established at the score ≥4. We assessed the association of Clarke/Gold positivity to CGM parameters obtained from 14 days: TIR, TBR and TAR. Further associations were made to the HbA1c, average CGM glucose (AG), standard deviation (SD) and coefficient of variation (CV). The statistic analyses were made with Kruskal-Wallis and chi-square tests.

Results: 203 children with T1D (52% male) filled out the Clarke and Gold questionnaires. Mean age at that time was 13,5±(11,3-5,6) years, diabetes duration 6,2±(3,5-8,5) years. 70% of children used insulin pumps and 30% insulin pens. Mean time of sensor use was 92,0±(89,0-95,0)%. Mean TIR was 76,0±(69,0-83,0)%, TBR 4,0±(2,0-7,0)% (TBR1 3,0±(1,0-5,0)%, TBR2 1,0±(0,0-2,0)%), TAR 18,0±(11,0-27,0)%. Mean HbA1c was 49,5±(44,0-56,0) mmol/mol, TDD of insulin 0,8±(0,7-0,9) IU/kg/day, BMI

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20,3±(18,0-23,0) kg/m2, AG 7,65±(7,0-8,38) mmol/l, SD 2,8±(2,3-3,2) mmol/l and CV 35,5±(31,2-39,8) %.

From the total of 203 children 54 (27%) have positive Clarke and 51 (25%) Gold score. Both questionnaires were positive for 25 (12%) of children. In the last year 4/203 (2%) children suffered severe hypoglycemia with unconsciousness, all of them had positive Clarke score and 2 had positive Gold score.

Clarke positive patients were significantly longer time in TBR1 than Clarke negative ones (4% vs. 3%, p=0,049). Other assessed parameters were not significantly associated with the Clarke positivity including the HbA1c levels (48 mmol/mol vs. 50 mmol/mol, p=0,35). No significant correlation to assessed parameters was found within the Gold positive group.

Conclusions: Children with T1D diagnosed by Clarke score with syndrome of hypoglycemia unawareness spent longer time bellow range level 1 however, they did not differ in other parameters of glycemic compensation. Based on this, clinical contribution of the questionnaire might be lower than in adult population but it may help to identify patients in the risk of severe hypoglycemia.

RFC5.6

Do females with Type 1 Diabetes have puberty earlier?

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Background: In the past, the majority of the pacients with Type 1 Diabetes (DM1) had late puberty due to hipogonadotropic hipogonadism as a result of insulin deficiency. However, the use of intensive insulin therapy nowadays, results in higher BMI what can lead to an earlier puberty. Insulin administered subcutaneously is not processed by the liver, which implies increased exposure to this hormone in the ovary leading to greater activation of theca and granulosa cells.

Our purpose is to evaluate if puberty is earlier in females with DM1 as respect to females without DM1.

Methods: The study population included are 100 girls with DM1 born between 1997 and 2007 followed up in the Paediatric Endocrinology unit of a single tertiary health care centre.

We analyzed the auxological characteristics, insulin dose, HbA1c at diagnosis, start of breast bud and menarche and compared them with girls without DM1 (data extracted from the literature). We also compared girls with diagnosis before and after the start of breast bud.

Data analysis is conducted using SPSS Software, version 20.0. Results are presented as mean (standard deviation) and correlation analyses performed using the Pearson and ANOVA tests

Results: Mean age at diagnosis is 7,28 years (3,6). At the moment of diagnosis 13,7% of the females are overweight and 3,2% obese. Overweight and Obese females decreased to 6,3% and 1,3% respectively at the moment of Tanner 2. (p< 0,001) During menarquie levels of overweight increased to 12,8% although obesity was maintained 1% in this stage (p=0,054)

Tanner 2 stage begins at 10,66 years (1,1), not earlier than compared with the Spanish population without DM1 (10,4 years). No cases were found of precocious puberty.

A moderate correlation exists (R=0,4) between BMI and earlier Tanner 2 (p<0,001). No significant relation was found with the dose of insulin, duration of the illness and HbA1c.

Menarche occurs at 12,74 years (1,11), at a similar age than in Spanish population (12,6 years). It exists a minor correlation (R=0,03; p<0,05) between higher BMI and earlier menarquie, also seen in DM1 females with a diagnosis after the Tanner 2. No differences between diagnosis before and after Tanner 2 were found.

1-The single variable determinant of early puberty in girls with DM1 is a high BMI.

2-Weight control in girls with DM1 is determinant for puberty control. Since our population does not have high BMI, early puberty is not observed, on the contrary to data from literature.

Pituitary, neuroendocrinology and puberty 1

RFC6.1

Clinical application of LH cut-off value in the diagnosis of CPP according to the international consensus

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Keywords Central precocious puberty; Luteinizing hormone; Precocious puberty

Gonadotropin-releasing hormone agnosit test

Background: 2019 International consensus on central precocious puberty (CPP) proposed that random serum luteinizing hormone (LH) ≥0.83IU/L and < 0.2IU/L has important reference value for the establishment or exclusion of CPP, but there is no corresponding diagnostic criteria in China. This study aims to verify the cut-off value by comparing the differences in basic LH level between children with CPP or premature thelarche (PT).

Method: All of the study subjects were selected from hospitalized children with precocious puberty who visited the Children's Hospital affiliated to Zhengzhou University from 2020 to 2022, who were diagnosed by GnRH stimulation test and clinical manifestations. The clinical manifestations, laboratory data and imaging results of the subiects were retrospectively analyzed. LH peak ≥5IU/L and LH peak /FSH peak ≥0.6 in GnRH stimulation test is viewed as the gold standard to the diagnosis of CPP, comparing the cut-off values of serum LH basal value 0.83 IU/L and 0.2IU/L to analyze the diagnostic accuracy of serum LH basal value in the diagnosis of CPP.

Results: The study subjects include 203 girls with CPP and 149 girls with PT. Basal LH, FSH, LH/FSH and E2 in CPP group were higher than those in PT group, with statistical significance (P<0.05).

There was a correlation between basal LH and LH peak after GnRH stimulation test and LH peak /FSH peak (P<0.05). When LH was 0.83IU/L, the sensitivity and specificity were 43.8% and 100%. When LH was 0.20 IU/L, the sensitivity was 87.7% and the specificity was 55.5%. When the cut-off value was 0.83IU/L, the breast Tanner stage, bone age, the difference between bone age and actual age, and pituitary height of CPP children with LH level ≥0.83IU/L were significantly higher than those of CPP children with LH level＜0.83IU/L (P<0.05).

Conclusion: When using chemiluminescence method to detect gonadal hormones in children with progressive precocious puberty, CPP can be diagnosed when the serum basal LH≥0.83IU/L combined with clinical, without GnRH stimulation test. LH≤0.2IU/L cannot be used as an exclusion criterion for CPP, and GnRH stimulation test should be selected according to clinical characteristics to assist in diagnosis.

RFC6.2

Psychosocial Evaluation of Girls with Rapidly Progressive Puberty Presenting with Early Menarche

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Keywords: *early puberty, mood change, GnRH analogue*

Introduction-Aim: In cases with early puberty, neuroendocrine, physical, and psychological changes are considered to result in several mood disorders. The aim of this research was to assess the mental problems of pubertal girls with rapidly progressive puberty (RPP) with menarche before the 10 years of age. To the best of our knowledge, there is no similar prospective cross-sectional research in the medical literature.

Method: In this prospective study, females with RPP (breast developmental Tanner stage ≥ 3 and basal LH value >0.3 IU/L) who presented with menarche under the age of 10 years were included in Group I. The control group (Group II) consisted of prepubertal girls aged 9 to 10 years. All cases were evaluated concurrently at the Department of Child and Adolescent Mental Health and Diseases. Cases with a previous diagnosis of mood disorder or psychiatric treatment for any reason or chronic diseases were excluded. All subjects underwent relevant psychiatric tests: 1) Affective Disorders and Schizophrenia Form-Now And Lifelong Form DSM-5- Turkish version (CDSG-PL-DSM-5-T), 2) Screen for Child Anxiety Related Disorders (SCARED), 3) Child Behavior Checklist (CBCL/6-18), and 4) the revised form of a Depression Rating Scale for children (CDRS-R).

Results: A total of 49 girls (Group I, n=28; Group II, n=21) were included in the study. Height, weight, and BMI SDS values were significantly higher in Group I (p<0,01) while target height was similar among groups. Predicted adult height was higher than target height in Group I. Mood disorder was detected in four cases: Group I (n=2, 7%, social phobia-depression/adjustment disorder with depressive symptoms) and Group II (n=2, 9.0%, childhood depression). There was no significant difference between the two groups in terms of the total and sub-group scores obtained from anxiety, behavior, and depression assessment criteria.

Conclusion: There was no significant difference in the prevalence of mood disorders between the early menarche and control groups. GnRH analogue therapy should not be based on the assumption that premature pubertal development will cause psychosocial effects and should only be considered after a thorough psychiatric evaluation.

RFC6.3

Exposure to Per- and Polyfluoroalkyl Substances and Pubertal Assessment by Ultrasound in Norwegian Boys and Girls: Data from the Bergen Growth Study 2

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Background and Aim: Per- and polyfluoroalkyl substances (PFAS) are a group of synthetic chemicals found in everyday consumer products. These chemicals are considered endocrine disruptive. However, their effect on pubertal onset and development is still unclear. The aim of the current study was therefore to explore the relationship between PFAS exposure and pubertal development using novel objective pubertal phenotyping, e.g., ultrasound-determined testicular volume and ultrasound-based breast staging collected in the Bergen Growth Study 2 (BGS2).

Material and Methods: BGS2, conducted in 2016, was the first Norwegian pubertal reference study. Pubertal status was assessed with Tanner staging and ultrasound measurements in a cross-sectional sample of 301 boys and 200 girls (8-16 years). In addition, serum samples were analyzed for 19 different PFAS. Testicular volume-for-age z-scores were calculated for boys, and girls were classified as early (n=32), average (n=106), or late maturing (n=62) based on ultrasound-measured breast development-for-age percentiles. To examine the associations between PFAS levels and age-adjusted degree of pubertal development, linear regression and logistic regression analysis were applied in boys and girls, respectively, and adjusted for age, height and educational level of parents.

Results: Perfluorooctanoic acid (PFOA), perfluorononaoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluorohexanesulfonic acid (PFHxS) and perfluorooctanesulfonic acid (PFOS) were included in the analyzes as all had more than 90% of the samples above the limit of quantification. Boys with higher levels of PFNA (estimated beta coefficient (β), -0.14, 95% confidence interval [CI], -0.62 to 0.03) and PFOS (β, -0.17, 95%CI, -0.19 to -0.01) were more likely to be late maturing. In girls, higher levels of PFOA were associated with a reduced odds of being early compared to average and late maturing (OR: 0.13, 95%CI: 0.02, 0.89), and higher levels of PFNA was associated with an increased odds of being late compared to early and average maturing (OR: 3.14, 95%CI: 1.17, 8.43). No other associations were significant at a 0.05 level.

Conclusions: Higher levels of PFAS were associated with being late maturing in both sexes based on age-adjusted ultrasound puberty scores.

RFC6.4

Earlier Occurrence of Puberty and Pubertal Hair Development in Boys and Girls - Insights from the DPV Initiative Data

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Introduction: Pubertal onset is signaled by thelarche (in girls) and gonadarche (in boys) and indicates the beginning of the hypothalamic-pituitary-gonadal axis activity. Thus, the onset of pubic hair development usually coincides with adrenarche. Girls worldwide are experiencing earlier puberty, but it is uncertain if this trend affects boys, or if it applies to children with type 1 diabetes (T1D).

Aim: The aim of this study is to analyze puberty onset and pubertal hair development in adolescents with T1D from a large, multicenter (German/Austrian/Swiss/Luxemburg) diabetes registry spanning 2000 to 2021.

Methods: The mean age of thelarche (♀), gonadarche (♂), and pubarche (all sexes) among adolescents with T1D was analyzed. Linear regression models were used and adjusted for diabetes duration, BMI, HbA1C, and migratory background. The results are presented in 5-year intervals (mean) for the periods ≤2005 and >2015.

Results: The onset of puberty has shifted forward over the last two decades in both girls and boys, according to the analyzed data from 20,064 children. The mean age for the onset of puberty in girls decreased from 11.46 years to 11.06 years, and in boys from 12.41 years to 12.19 years. Additionally, an annual advance of thelarche by 0.26 years or 3.17 months per decade in girls and an annual advance of gonadarche by 0.15 years or 1.78 months per decade in boys was observed.

The study also found that children with overweight (BMI SDS ≥ 90th percentile) had a significantly earlier onset of puberty than those with normal weight or underweight. An HbA1C value of ≤ 7.5% was associated with a significantly earlier onset of puberty in both sexes than a value of >7.5% to <8.5% or ≥ 8.5%.

The mean age at documentation of Tanner P2 for girls decreased from 11.47 years in 2000 to 10.97 years in 2021, with a change of -0.0227/ year or a decrease of 2.72 months/ decade. For boys, the mean age at documentation of Tanner P2 decreased from 12.06 years in 2000 to 11.57 years in 2021, with a change of -0.0222/ year or a decrease of 2.67 months/ decade.

Discussion/ Conclusion: In summary, this study provides the first evidence of a decline in pubertal age in young male adolescents, consistent with the known and demonstrated age regression of pubertal onset in girls. Moreover, the development of pubertal hair shows a similar pattern in both sexes. These results highlight pubertal complexity and indicate further research needed

RFC6.5

Efficacy and security of gonadotropin treatment in adolescents with congenital hypogonadotropic hypogonadism

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Objective: To describe efficacy and security of treatment protocol with gonadotropins in adolescents with hypogonadotropic hypogonadism (HH).

Methods: Prospective study of patients with HH who received hGH and rhFSH in puberty.

HH diagnosed during first months of life or in adolescence (testicular volume<4cc in >16 year-old with FSH<1.2UI/L, testosterone <40ng/dL and GnRH-test with LH-peak<6UI/L)

Treatment Protocol:

First phase: rFSH 75IU/twice-weekly during 2-4 months.

Second phase*: rFSH 75-150IU/twice-weekly + hCG 250IU/twice-weekly during 6-12 months.

Third phase*: rFSH 150IU/thrice-weekly + hCG at increasing doses (500IU/thrice-weekly during 6-12 months, 1000IU/thrice-weekly during 6 months, 1500IU/thrice-weekly during 6 months, adult doses 1500-2500IU).

*hCG and rhFSH doses adjusted according to testosterone and inhibin-B levels respectively.

***Efficacy*:**

- Testicular volume(TV): mean of both testicles(mL)
- Testosterone and inhibin-B levels.
- Spermiogarm in phase 3 (OMS2010).
- Adult height (AH) Z-score and Δadult-height-mean parental height (MillennialsGrowth2018).

***Security*:** Blood count, biochemistry and hormonal analysis performed periodically. BMD at onset and end.

Results: 6 patients described in Table1.

Patients 1 and 4 began pubertal induction with intramuscular testosterone and afterwards, received gonadotropin treatment. The rest, started and completed pubertal induction with gonadotropins presenting normal pubertal development.

Conclusions:

- Gonadotropin treatment is secure for pubertal induction.
- Testicular volume was increased, although limitedly in severe forms.
- Spermatogenic response was scant/null in congenital forms with cryptorchidism (except in one patient).
- Clinical parameters (onset and severity of gonadotropin deficiency) may predict treatment response.
- Low sample-number limits this study; further research is needed.

Table1. Parameters in patients that underwent treatment with rhFSH-HCG

Patient	Etiology (age at diagnosis)	Age at onset(years)	Basal TV (mL) mean*	Basal InhibinB (pg/mL)	Basal testosterone (ng/dL)	Duration (years)	Final TV (mL) mean*	Final InhibinB (pg/mL)	AH (cm)	Z-score ΔH-mean parental H	Spermiogram Nº performance, count and mobility
1	Acquired Idiopathic intracranial hypertension (15 years)	16.6	4.5	23.8	<10	3.6	20	188	172	+0.12	3rd: 100x10E6/mL, 24% progressively mobile, 2% normal
2	Congenital panhypopituitarism (Neonatal)	12.7	2 (inguinal)	25	<7	4.4	7 (scrotal)	105	167	0.6	1st: Azoospermia
3	Kallmann (Neonatal)	14.7	2	20	18	3.4	7	112	146	0.4	1st, 2nd: Azoospermia
4	Acquired Craneofaringioma (14 years)	17.3	3	58	<10	0.8	8	143	185	0	Without result
5	Congenital panhypopituitarism (Neonatal)	14.9	2	31.2	<7	4	7	77	175	1.4	1st: azoospermia 2nd: 0.34x10E6/mL, 83% no-mobility
6	Kallmann (Neonatal)	12.1	1.5 (inguinal)	20.7	39	5.5	9	104	161.6	-0.4	1º: 1.06 X10E6/mL 37% mobile, 14% progressively mobile 63% immobile

*Prader-orchidometer

RFC6.6

Evaluation of Serum MKRN3 and DLK1 Concentrations for Predicting Variant Detection in MKRN3 and DLK1Genes in Patients with Central Precocious Puberty

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Introduction: Loss-of-function mutations in genomically imprinted MKRN3 and DLK1 genes cause familial central precocious puberty (CPP) and may result in low serum concentrations of these proteins. This study aimed to evaluate the predictive value of serum MKRN3 and DLK1 concentrations for detecting variants in related genes.

Material-Method: This retrospective study included 26 girls with CPP, of which 11 were receiving GnRH analog(a) therapy (Group-1), while the others had not yet been treated (Group-2). The control group consisted of 26 healthy girls. The serum concentrations of MKRN3 and DLK1 were measured by ELISA, and MKRN3 and DLK1 genes were performed by Sanger sequence. Statistical analysis was performed using the Jamovi package program (version 2.3).

Results: In Group-1, the median (IQR) age was 7.6(1.1) years, with height and BMI-SDS of +1.4 (1.5) and +0.8 (0.7), respectively. In Group-2, the median age was 7.9 (0.7) years, with height and BMI-SDS of +1.6 (1.1) and +0.4(1.4), respectively. In the control group, the median age was 7.1(1.4) years, with height and BMI-SDS of 0.7(1.4) and -0.01(1.9), respectively. In Group-1, a known pathogenic c.482dupC/p.(Ala162Glyfs*15) variant in the MKRN3 gene was detected in one patient, whose serum MKRN3 concentration was 0.127 ng/mL. The median MKRN3 and DLK1 serum concentrations of patients other than the case with the variant detected in Group-1 were 1.32 (0.7) ng/mL and 0.62 (0.4) ng/mL, respectively. In Group-2, these concentrations were 1.2 (0.6) ng/mL and 0.62 (0.2) ng/mL, respectively. There was no statistically significant difference in serum concentrations between Group-1 and Group-2 (p=0.279;p=0.338). In the control group, mean±SD serum concentrations of MKRN3 and DLK1 were 1.31±0.5 and 0.81±0.4, respectively. When the control group was compared with the whole group, except for the case with the variant, no difference was found between the concentrations (p=0.917;p=0.674).

Conclusion: MKRN3 and DLK1 serum concentrations are not significantly different between CPP patients receiving GnRHa therapy, those not yet treated, and the control group. However, a known variant in the MKRN3 gene was detected in a patient with a significantly low serum MKRN3 concentration. This highlights the potential utility of serum concentration measurement in detecting variants in the related gene. Moreover, it is essential to note that variants in these genes can be familial, even in individuals without a family history, due to the paternal inheritance pattern, and family segregation studies should be performed.

Sex differentiation, gonads and gynaecology or sex endocrinology

RFC7.1

Penile width increases more clearly than penile length during minipuberty: a longitudinal study of 136 healthy infant boys

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Background: In minipuberty, the male hypothalamic-pituitary-gonadal (HPG) axis is transiently activated triggering a surge in reproductive hormones causing growth of the genitalia. Longitudinal individual growth of the infant penis during minipuberty and associations to the HPG axis and IGF-I have not been thoroughly assessed.

Aim: To describe the development of penile length and width as well as their relation to serum concentrations of testosterone and IGF-I during minipuberty of healthy boys.

Methods: In total, 136 boys participated in the postnatal follow up in the longitudinal, prospective The COPENHAGEN Minipuberty Study (ClinicalTrials.gov ID: NCT02784184), where stretched penile length (SPL) and penile width (PW) were measured in 118 boys. All boys were examined up to six times during the first year of life including serum sampling. In total the 118 boys underwent n=606 clinical examinations. Testosterone was measured by liquid chromatography-tandem mass spectrometry (LC/MS-MS), IGF-I was measured using chemiluminescence immunoassay. Wilcoxon signed rank test was used to assess the development of penis size throughout minipuberty. Spearman's rank correlation coefficient (r) was used to assess the correlation of penile width and length in relation to hormone levels.

Results: SPL increased significantly from 0 to 2.5 months of age (median (IQR) 32 (29-36) mm to 35 (31-38) mm, p=0.01), followed by a period up to 6 months of age, where SPL declined to 33 (29-36) mm, p<0.01. Hereafter, a more stable length was maintained until 1 year of age. PW increased more clearly from 0 to approximately 6 months of age; median (IQR) 11.2 (10.5-12.3) mm to 13.3 (12.1-14.2) mm, p<0.01, followed by more stable levels until 1 year of age, 12.9 (12.0-13.9) mm, p=0.54.

The SPL/body weight ratio was positively correlated with circulating levels of testosterone and IGF-I; r=0.7 and 0.6, respectively, both p<0.01. Likewise, the PW/body weight ratio was positively correlated with testosterone and IGF-I, r=0.8 and 0.7, respectively, both p<0.01.

Conclusion: In this longitudinal study of healthy infant boys, penile width increased more clearly than penile length during minipuberty. Both penile length and width were positively correlated with circulating levels of testosterone as well as IGF-I. We speculate that penile width rather than penile length may be a valuable tool as predictor of hypogonadism in boys with micropenis.

RFC7.2

International Evidence-Based Guidelines for PCOS 2023: Recommendations in Adolescent Girls

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Objective: The original consensus-based Rotterdam criteria, now evidence-based criteria, is recommended for the diagnosis of PCOS in adult women. These criteria state that PCOS can be diagnosed when two of three major criteria (anovulatory cycles, clinical/biochemical hyperandrogenism, and polycystic ovary morphology or elevated AMH levels) are present and other potential etiologies have been excluded. Use of these criteria in adolescent girls is problematic because adolescent girls commonly experience irregular menses, acne, and multi-follicular ovaries. Using best practice guideline methods, rigorous updated comprehensive evidence-based guidelines for diagnosis, assessment and treatment for adolescent women with polycystic ovary syndrome (PCOS) were developed.

Methods: Governance involved an international advisory board, project board and five guideline development groups with 52 members representing 36 organisations across 6 continents. Health professionals and patients/consumers performed extensive meta-analyses and evidence synthesis of 55 prioritised clinical questions. This process involved best practice evidence-based guideline development and extensive evidence synthesis following review of available clinical studies. The GRADE framework covered evidence quality, feasibility, acceptability, cost, implementation and ultimately recommendation strength.

Results: This process generated evidence-based and consensus recommendations with clinical practice points. For adolescent girls who are >2 years post-menarche, PCOS can be diagnosed based on ovulatory dysfunction and clinical/biochemical hyperandrogenism following exclusion of other disorders. Girls with symptoms typical of PCOS who do not meet criteria can be considered as "at risk for PCOS". Pelvic ultrasound is not recommended until 8 years post-menarche for PCOS diagnosis. Due to poor specificity, AMH levels are not recommended in adolescence. Health professionals and patients should address viable treatment options and management of psychological and physical PCOS features using a shared decision-making approach.

Conclusions: A lifelong health plan is recommended focusing on overall health, prevention of weight gain, and weight management. Weight bias and stigma should be minimized, and healthcare professionals should seek permission to weigh women with explanation of weight related risks. Combined oral contraceptive pills are first line pharmacological treatment for menstrual irregularity and hyperandrogenism, with no specific recommended preparation, and a preference for lower dose preparations and those with fewer side-effects. Metformin is recommended primarily for metabolic features. No specific diet or physical activity regimen has benefits over others in PCOS. Overall evidence in PCOS is low to moderate quality. Based on high prevalence and significant health impact, greater priority for funding and research in PCOS alongside education for health professionals and those affected by PCOS is urged.

RFC7.3

Histone code, cryptorchidism,infertility

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Introduction: Multiple studies have demonstrated that histone lysine methyltransferases regulate gene transcription, thereby influencing cell proliferation, cell differentiation, cell migration, and tissue invasion.

Aim of the Study: Here we describe the key functions of histone lysine methyltransferases and chromatin remodeling genes and summarize their role in infertility.

Patients and Methods: The patients, biopsy samples, histological analyses, and RNA sequencing protocol were described in detail in the previous study.(1) Here, we interpreted the gene expression patterns observed in different prepubertal testicular cell types using our own RNA profiling data. Cryptorchid boys with defective mini-puberty and impaired differentiation of Ad spermatogonia (High Infertility Risk) compared to patients with intact differentiation of gonocytes into Ad spermatogonia (Low Infertility Risk).

Results: HIR samples have altered expression of several genes encoding histone methyltransferases and together with the diminished expression of histone deacetylases and increased expression of HDAC8 decrotonylase, indicating altered histone marks and, thus, a perturbed histone code. Curative GnRHa treatment induces normalization of histone methyltransferase, chromatin

Table 1. Gene expression profiles in testicular cells before and after GnRHa treatment. RNA-Seq data are indicated for biopsies from high/low infertility risk patients before (-) and after (+) GnRH treatment. RNA levels (reads per kilobase and million, RPKM), log2 fold changes (log2FC), and false discovery rates (FDRs) are given. n.s., not significant.

Gene symbol	-/+ GnRHa treatment (RPKM)	log2FC/FDR
Class 1		
KDM6A	19.9/11.3	-0.81/0.0009
TET1	11.9/7.1	-0.73/0.002
Class 2		
ARID4A	12.5/9	-0.48/0.03
ARID5B	21.6/15.3	-0.49/0.03
ATRX	33.7/19.3	-0.79/0.002
DNMT3A	24.6/19.86	n.s.
EPC1	23.0/14.1	-0.7/0.002
HDAC1	22.2/12.7	-0.80/0.0008
HDAC2	15.5/9.7	-0.67/0.004
HDAC3	22.2/16.2	-0.45/0.045
HDAC8	7.7/5.7	-0.48/0.052
INO80D	12.1/7.9	-0.60/0.01
KDM4A	27.6/20.3	-0.44/0.052
KMT2E	35.8/24.2	-0.56/0.02
PBRM1	27.2/16.6	-0.7/0.004
PRMT2	27.5/16.9	-0.69/0.004
SETD7	22.3/12.3	-0.85/0.0006
SMARCA1	96.2/52.6	-0.87/0.0004
SMARCA2	37.3/24.0	-0.87/0.0009
TSPYL4	12.4/9.2	-0.43/0.054
Class 3		
ARID2	19.3/11.6	-0.72/0.003
ASH1L	43.3/36.8	-0.62/0.01
BAZ2B	47.0/27.6	-0.76/0.003
SCML2	26.3/14.5	-0.85/0.0005
SETD2	40.0/24.5	-0.7/0.005
TRDMT1	4.89/3.5	-0.45/0.048

remodeling, and histone deacetylase gene expression. (Table 1) If lncRNAs can cooperate with chromatin-modifying enzymes to promote epigenetic regulation of genes, GnRHa treatment may act as a surrogate for mini-puberty by triggering the differentiation of Ad spermatogonia via lncRNA-mediated epigenetic effects. Our observations indicate that Linc00261, FENDRR, HOTAIR, and FOXA1 participate in the alternate pathway for curative GnRHa treatment to rescue impaired fertility.

Conclusions: Our findings suggest that epigenetic mechanisms are critical to better understanding the root causes underlying male infertility related to cryptorchidism and its possible transgenerational transmission.

RFC7.4

Serum steroid metabolome dynamics during infancy: a prospective, longitudinal cohort of healthy boys

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Background: The circulating steroid metabolome in boys undergoes significant changes during infancy reflecting functional and structural rearrangements of the adrenal glands as well as the transient activity of the hypothalamic–pituitary–gonadal axis, also called minipuberty. Studies investigating the serum steroid metabolome dynamics during infancy in a longitudinal manner are however sparse.

Objective: We aimed to explore the dynamics of the serum steroid metabolome in healthy, term male infants and establish male-specific reference curves for steroid hormones in infancy.

Participants & Methods: In a prospective, longitudinal cohort (The COPENHAGEN Minipuberty Study, 2016-2018) we followed healthy, term, newborns from birth onwards with repeated clinical examinations including blood sampling during a one-year follow-up. Serum levels of 16 steroid hormones were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Age-specific reference values (Standard deviation scores, SDS) were modelled using GAMLSS. Correlations were analyzed using the Spearman rank correlation method.

Results: The steroid metabolome exhibited a distinct pattern with increasing Cortisol and Corticosterone levels as well as sharply decreasing 11-deoxycortisol, Androstenedione, 17-OHP and Progesterone levels. The majority of steroid hormones decreased to <50% of their maximum value within three months of age. Testosterone concentrations peaked around 1-2 months after birth. Mean steroid hormone SDS exhibited predominantly positive and partially strong correlations during the first year of life, e.g. 17-OHP vs. 11-deoxycortisol (rs = 0.7) and 17-OHP vs. Androstenedione (rs = 0.6). However, correlations exhibited marked alterations over time, e.g. Corticosterone vs. 17-OHP (0-60 days: rs = 0.0; 180-400 days: rs = 0.7) or DHEAS vs. Androstenedione (0-60 days: rs = 0.6; 180-400 days: rs = 0.2).

Conclusions: Our findings provide a detailed description of the serum steroid metabolome dynamics. In addition, changes in ratio between individual steroids may provide insights in changes in steroidogenic enzyme activity during the first year of life. The detailed age-specific reference ranges can be used in clinical settings like diagnosis and monitoring of treatment of rare steroidogenic disorders.

RFC7.5

Sex differences in endocrine mechanisms during early human fetal brain development

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Introduction: The influence of sex chromosomes and sex hormones on early human brain development is still poorly understood. Expression of Y chromosome genes may influence aspects of brain maturation in the 46,XY fetus, but the contribution of different Y genes is unknown. Furthermore, a marked increase in testicular testosterone biosynthesis/release from the testis occurs at around 8 weeks post conception (wpc) in the 46,XY fetus, but it is unclear whether testosterone gets converted to dihydrotestosterone in the brain, and when/where androgen receptors (AR) are expressed.

Aims: We aimed to study global sex differences in gene expression and components of the androgen pathway in early human fetal brain cortex development.

Methods: Two independent datasets of fetal brain cortex samples were used (Brain-Seq1 and Brain-Seq2), each having a total of four 46,XY and four 46,XX samples at specific time points of development: CS22-23 (7.5-8wpc), 9wpc, 11-12wpc, 15-17wpc (32 samples in each dataset; total n=64). Total RNA was extracted and bulk RNA-sequencing was carried out in Brain-Seq1. RNA-sequencing data for Brain-Seq2 was obtained from the Human Developmental Biology Resource. Principle components analysis (PCA) and differential gene expression analysis were undertaken in R using the DESeq2 bioinformatic package. Matched control tissue analysis determined brain specificity. Public repositories of brain single-cell RNA-sequencing data were also analysed.

Results: PCA showed a major contribution of karyotype to PC2 (19-20%). By overlaying differential gene expression patterns (46,XY versus 46,XX) across stages in both datasets, we identified a “core” group of 18 differentially expressed Y chromosome genes in the developing 46,XY brain. Of these, *PCDH11Y* - a gene unique to humans - showed high brain specificity, and is enriched in adult brain (HPA and GTEx consensus dataset). The only consistently differentially expressed genes in the 46,XX brain were *XIST* and *TSIX*, X-chromosome inactivation regulators. Analysis of global *AR* expression in telencephalon/cortex showed a stepwise decrease in both sexes across time. Minimal/no expression of *SRD5A2* was observed, although *SRD5A1* and *SRD5A3* were expressed. Analysis of single-cell repositories revealed more localised developmental *AR* expression in pituitary corticotropes and hypothalamic supramammillary nucleus during development.

Conclusion: Human fetal brain cortex gene expression patterns showed global sex differences, influenced by Y chromosome genes and X-inactivation regulators, but the biological effect at this early stage is unclear. Relative *AR* expression in the cortex decreased in both sexes across this critical time course, with localised *AR* expression emerging in key regions influencing endocrine regulation.

RFC7.6

Prenatal AnoGenital Distance (AGD) by ultrasonography in 571 fetuses and correlation to postnatal AGD: A longitudinal cohort study of healthy males and females

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Background: The anogenital distance (AGD) is a well-known measure in rodents used to distinguish male and female pubs. Likewise, AGD display sex-specific differences in humans. It is considered a postnatal readout of early androgen exposure in fetal life. Thus, in postnatal life AGD is longer in boys than in girls, reduced in infants born with cryptorchidism and hypospadias as well as in boys exposed to anti-androgenic agents in fetal life. However, little is known on the development of this sex-specific measure during human fetal and postnatal life.

Aim: The aim of this study is to describe fetal AGD in males and females, and to evaluate if fetal AGD correlates with infant AGD.

Methods: The Copenhagen Analgesic Study (COPANA) (ClinicalTrials.gov NCT04369222) is a prospective cohort study evaluating prenatal exposure of mild analgesics on gonadal function in infants. AGD was measured from the center of the anus to the posterior base of the scrotum (AGDas), and the posterior converge of the fourchette (AGDaf) in males and females, respectively. Fetal AGD was measured by transabdominal ultrasound in the axial plane at gestational week (GW) 29-34 in healthy, singleton fetuses who were subsequently born AGA. Infant AGD was subsequently measured during minipuberty (median age 3.8 months (males) and 4.2 months (females)) with TIDES method. All fetal ultrasound scans were performed by a single sonographer while 6 examiners performed the infant examinations. Three repeated measurements were assessed, and the average was used.

Results: AGD was available in 571/590 (97%) fetuses (275 males) and 588/590 (99%) infants (287 males). AGD was completely separated between sexes with male AGD significantly longer than female AGD as early as the third trimester of pregnancy continuing into infancy: fetal male AGDas median (IQR) 21.3 mm (18.9-23.5), female fetal AGDaf; 12.8 mm (11.1-14.2), p=0.001 (Mann Whitney U (MWU); male infant AGDas 31.8 mm (28.1-36.1), female infant AGDaf 15.7 mm (13.5-17.77), p=0.001. Fetal AGD adjusted for birthweight were positively correlated with AGD in infancy adjusted for body mass index for both male and females (Spearman's r=0.24 (p=0.001), and r=0.14 (p=0.021), respectively).

Conclusions: AGD is sexually dimorphic as early as GW 29 and the separation continues during infancy. We found a positive correlation between fetal and postnatal AGD in both sexes, however strongest for male infants. Future studies will unravel fetal AGD as a new marker of androgen exposure during early fetal life.

Fat, metabolism and obesity 2

RFC8.1

A novel heterozygous likely pathogenic variant in *GNB1* causing hyperphagia, severe early onset obesity and neurodevelopmental disorder

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The proband is a 12 yr old Caucasian European girl with grade 3 obesity, developmental delay and hyperphagia. She was born at term via an uncomplicated pregnancy and exhibited neonatal hypotonia, difficulty feeding, failure to thrive and delayed attenuation of milestones. At the age of 2 years she started developing hyperphagia and rapid excessive weight gain. Molecular analysis for Prader Willi syndrome and array CGH were negative. At the age of 10 yrs she was diagnosed with autoimmune hypothyroidism and was started on L-T4 replacement therapy. First menstrual period was at the age of 11 yrs however on ultrasound imaging ovarian size is small despite normal pubertal uterine size. She developed insulin resistance and was started on metformin for one year, recently transitioned to daily GLP-1 analog. She exhibits dysmorphic features, mild intellectual delay, autism spectrum disorder and depressive symptoms. Family history is unremarkable for other similarly affected individuals.

WES performed by 3billion, Seoul, South Korea, revealed a novel heterozygous likely pathogenic variant in *GNB1 (*NM_002074.5:c.93_94del,p.Gln32AspfsTer46). This is a frameshift mutation predicted to result in a loss or disruption of normal protein function through nonsense-mediated decay (NMD) or protein truncation. This variant is not observed in the gnomAD_v2.1.1 dataset.

GNB-1 is associated with autosomal dominant 'Intellectual developmental disorder, autosomal dominant 42 (OMIM: 616973)'. It encodes a subunit of a heterotrimeric G-protein complex that transduces intracellular signaling cascades. Disruptions to the gene have previously been shown to be embryonic lethal in knockout mice and to cause complex neurodevelopmental disorders in humans. Recently two patients with novel LoF variants in *GNB1* and neurodevelopmental phenotypes including intellectual disability, hypotonia, psychiatric symptoms and obesity were described.

We propose that *GNB-1* could be considered a candidate gene associated with severe early onset obesity, hyperphagia and neurodevelopmental delay. Functional analysis of our proband's mutation can provide additional insights on how perturbation in heterotrimeric G protein function contributes to the phenotype of the disease.

RFC8.2

Acute rise of leptin after five days of dexamethasone and its association with hunger, fat mass, sleep and fatigue, in children with acute lymphoblastic leukemia

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Background & Aims: Children with acute lymphoblastic leukemia (ALL) frequently receive high doses dexamethasone during treatment, which may induce acute side effects. The aims of the current study were to determine the influence of a five-day dexamethasone course on changes in leptin, fat mass, body mass index (BMI), hunger, sleep and fatigue and to explore the associations between these changes.

Methods: Pediatric ALL patients were included during maintenance treatment. Data was collected before (T1) and after (T2) a five-day dexamethasone course (6mg/m^2/day). BMI, fat mass (bioelectrical impedance analysis) and leptin were assessed on both timepoints, as well as parent-reported questionnaires regarding hunger, fatigue and sleep problems. Changes after five days of dexamethasone (T2 versus T1) were assessed using paired tests. Correlation coefficients were calculated to assess associations between the changes during a dexamethasone course (Delta scores: T2-T1). Univariable regression analyses were used to explore possible contributing factors for high leptin on T1 (defined by a Z-score >1,5).

Results: We included 105 children with a median age of 5.4 years (range 3.0-18.8). Leptin and fat mass, as well as hunger scores, fatigue and sleep deteriorated significantly after five days of dexamethasone (p<0.001), in contrast to BMI (p=0.12). No significant correlations between delta leptin and delta fat mass, BMI, hunger, fatigue or sleep were found. Elevated leptin on T1 was associated with older age (odds ratio (OR) 1.51, 95%-confidence interval (95%-CI) 1.28-1.77), higher fat mass (OR 1.19, 95%-CI 1.07-1.33) and earlier maintenance week (OR 0.96, 95%-CI 0.92-0.99).

Conclusions: Five days of high dose dexamethasone treatment lead to direct and significant changes in leptin, hunger scores and fat mass, which may suggest a dexamethasone-induced state of acute leptin resistance. Since children with ALL are at increased risk for metabolic adverse events, it is important to understand the underlying mechanisms, and leptin resistance might play a role.

RFC8.3

Higher levels of serum α-Klotho are longitudinally associated with less visceral fat accumulation in apparently healthy girls experiencing weight gain

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Introduction: Klotho is an anti-aging protein that reduces adiposity and increases caloric expenditure, among others. Although associations between secreted α-Klotho levels and obesity have been described, its relationship with central obesity and visceral fat accumulation during childhood is poorly understood. Our objective was to study the longitudinal associations between serum α-Klotho concentrations and obesity parameters in apparently healthy children.

Subjects and Methods: We studied a cohort of 208 apparently healthy school-age children (107 girls and 101 boys) assessed at baseline (mean age 8.5 ± 1.8 years) and at follow-up 4 years later. Serum α-Klotho concentrations were measured at baseline in all subjects. Obesity parameters, such as BMI, waist circumference, body fat mass, visceral fat mass, triglyceride levels, HOMA-IR index, and C-reactive protein were studied. Boys and girls were classified into 3 groups based on weight gain between baseline and follow-up visits (BMI increase greater than 0.35 SD, no BMI change, or BMI decrease greater than 0.35 SD).

Results: In girls (N=107), we observed negative associations of serum α-Klotho protein with BMI, waist circumference, body fat mass, visceral fat mass, HOMA IR index, and C-reactive protein at baseline and also at follow-up, which were not observed in boys. In the subgroup analysis, negative associations of α-Klotho and obesity parameters were more evident in girls who exhibited weight gain [increase in BMI greater than 0.35 SD]. In such girls, multivariate regression analyses (adjusting for age and baseline weight/height ratio) showed that α-Klotho protein was negatively associated at follow-up with BMI, waist circumference, and visceral fat mass (p=0.03 to 0.003). For each 1 SD-increase in baseline α-Klotho, follow-up waist circumference decreased by 4.15 cm and visceral fat mass by 1.38 mm.

Conclusions: In school-age girls, serum α-Klotho concentrations are longitudinally related to a more favorable metabolic profile. In girls experiencing weight gain, α-Klotho may prove to be a protective factor against the accumulation of visceral fat.

RFC8.4

Understanding the genetics of early onset obesity in a cohort of children from Qatar

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Context: Monogenic obesity (MO) is a rare form of obesity due to pathogenic variants in genes implicated in the leptin-melanocortin signaling pathway and accounts for around 5% of severe early-onset obesity. Mutations in the *MC4R* and Leptin genes are the commonest causes of MO. Determining the genetic causes has important clinical benefits as novel therapeutic interventions were developed for some forms of MO.

Objective: This study aimed to unravel and understand the epidemiology and genetic causes of early onset childhood obesity in the population of Qatar.

Methods: 324 patients with early-onset obesity below 10 years with a BMI percentile above the 95th percentile were enrolled. All the coding regions and exon-intron boundaries of 52 genes associated with obesity were sequenced using a targeted gene panel. To analyze, classify and interpret the pathogenicity of the variants identified, several in silico prediction tools were used.

Results: Thirty-one potentially disease-causing variants were identified in 36 probands (14.8%) in 15 candidate genes (*LEP, LEPR, POMC, MC3R, MRAP2, SH2B1, BDNF, NTRK2, DYRK1B, SIM1, GNAS, PPARG, ADCY3 and RAI1, and BBS2*). Twenty-four of the variants were novel, and the rest, seven variants, were previously reported in literature. Variants in the MC4R gene were the most common in our cohort, and the variant c.485C>T p.T162I in this gene was the most frequent variant seen in five unrelated Qatari probands. Moreover, the

majority of the probands carried either variants of uncertain clinical significance (56.4%) or no variants (28.8%) in the 52 genes included in the gene panel.

Conclusion: This study represents the largest MO cohort in this understudied Middle Eastern population which identified variants that seem to explain the phenotype in 14.8% of the cohort. Variants in the MC4R gene seem to be the commonest cause of MO in this population. Early diagnosis potentially improves obesity management and early interventions and helps to identify patients who may benefit from the emerging personalized therapeutic interventions for MO.

RFC8.5

Effects of leptin knockdown on a human preadipocyte model

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Obesity presents a major worldwide challenge, due to its numerous, severe adverse effects on health. This leads to a necessity to further investigate the mechanisms underlying lipid accumulation. The adipocytokine leptin may contribute to this process. While there already has been thorough research into central leptin action, deepening our understanding of leptin's effects on whole-body energy homeostasis, relatively little is known about its auto- and paracrine effects. Ingrained in the larger effort of understanding the pathomechanisms underlying obesity and lipid accumulation, the aim of this study is to further elucidate possible auto- and paracrine functions of leptin on human adipocyte progenitor cells.

Our group identified a somatic leptin variant (c.250C>A) present in a spontaneous lipoma of a lean male person. Computer modeling predicted a reduced leptin - leptin receptor interaction and potential destabilization of the protein for this genetic variant. This suggests that this variant is likely pathogenic and may play a role in the increased lipid accumulation in lipoma. To simulate this potential loss of function of leptin we successfully performed leptin knockdown using siRNA in a LipPD1 cell model.

Differentiation was studied by staining lipids with fluorescent Nile-Red dye and Oil Red O staining. Implications of leptin knockdown on adipogenesis marker expression were analyzed using qPCR. Proliferation was assessed by fluorescent Hoechst and proliferation marker Ki-67 staining. Effects on lipolysis were examined by measuring basal glycerol in the culture medium of LipPD1 cells, which were differentiated into adipocytes. The experiments were conducted at least three times independently.

Leptin knockdown resulted in a reduction in the accumulation of lipid droplets, evidenced by an approximately 0.8 fold decrease in Nile Red and 0.7 fold decrease in Oil Red O staining, compared to the control group. This was accompanied by a decreased expression of the adipogenesis markers adiponectin, fatty acid synthase (FASN) and proliferator-activated receptor γ (PPARγ). Furthermore, leptin knockdown led to an 1.1 fold increase in cell number, compared to the control group, after 7 days of incubation.

Collectively, our preliminary results suggest that adipogenesis is impacted by leptin deficiency. It attenuates differentiation and expression of adipogenesis markers but stimulates proliferation in LipPD1 cells.

RFC8.6

Leukocytes and Neutrophil–Lymphocyte Ratio as Indicators of decreased insulin sensitivity in NGT Overweight and Obese Children with high 1-hour post-load plasma glucose levels

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Introduction: Obese children with normal glucose tolerance (NGT) but with 1-hour post-load plasma glucose (1hPG) ≥ 132.5 mg/dl are at higher risk of developing type 2 diabetes (T2D) and cardiometabolic complications. In addition, new markers of systemic inflammation derived from blood cell count could be used as indicators of insulin resistance, thus predicting worse metabolic profile.

Objective: The aim of our study was to assess whether metabolic abnormalities documented in overweight and obese children with 1hPG ≥ 132.5 mg/dl are related to unfavourable blood cell count indexes.

Methods: Data from medical records of 247 overweight/obese children and adolescents (110/122 M/F; age: 11.1 ± 2.7 years), who had undergone an oral glucose tolerance test (OGTT), were analyzed. In the analysis only NGT children were included, thus the study population was divided into two groups according to 1hPG (low NGT Group: 1hPG < 132.5 mg/dl; high NGT Group: 1hPG ≥ 132.5 mg/dl). Anthropometric, biochemical and haematological measurements including blood cell count data were collected from the hard copy archive. Particularly, leukocyte (WBC) and platelet counts (PLT), the neutrophil-to-lymphocyte (NLR) and the monocytes-to-lymphocyte ratio (MLR) have been considered as markers of inflammation. Fasting and 2h-blood glucose and insulin values were evaluated and the indexes of insulin sensitivity (WBISI) and insulin secretion and beta-cell function (Insulinogenic Index-IGI, Disposition Index) were calculated during the OGTT.

Results: Of the 247 records analyzed, 232 fulfilled criteria for NGT and had complete biochemical data. Among NGT patients, 66 (28.4%) showed 1hPG ≥ 132.5 mg/dL (high-NGT), while 166 (71,6%) had 1hPG < 132.5 mg/dL (low-NGT). The two groups were similar for gender, pubertal stage and age. No significant difference for anthropometric parameters (weight SDS, Heigth SDS, BMI SDS, SBP SDS, DBP SDS) was documented. The group of high-NGT showed a WBC, PLT and NLR values significantly higher compared with the low-NGT group (P<0.001, P=0.03 and P=0.03, respectively). The high-NGT group also showed a significant lower WBISI, IGI and DI as well as increased glucose excursions during OGTT compared with the low-NGT group. On the other hand, no significant differences in terms of fasting insulin were documented between the two groups. In addition, DI correlated significantly with WBC and PLT values in the entire population.

Conclusions: Increased WBC and PLT values and a higher NLR are documented in overweight and obese NGT youth with a 1hPG ≥ 132.5 mg/dL are related to impaired glucose metabolism and insulin sensitivity.

Diabetes and insulin 2

RFC9.1

The association of dietary glycemic index and load with insulin sensitivity and secretion from early childhood to late adolescence: the QUALITY cohort

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Introduction: With the increasing prevalence of obesity, prediabetes and type 2 diabetes (T2D) in youth are on the rise. Prevention is paramount for these multifactorial diseases. Dietary interventions targeting a reduction of dietary glycemic index (GI) and glycemic load (GL) are potential strategies for improving insulin resistance. However, the association between GI and GL and T2D risk in children remains uncertain.

Objectives: To investigate cross-sectional and prospective associations between dietary GI and GL among children recruited at 8-10 y and insulin dynamics, from childhood to late adolescence.

Methods: We used data from the QUébec Adipose and Lifestyle Investigation in Youth (QUALITY) Cohort, an ongoing study of 630 Caucasian children with a parental history of obesity in Québec (Canada). Children were evaluated at three timepoints: baseline (8-10y, n=630), first follow-up (10-12y, n=564) and second follow-up (15-17y, n=377). Dietary habits were evaluated using three non-consecutive 24h-dietary recalls (including one weekend day) at baseline. Daily average GI was calculated using the International Table of GI Values; GL was obtained by multiplying GI by the available carbohydrate content in each food. Insulin sensitivity was measured using the Matsuda Insulin Sensitivity Index. Insulin secretion was calculated as the ratio of the area under the curve of insulin to glucose over 30 min (1st phase) and 120 min (2nd phase) during an oral glucose tolerance test. Multivariable linear regression models were adjusted for baseline age, sex, pubertal status, body mass index z-score, physical activity (accelerometry), screen time (questionnaire), the Diet Quality Index-International, and an indicator variable capturing participant underreporting of food intake (based on the Goldberg equation for energy requirements). Sensitivity analyses included associations stratified by weight status.

Results: At baseline, 46% of participants were girls, 78% were prepubertal and 43% had overweight/obesity. A one unit increase in GL at baseline was associated cross-sectionally with 0.28% lower insulin sensitivity (95% CI -0.50% to -0.06%) and 0.14% higher 2nd phase insulin secretion (95% CI 0.01% to 0.28%). We observed no meaningful associations between GI/GL at baseline and insulin sensitivity or insulin secretion at 10-12y nor at 15-17y. Among children with overweight/obesity, those with higher GI at baseline had a 2.1% higher 2nd phase insulin secretion at 10-12 yrs (95% CI -0.26% to 4.5%), albeit not reaching statistical significance.

Conclusion: Although lower GI and GL diets were associated with slightly better insulin dynamics in cross-sectional analyses, these results were not observed longitudinally.

RFC9.2

Two new candidate genes, *OGDH* and *FGFR1* discovered in an insulinoma from a fifteen-year-old male

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The present study aimed to determine the mutational and molecular landscape of a 17 mm insulinoma from a fifteen-year-old male. Using targeted exome sequencing and microarray, we investigated somatic candidates in the insulinoma. The microarray analysis was conducted using 12 other insulinomas as a control group and revealed a total of 1907 differentially expressed genes (p-value < 0.05, FDR p-value < 0.05). After thorough gene variant filtering, we identified two putative candidate genes: OGDH and FGFR1. Both variations were detected as missense variants, located in highly conserved regions, and predicted to be damaging by five different prediction tools.

OGDH encodes a pivotal subunit of the 2-oxoglutarate dehydrogenase complex, which is an enzyme in the citric acid cycle catalyzing the conversion of 2-oxoglutarate (α-ketoglutarate) to succinyl-CoA and CO2. Interestingly, the enzyme also has a nuclear function in complex with KAT2A, where the enzyme activity is crucial for the succinylation of H3K79, and dysregulation is observed in several cancer types. We identified a missense variant (variant allele frequency: 0.10) located in the active site of the enzyme (Ser458Pro). The alteration diminishes two hydrogen bonds, thus probably affecting the stability of the protein structure. The potentially compromised structure affects the enzyme reaction, leading to an accumulation of the substrate α-ketoglutarate. This may induce the reductive citric acid cycle, which stimulates insulin secretion via NADPH-mediated insulin exocytosis.

The second candidate gene FGFR1 encodes the fibroblast growth factor receptor 1, responsible for e.g. survival and proliferation. The insulinoma contained a variant (Glu692Lys, variant allele frequency: 0.11) in the tyrosine kinase domain and identical variants have been detected earlier in analogous residues in the growth factor receptors FGFR4 (residue Glu681Lys) and ERBB2 (residue Glu914Lys) in lung adenocarcinoma and glioblastoma, respectively. Additionally, our microarray analysis indicated that the gene expression of FGFR1 was increased by 3.85 fold (p-value: 0.0023, FDR p-value: 0.0305). A direct association between FGFR1 activity and the pancreatic transcription factor PDX1 has been proposed, and the latter plays a crucial role in the establishment, functionality and maturity of beta cells. The activation of FGFR1 induces the gene expression of PDX1, which works as a transcriptional activator of insulin and somatostatin amongst others. Consistently, the gene expression of SST, which encodes somatostatin, was increased 1494 fold compared to the other 12 insulinomas analyzed using microarray.

These findings reveal two new insulinoma candidate genes with functional roles associated with regulation of insulin secretion.

RFC9.3

Impaired Insulin Secretion as a Pathophysiology Underlying Abnormal Glucose Metabolism in Pediatric Acute Lymphoblastic Leukemia (ALL) Survivors: A Study Comparing Glucose Metabolism between ALL Survivors and Simple Obese Children

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Background: Pediatric acute lymphoblastic leukemia survivors (pALL-S) carry a risk for developing metabolic abnormalities,

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including obesity, abnormal glucose metabolism (AGM) and dyslipidemia. Previous studies showed conflicting data regarding the pathophysiology of AGM in those survivors. Additionally, there has never been a study comparing glucose metabolism between pALL-S and simple obese children (Ob-C). This study aimed to assess glucose metabolism in pALL-S in comparison with Ob-C.

Methods: pALL-S and age-matched Ob-C were enrolled. All of them underwent oral glucose tolerance test (OGTT) and body composition analysis. Data of Ob-C were derived from our previous study. Abnormal OGTT results i.e. AGM were defined as hyperinsulinemia, impaired fasting glycemia, impaired glucose tolerance or diabetes mellitus. Insulin sensitivity and secretion indices were calculated from the serum glucose and insulin levels derived from the OGTT. Comparisons of these parameters between pALL-S and Ob-C were performed.

Results: There were 91 pALL-S and 100 Ob-C included. Twenty-seven (30%) out of 91 pALL-S were overweight or obese. Median (IQR) ages of pALL-S and Ob-C were 14.8 (12.4, 17.1) and 14.4 (13.8, 15.4) years, respectively. Median (IQR) BMI Z-scores were 0.2 (-0.6, 1.8) and 2.7 (2.4, 3.0) in pALL-S and Ob-C groups, respectively. AGM were demonstrated in 40 (44%) of pALL-S and in 76 (76%) of Ob-C. Comparing between pALL-S and Ob-C with AGM, fat mass index (FMI) was lower in pALL-S [7.6 (5.4, 10.5) vs 13.8 (11.7, 16.1) kg/m2, p <0.001]. However, FMI of pALL-S was slightly greater than that reported in age-matched lean children of 5.4 kg/m2. As expected, Ob-C with AGM had greater insulin resistance as demonstrated by having greater homeostasis model assessment of insulin resistance [4.4 (3.5, 6.9) vs 1.9 (1.1, 2.8), p <0.001] and lower whole body insulin sensitivity index [1.6 (1.2, 2.5) vs 3.7 (2.6, 5.3), p <0.001]. Interestingly, pALL-S with AGM had lower insulin secretion index, homeostasis model assessment of beta-cell function (HOMA-β) [175 (117, 301) vs 474 (270, 808), p <0.001]. Additionally, HOMA-β of pALL-S was lower than that reported in age-matched lean children of 213. The findings indicated that impaired insulin secretion was the main pathophysiology underlying AGM in pALL-S.

Conclusions: Despite not being obese, a number of pALL-S had AGM (44%). AGM could occur in pALL-S at lower BMI and FMI as compared with Ob-C. The pathophysiology underlying AGM in pALL-S was impaired insulin secretion rather than insulin resistance which was in contrast with Ob-C.

RFC9.4

Clinical and genetic characteristics of patients suspected to have Maturity-Onset Diabetes of the Young in the Czech Republic

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Introduction: Maturity-Onset Diabetes of the Young (MODY) represents the most frequent form of monogenic diabetes. Genetic testing of Czech patients with clinical suspicion on MODY began 22 years ago. Aim of the study was to describe the prevalence of MODY subtypes among referred probands with diabetes and to define their clinical characteristics and possible differences.

Methods: Clinical criteria for genetic testing of MODY genes include age at diagnosis between 6 months and 40 years and absence of pancreatic antibodies. Supporting criteria, of which at least some must be fulfilled, are: positive family history of diabetes, detectable C-peptide several years after diagnosis and absence of metabolic syndrome. Patient's samples are referred from both paediatric and adult diabetologists from the whole Czech Republic. Main genetic method used is Sanger sequencing. Since 2018, next generation sequencing of genes linked to monogenic forms of diabetes has complemented the genetic investigation.

Results: The Czech registry of MODY consists of 1,788 families (3,539 persons) of which MODY has been genetically clarified in 1,385 patients from 686 families (38%). Glucokinase diabetes (GCK-MODY) was the prevailing MODY subtype (69%) being diagnosed in 962 subjects from 473 families. Second most prevalent MODY subtype (16%) was HNF1A-MODY detected in 111 families (233 persons). HNF4A-MODY represented the third most prevalent subtype (131 persons, 60 families, 9%). Remaining 6% (42 families, 59 patients) of confirmed MODY represented rare forms of monogenic diabetes caused by pathogenic variants in the genes *MT-TL1, HNF1B, INS, INSR, WFS1, ABCC8, KCNJ11, RFX6* and *CEL*.

Considering variations between MODY and non-MODY probands who were pharmacologically treated, statistically significant differences were observed at age at diagnoses (non-MODY vs GCK-MODY, HNF1A-MODY, rare MODY, respectively: p≤0.0078) and HbA1c (non-MODY vs GCK-MODY: p=0.0001).

Conclusion: Three subtypes of MODY strongly dominate in the Czech registry of MODY. Patients with no genetic findings in genes tested were diagnosed later and had more variable levels of HbA1c compared to persons with MODY.

	GCK-MODY	HNF1A-MODY	HNF4A-MODY	rare MODY	non-MODY*
Female/Male	266/207	72/39	36/24	21/21	580/522
Age at diagnosis in years: median (intequartile range, IQR)	12 (8-19)	15 (13-21)	20 (15-28)	15 (12-21)	24 (13-33)
HbA1c in mmol/mol (IFCC): median (IQR)	46 (43-50)	54 (46-62)	51 (43-65)	52 (44-59)	47 (39-61)
HbA1c in % (DCCT): median (IQR)	6.4 (6.1-6.7)	7.1 (6.4-7.8)	6.8 (6.1-8.1)	6.9 (6.2-7.5)	6.5 (5.7-7.7)
No treatment or diet/Pharmacological treatment	372/91	26/77	10/49	7/33	397/670

*Probands with no genetic findings in genes tested.

RFC9.5

Insulin secretion defect in children and adolescents with obesity: Clinical and molecular genetic characterization

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Introduction: Childhood obesity shows increasing numbers worldwide and presents as a global health issue due to multiple metabolic comorbidities. About 1 % of adolescents with obesity develop type 2 diabetes (T2D), however little is known about the genetic and pathophysiological background in young age. Genome-wide association studies in adults revealed genes with increased diabetes risk, most of them regulating insulin secretion.

The objective of this study was to assess the prevalence of impaired glucose regulation (IGR) in a large clinical cohort of children and adolescents with obesity and to characterize insulin sensitivity and insulin secretion using data from the oral glucose tolerance test (OGTT). We also wanted to investigate adolescents with insulin secretion disorders more closely and analysed possible candidate genes of diabetes in a subcohort.

Methods: We included children and adolescents with overweight or obesity who completed an OGTT (glucose + insulin) in outpatient clinic. We calculated Matsuda Index, the area under the curve (AUC (Ins/Glu)) and an oral Disposition Index (ISSI-2) to estimate insulin resistance and beta-cell function. We identified patients with IGR and low beta cell function (maximum insulin during OGTT <200 mU/l) and tested a subgroup using Next Generation Sequencing (NGS) to identify possible mutations in 103 candidate genes (MODY, neonatal diabetes, syndromic diabetes, T2D susceptibility genes).

Results: The total group consisted of 903 children and adolescents with overweight or obesity. 4.5 % showed impaired fasting glucose, 9.4 % impaired glucose tolerance (IGT), and 1.2 % T2D. Matsuda Index (as a surrogate parameter of insulin sensitivity) and Total AUC (Ins/Glu) (as a surrogate parameter of beta cell function) showed a hyperbolic relationship. Out of 39 patients with low beta-cell function we performed genetic testing in a subgroup of 12 patients. We found 5 monogenetic defects (ABCC8 (n=3), GCK (n=1), GLI2/PTF1A (n=1)).

Conclusion: Using surrogate parameters of beta-cell function and insulin resistance can help to identify patients with insulin secretion disorder in clinical routine. The prevalence of 40 % mutations of known diabetes genes in the subgroup with low beta-cell function suggests a minimum of about 1.7 % monogenic T2D in a cohort of adolescents with obesity. A successful molecular genetic diagnosis can help to improve the individual therapy and enables genetic consultation of the family.

RFC9.6

Wharton jelly derived mesenchymal stem cells exosomes protect pancreatic beta cells from inflamation

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Background: Type 1 diabetes is an autoimmune disease initiated by the invasion of pancreatic islets by immune cells that selectively kill the β cells. The loss of beta cells in Type I diabetes ultimately leads to insulin dependence and major complications that are difficult to manage by insulin injections. Regulation of immune response is a key strategy to control the autoimmunity in diabetic patients. Mesenchymal stem cells have been shown to have an apparent potential in modulating the immune reactions. However, treatment with stem cells is combined with concerns about safety issues. To overcome these concerns, in this study, we investigated the regenerative potential of exosomes isolated from wharton jelly derived mesenchymal stem cells(WJ-MSCs) to restore the β-cell mass and insulin secretion in type 1 diabetes.

Methods: WJ-MSCs exos were isolated, and dynamic light scattering, scanning electron microscopy, and transmission electron microscopy were used to analyze their physical properties. The MTS test and migration assay were used to investigate the effect of WJ-MSCs exosomes on cell proliferation and migration, and the quantitative polymerase chain reaction (qPCR) was done to assess regeneration of pancreatic beta cells by measuring insulin, Pdx1, Smad2, Smad3 and TGFβ genes. Additionally, immune-histochemical examinations were done to confirm beta cell regeneration.

Results: According to the results of the cell viability assay, the nontoxic concentration of WJ-MSCs Exos (100 µg/ml) was chosen for the subsequent investigations. The qPCR results indicated that WJ-MSCs exosomes significantly reduced the expression of inflammatory cytokines such as TNF-α, IL-1β, and IL-6 in beta cells. Regarding the assessed genes (insulin, Pdx1, Smad2, Smad3 and Tgfβ) gene expression in WJ-MSCs exosomes treated group showed significant increase compared to control group (p value < 0.001).

Conclusion: Our results suggest that WJ-MSCs exosomes improved β-cell function and regulate the insulin secretion. It may provide some useful insights into the future treatment modalities for antidiabetic purposes.

Fetal, neonatal endocrinology and metabolism (to include hypoglycaemia) & Multisystem endocrine disorders

RFC10.1

A novel maternally inherited *GNAS* variant in a family with hyperphagia and obesity

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Introduction: Heterozygous inactivating mutations in the maternal allele of the *GNAS* gene typically result in pseudohypoparathyroidism (PHP), characterised by developmental delay, short stature, obesity, hormone resistance and bone abnormalities. *GNAS* variants were recently described in 1% of patients in the UK Genetics of Obesity cohort, resulting in reduced MC4R signalling.

Here, we report another novel *GNAS* variant in a family with hyperphagia and obesity and only mild features of PHP.

Case: A six-year-old female presented with hyperphagia and obesity from the age of three years. BMI was 30.4 (4.1 SDS) with height +1.9 SDS, and head circumference (HC) + 3.0 SDS. She had subtle brachydactyly, short toes and a café au lait patch. Developmental milestones and cognitive achievements were mildly delayed. Her 12-year-old brother [height +2.1 SDS, weight +3.1 SDS, BMI 29.55 (2.9 SDS), HC +3.6 SDS] had been followed in an obesity clinic with hyperphagia, obesity, delayed developmental milestones and a diagnosis of autism. He also had subtle brachydactyly, as did the mother, who was obese (BMI 38.9) with normal height and cognition.

Results: In the proband, initial investigations did not suggest hormone resistance. At 8.7 years, PTH was mildly raised [9.5 pmol/L (0.7-5.6)] with normal calcium and Vitamin D; TSH 6.6 mU/L (<6), FT4 11.8 pmol/L (10.8 - 19.0) in the proband. She had hyperlipidaemia, fatty liver, and generalised mild brachydactyly with a short right fifth metacarpal on X-ray.

In the brother, biochemistry at 12.9 years showed: PTH18.4 pmol/L (1.6-6.9), normal calcium, Vitamin D and TFTs.

Next Generation Sequencing using the Cambridge Obesity gene panel detected a novel heterozygous (c.791A>C, p.(Asn264Thr) variant in exon 10 of GNAS in the proband and subsequently in the mother and brother, confirming maternal inheritance. This variant has not been reported in control databases (1000 Genomes, ESP, ExAC and gnomAD, Human Gene Mutation Database and ClinVar). The variant is in a highly conserved region susceptible to missense mutations and has been classified as pathogenic using ACMG and ACGS guidelines.

Discussion: In conclusion, we describe a novel heterozygous inactivating *GNAS* variant c.791A>C, p.Asn264Thr resulting in hyperphagia, obesity, developmental delay, macrocephaly, mild brachydactyly, tall stature and variable biochemical mild hormone resistance in two siblings and obesity, mild brachydactyly, normal height, without cognitive impairment in the mother. We recommend that screening for PHP and *GNAS* variants should be performed in patients presenting with obesity, even in the absence of classical signs of PHP.

RFC10.2

Utility of Continuous Glucose Monitoring (CGM) during pancreatic surgery in patients with Congenital Hyperinsulinism

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Introduction: Congenital Hyperinsulinism (CHI) is a rare disease of hypoglycaemia due to excess insulin production. Patients with both focal and diffuse forms of CHI may have severe hypoglycaemia not responsive to medical therapies. Such patients require lesionectomy or subtotal pancreatectomy with a corresponding necessity for enhanced glycaemic monitoring during the peri-operative period. Subcutaneous Continuous Glucose Monitoring (CGM) provides real-time high-frequency glucose readings in contrast to infrequent fingerpick blood glucose (BG) testing, although accuracy of detection of true hypoglycaemia remains circumspect. CGM has reported benefit for CHI patients in the outpatient setting but there is no data of the use and utility in patients undergoing surgery. We aimed to describe the use of CGM in one highly specialised centre through questionnaire survey of professionals and assessment of CGM accuracy in the peri-operative period.

Methods: Dexcom G6 CGM was used during pancreatic surgery for 10 patients over a 2-year period. Professional (anaesthetist, surgeon, endocrinologist, and specialist nurse) perception of CGM was assessed by 1-5 Likert scale and open questions in a questionnaire. Accuracy of CGM was tested on the Hypoglycaemia Error Grid.

Results: Seventeen professionals (5 Anaesthetists, 2 Surgeons, 7 Endocrinologists, 3 Specialist Nurses) completed questionnaires. All but one respondent found CGM very helpful or extremely helpful in the peri-operative period. A single endocrinologist was neutral on the utility of CGM in this setting due to concerns of device accuracy. Anaesthetists reported enhanced patient safety in avoiding hypo/hyperglycaemia with CGM, while surgeons commented on its use, in conjunction with histopathology, to identify successful surgery. Endocrinologists/specialist nurses highlighted that CGM reduced the frequency of fingerpicks and supported glucose reduction post-operatively.

Peri-operative CGM glucose levels were significantly higher than those normally found outside the peri-operative period (mean (SD) 11.4mmol/L (4.1) vs 6.4mmol/L (2.2)). Accuracy was comparable to the outpatient setting with mean absolute difference (MAD) of 1.4mmol/L. Due to the rarity of hypoglycaemia in

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the peri-operative setting, and the high tolerance of CGM error at hyperglycaemic levels on the Hypoglycaemia Error Grid, 98% of values were classed as clinically safe.

Conclusion: In spite of low point accuracy, the low impact of CGM error at normal/high glucose levels ensures the safety of CGM as a surgical adjunct.

Professional consensus is that CGM use in the peri-operative period has utility in the management of patients undergoing pancreatic surgery. CGM highlights surgical hyperglycaemia, prompting timely reductions in high concentration glucose infusions.

RFC10.3

Non-coding Variants in *HK1* Account for 5% of Cases of Congenital Hyperinsulinism Without an Identified Genetic Cause

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Background: The genetic etiology of non-syndromic HI remains unknown in over 20% of all cases, and over 50% of diazoxide-responsive cases. Non-coding variants in *HK1* have been suggested to cause HI by linkage-analysis (Pinney et al., 2008). More recently, variants within a regulatory region of *HK1* intron 2 were reported in 17 individuals with HI (Wakeling et al., 2022). These variants have been proposed to cause HI by disrupting normal postnatal silencing of *HK1* expression in beta-cells.

Objectives: Identify cases of HI due to non-coding variants in *HK1* in a large, single-center cohort of children with HI with genetics negative HI, describe clinical characteristics, and evaluate *HK1* expression in identified cases.

Methods: A 350bp region in intron 2 of *HK1* was sequenced in children with genetics negative HI evaluated at our center (January 1997-April 2023). In cases where *HK1* variants were identified and pancreatic specimens were available, *HK1* expression in resected pancreas tissue was evaluated by immunofluorescence (IF) and/or qPCR.

Results: Twenty-eight percent (n=309/1117) of children genotyped at our center had genetics negative HI (n=49/666, 7% diazoxide-unresponsive; n=260/451, 58% diazoxide-responsive). *HK1* intron 2 sequencing has been performed in 76% of genetics-negative cases (n=234/309). This identified 10 unique non-coding variants in intron 2 of *HK1* in 13 children (5.6%, n=13/234). The *HK1* variant was de novo in 9 cases, inherited from an asymptomatic parent in 2 cases, and inherited from an affected parent in 2 cases. Age of presentation ranged from 1 day-21 months. Five cases (38%) were diazoxide responsive. The remaining 7 cases were diazoxide unresponsive, and 5 had pancreatic surgery (3 near-total resection, 2 biopsies only) at ages 6 months-3 years. HK1 protein expression (IF) in islets of resected pancreas tissue from affected cases (n=5) was increased compared to control pancreas (n=2) and compared to surrounding acinar tissue. In RNA extracted from isolated islets (n=3), *HK1* expression appeared to be increased in one case compared to control.

Conclusion: Non-coding variants in intron 2 of *HK1* may represent over 5% of genetics negative HI cases. The clinical phenotype appears to be heterogenous, evidenced by variable age of presentation, diazoxide responsiveness, and pancreatectomy requirement. The hypothesis that these variants disrupt the normal suppression of *HK1* expression in beta-cells is supported by IF staining in resected pancreatic tissue, but was not replicated by qPCR. Work is ongoing to elucidate the underlying mechanism by which these variants may result in HI.

RFC10.4

Clinical phenotypes of a multicentric cohort of ROHHAD patients

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Background: ROHHAD syndrome (rapid-onset obesity with hypothalamic dysfunction, central hypoventilation, autonomic dysregulation) – also defined as ROHHADNET when associated with neural tumors - is a rare condition with a high mortality rate. The aim of this study is to describe the phenotypes of a multicentric cohort of ROHHAD patients.

Patients and Methods: We retrospectively analyzed clinical data from 22 patients(10M,12F) with ROHHAD syndrome, followed at four centers in Glasgow, London(UK), Turin and Genova(Italy). ROHHAD diagnosis was based on at least three criteria: early, rapid-onset obesity, central hypoventilation, neural tumor, hypothalamic/pituitary disorders, and autonomic dysfunction, after excluding other forms of syndromic obesity. Median follow-up was 7.4 years.

Results: Rapid-onset weight gain leading to early obesity was the first symptom in 20 patients (94.7%) at a median age of 3.0 years (1st-3rd quartile:2.1-3.7yrs); one patient was overweight but has not developed overt obesity as yet; in 4 patients, cardiovascular symptoms, water-electrolyte imbalance or autonomic dysfunction were present at diagnosis. Six patients (27.3%) were diagnosed with neural tumors at median age of 5.3 years (4.4-8.9yrs), with no gender difference in NET prevalence. Twenty patients (90.9%) had hyperprolactinemia – generally asymptomatic, 16(72.7%) GHD, 15(68.2%) central hypothyroidism, and 11(50.0%) central adrenal insufficiency. Median GH peak after stimulation test was 0.49ng/ml (0.27-1.32). Early puberty was observed in females only (5/22, 22.7%, P=0.04), delayed puberty in 5/7subjects (2M,3F,71.4%). 20 patients (90.9%) developed sleep-related breathing disorders (either OSAS or central hypoventilation) during follow up. Excessive sweating was present in 9patients(40.9%), temperature dysregulation in 8(36.4%), and strabismus in 8(36.4%). 4 patients (18.2%, 1M, 3F) died from respiratory complications at a median age of 13.0 years.

BMI SDS – both maximum and at latest visit – were lower in ROHHAD patients with GHD vs those without (3.7 vs 4.3 SDS,P=0.039 and 4.2 vs 6.2 SDS, P=0.007, respectively). Insulin insensitivity was more frequent in females (P=0.027).

Given the unknown aetiology of ROHHAD/ROHHADNET syndrome, we performed molecular analysis using either Whole exome-(WES) or Whole Genome-(WGS)Sequencing in 9 individuals with identification of some potential candidate genes which are currently under further investigation.

Conclusions: These data highlight that early and rapid onset of obesity and hypothalamic dysfunction, including hyperprolactinaemia, are suggestive signs and symptoms of this condition. Due to its rarity, an effort on combining ROHHAD cohorts with careful phenotypic characterization is essential to improve our understanding and to strengthen our ability to manage this life-threatening disease.

RFC10.5

Insulinoma in childhood: A multicenter retrospective study of 28 patients

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Background: Insulinomas are very rare in childhood with sparse knowledge on the clinical aspects and the presence of Multiple Endocrine Neoplasia type 1 (MEN1).

Methods: We conducted a multicentre retrospective review of patients diagnosed with insulinoma between 1995-2021. Clinical, biochemical, genetic, imaging and histological data were collected. In addition, follow-up and family data were obtained.

Results: A total of 28 children (female, n=17) aged 5-16 years were identified. The median (range) gap between the first hypoglycaemia symptoms and diagnosis was 12 (1-46) months. Thirteen children (46.4%) were misdiagnosed to have epilepsy and were treated with anticonvulsants before hypoglycemia was revealed. Contrast enhanced MRI and/or CT were accurate to localize the lesion in 78.5% (n=22). Additionally endoscopic ultrasound (n=4), 18FDOPA PET/CT (n=1) and DOTA PET/CT (n=1) were needed to visualize the tumor. Six patients (21.4%) had multiple pancreatic lesions. All children underwent surgical treatment. The median (range) diameter of removed tumors was 1.5 (0.3-6) cm. Histopathological studies confirmed the presence of insulinoma in all cases. Immunohistochemical studies revealed G2 differentiation grade in 13 out of 21 cases. One patient had G3 grade. Two patients were diagnosed with metastatic insulinoma. One of them had metastases at the time of insulinoma diagnosis, while the other was diagnosed with liver metastases eight years after the surgery. Eleven children (39%) were found to carry *MEN1* mutations (inherited n=6, de novo n=2, no data n=3). Children with MEN1 had significantly higher number of pancreatic tumors compared to sporadic cases. Ten out of 11 developed additional MEN1 symptoms during the following 2-13 years. In the six patients with inherited *MEN1*, seven family members had hitherto undiscovered MEN1 manifestations.

Conclusions: In this large cohort of children with rare pediatric insulinomas, MEN1 syndrome and G2 tumors were frequent, as well as hitherto undiscovered MEN1 manifestations in family members. Our data emphasize the need of genetic testing in all children with insulinoma and their relatives, even in the absence of any other features, as well as the importance of a prolonged follow-up observation.

RFC10.6

Two novel mutations in the DCAF17 gene in two Palestinian families with primary amenorrhea revealing molecular genetics in Woodhouse-Sakati syndrome & unique presentation

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Background: Woodhouse-Sakati syndrome (WSS) is an extremely rare autosomal recessive multisystem disease. Ectodermal system findings, such as alopecia and changes in facial skin, endocrinological problems including hypogonadism, hypothyroidism, diabetes mellitus (DM), and decreased levels of insulin-like growth factor I (IGF-I), neurological disorders such as hearing loss and progressive extrapyramidal involvement are the components of this syndrome. The syndrome is caused by homozygous or compound heterozygous mutations in DCAF17, and has been implicated in the development of both male and female gonads, thus resulting in hypogonadism.

This gene encodes a nuclear transmembrane protein that associates with cullin 4A/damaged DNA binding protein 1 ubiquitin ligase complex.

Alopecia and loss of hearing are generally present before puberty. Puberty is delayed in all cases, and primary amenorrhea is typically present in girls. Hypothyroidism and DM may be added to the manifestation after puberty, and neurological disorders in later decades.

Here we describe a two novel homozygous DCAF17 mutations in 2 consanguineous Palestinian families presenting with primary amenorrhea.

Clinical Data: The 2 Palestinian females, presented with absence of spontaneous puberty, primary amenorrhea and hypergonadotropic hypogonadism (LH: 30.5 & 31.2, FSH: 75 & 31.2 respectively), Karyotype was 46, XX and pelvic MRI detected a small uterus but no ovaries in both affected patients. They did not develop alopecia, endocrinological and neurological disorders till now.

Molecular Data: next generation sequencing revealed a novel c.G395C, p.R132P mutation in the DCAF17 gene, both parents were heterozygous.

Conclusion: The two novel R132P mutations in DCAF17 gene causes hypergonadotropic hypogonadism and primary amenorrhea in 2 Palestinian families. The predicted change may compromise protein function which is currently studied. 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. Paving the way for genetic testing of hypogonadism cases in Palestine.

GH and IGFs

RFC11.1

The genetic aetiology of primary multiple pituitary hormone deficiency: a next-generation sequencing analysis of a single-centre cohort

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Introduction: Primary multiple pituitary hormone deficiency (MPHD) is caused by impaired development of the pituitary gland during the intrauterine period. Pathogenic variants in numerous genes affecting pituitary morphogenesis or differentiation have been proven to cause MPHD. However, in most people, genetic examination still fails to bring a conclusive finding explaining the cause of MPHD. The aim of our study was to identify the genetic aetiology of MPHD using next-generation sequencing (NGS) in a single-centre cohort of children treated with growth hormone (GH).

Patients and Methods: Currently, a total of 38 children with primary MPHD (GH deficiency combined with the impaired secretion of at least one other pituitary hormone) are treated with GH in our centre. Their median age is 12.7 years (IQR 8.2 to 14.5 years), height prior to GH treatment initiation -3.0 SD (-4.0 to -1.8 SD), pre-treatment IGF-1 -1.8 SD (-2.0 to -1.7 SD) and maximal stimulated GH 1.4 ug/L (0.4 to 3.4 ug/L). Out of them, 31 (82%) have central hypothyroidism, 29 (76%) central hypocortisolism, 6 (16%) hypogonadotropic hypogonadism diagnosed so far and 3 (8%) central diabetes insipidus. The brain MRI detected a midline defect in 27/38 (71%) children, 15 children (39%) had psychomotor retardation and 15 (13%) epilepsy. Children with a clinical suspicion of specific genetic disorder underwent standard genetic examination prior to the study. The children with unknown genetic cause were examined by targeted NGS panel containing 398 genes known to influence growth. All the variants with a potential clinical significance were evaluated by the American College of Medical Genetics standards.

Results: Causative genetic aetiology was confirmed in 10/38 (26%) children with MPHD. Out of these, 6 children carried causative genetic variant in genes known to play an important role in pituitary development and are known to cause MPHD (*OTX2* [2], *PROP1*, *POU1F1*, *GLI2*, *TBX3*). The remaining 4 children had a genetic variant corresponding with their complex syndromic phenotype, but the genes have not been described with MPHD yet (*PMM2*, *GNAO1*, *FLNB* and a complex chromosomal aberration). Moreover, in an additional 6/38 (16%) children with MPHD we found a variant of unknown significance (*GLI2* [2], *FBN1* [2], *LZTR1*, *FLNB*) potentially causing MPHD.

Conclusion: Genetic aetiology of MPHD is complex. In substantial number of cases, the mechanisms leading to MPHD remain to be elucidated. Our study suggests some new candidate genes potentially responsible for MPHD.

RFC11.2

Are pappalysins and stanniocalcins involved in modifying the bioavailability of IGF-I in children with onset of type 1 diabetes mellitus?

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Introduction: Both poor and optimal metabolic control of type 1 diabetes mellitus (T1DM) in children can impact longitudinal growth. A decrease in insulin-like growth factor (IGF)-I and its binding protein 3 (IGFBP3) has been described in these patients. New growth regulatory factors [pappalysins (PAPP-As) and stanniocalcins (STCs)] could modulate the bioavailability of IGFs by regulating the concentrations of intact and free IGFBPs.

Aims: To study the effect of insulin treatment on serum concentrations of pappalysins and stanniocalcins and the possible

Analyte (SD)	Onset [median (IQR)]	6 months [median (IQR)]	12 months [median (IQR)]
Total IGF-I	-1.20 (-1.56,-0.50)	-0.04 (-0.77,0.3)***	-0.53 (-0.89,0.25)$^{\#}$
Free IGF-I	-1.59 (-1.78,-1.18)	-1.56 (-1.8-0.97)	-1.29 (-1.8,0.65)
Total IGF-II	0.54 (0.01,1.68)	1.08 (0.39,1.63)	1.71 (1.08,2.41)$^{\#}$
ALS	-0.94 (-1.59, 0.15)	0.53 (-0.24,1.18)***	0.41 (0.11,1.01)$^{\#\#}$
IGFBP-2	-0.48 (-1.42,0.49)	-0.83 (-1.43,-0.07)	-0.47 (-1.19,0.12)
Total IGFBP3	0.15 (-0.71,0.88)	0.24 (-0.32,0.44)	0.34 (-0.13,0.73)
Intact IGFBP3	-1.07 (-1.89,-0.62)	-0.22 (-0.97,0.11)***	-0.09 (-1.01,0.15)$^{\#\#}$
Total IGFBP4	-0.24 (-0.64,0.24)	-0.16 (-0.58,0.97)	0.98 (0.45,1.32)$^{\#\#\#}$
Intact IGFBP4	-0.72 (-1.04,-0.23)	-0.47(-0.73,0.45)	-0.13 (-0.47,0.65)
IGFBP5	-0.93 (-1.35,-0.03)	0.45 (-1.8,-0.97)***	1.95 (0.72,2.42)$^{\#\#\#}$
STC1	-1.23 (-1.56,-0.84)	-1.19 (-1.37,-0.94)	-1.26 (-1.35,-0.85)
STC2	-1.31 (-1.97,-0.39)	0.07 (-0.37,0.69)***	0.52 (-0.76,0.90)$^{\#\#\#}$
PAPP-A	0.63 (-0.08,1.33)	0.80 (-0.3,1.27)	0.93 (0.76,1.92)
PAPPA-A2	1.05 (0.68,1.63)	0.49 (-0.07,0.92)***	0.13 (-0.16,0.52)$^{\#\#\#}$

ANOVA p value of onset versus 6 months (*p<0.05, ** p<0.01, ***p<0.001) and onset versus 12 months (#p<0.05, ## p<0.01, ###p<0.001)

correlation with markers of the growth axis, beta-cell insulin reserve, auxology and nutrition in children with T1DM.

Methods: 47 patients were included (59.5% females), with diabetes onset at age 9.08 +/- 5.8 years (median +/- interquartile range). Blood was extracted and anthropometric data collected at onset, 6 and 12 months. Serum concentrations were obtained using ELISAs, except PAPP-A2 (chemiluminescence immunoassay); all were standardized for age, sex, and pubertal development.

Results: Table 1 shows the results of the serum concentrations. At 6 and 12 months after T1DM onset, there was improvement in the metabolic control [decrease in HbA1c at 12 months -3.66 IC95%(-4.81,-2.05), p=0.001], certain nutritional markers [30.91 IC95%(0.36,61.47) p<0.05 for transferrin], body mass index SDS and height SDS (not statistically significant).

Conclusions: Our preliminary results indicate that implementation of insulin treatment after T1DM onset modifies various members of the circulating IGF system, including those of PAPPA-A2 and STC2. How these modifications correlate with linear growth are under investigation.

RFC11.3

Longitudinal assessment of health-related quality of life (HRQoL) & behavior in adults born small for gestational age (SGA) who were treated with growth hormone during childhood

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Background: Short stature has been associated with a reduction in health-related quality of life (HRQoL) and more problem behavior in children and adults. In adolescents who were treated with growth hormone (GH) because of persistent short stature after being born SGA, an increase in HRQoL and decrease in behavioral problems was seen during or right after cessation of GH-treatment. However, long-term data, to analyze if these positive effects remain many years after GH-cessation, are lacking.

Objective: To longitudinally assess HRQoL and behavioral aspects in 30-year old adults born SGA who were treated with GH during childhood (SGA-GH).

Methods: HRQoL was assessed at 6 months, 2 years, 5 years and 12 years after GH cessation using the TNO-AZL Adults Quality of Life questionnaire (TAAQOL), which consists of 45 items and contains 12 scales; scales were scored from 0-100, 100 indicating the highest HRQoL. At similar time points, behavioural aspects were assessed using the Adolescent Behavior Check List (ABCL), which consists of 113 questions divided in 8 subscales and 3 main scales; total problem, externalizing ("conflicts with other people and with social mores") and internalizing ("conflicts within the self") problem behavior. Scales were transformed into standardized T-scores with a mean of 50 and standard deviation of 10, higher scores indicating more problem behavior. Different models for repeated measurement analysis were used, namely linear mixed model (LMM), Poisson LMM and Hurdle-Poisson model.

Results: We included 176 SGA-GH adults in the longitudinal assessment; 145 completed the TAAQoL questionnaire (56 at 6 months, 32 at 2 years, 79 at 5 years and 69 at 12 years after GH-cessation) and 107 completed the ABCL questionnaire (26 at 2 years, 53 at 5 years and 58 at 12 years after GH-cessation) at least at one of the follow-up visits. Mean birth length SDS was -3.4, mean adults height SDS was -1.7. HRQoL did not change over time in 8 subscales, in 3 subscales (gross motor functioning, pain and sleep) a decrease in HRQoL was found. No changes in behavioral aspects were found over time in the internalizing and total score, and a decrease in problem behavior was found in the externalizing score.

Conclusion: During 12 years after GH cessation, HRQoL remained similar in 9 of the 12 subscales and declined in 3 subscales, while problem behavior remained similar or decreased over time.

RFC11.4

Functional analysis of a novel mutation of IGF1R gene in two twins with growth failure. An example of genotype-phenotype heterogeneity

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Background: IGF1 receptor (IGF1R) mutations are associated with pre- and post-natal growth retardation. We describe two monozygotic twins, one of them born small for gestational age (SGA), referred at the age 4 years and 2 months for short stature.

Case Presentation: The twins were born from non-consanguineous parents at 37-weeks gestational age by caesarean delivery. At birth: patient 1 had weight 2.076 kg (−2.4 SDS), length 43 cm (−2.7 SDS) and head circumference 32 cm (-1.2 SDS); patient 2: weight 2.320 Kg (-1.9 SDS), length 48 cm (-0.63 SDS) and head circumference 33 cm (-0.9 SDS). There was no family history of congenital anomalies or other relevant disease. Mid-parental height was 173.5 cm (25th percentile). Growth retardation was noticed since the first years of life. At first evaluation, they presented with mild short stature (height -2.2 SDS). At physical examination, some facial dysmorphisms like frontal bossing, micrognathia, thin upper lip, small and low set ears were observed. The patients showed a normal GH peak response to GHRH plus arginine stimulation test. IGF1 and IGFBP3 concentrations were normal. Bone age was 3 years and 6 months at 4 years and 2 months of chronological age. At the age of 7.6 years their height was -2.63 SDS and growth deceleration was observed (3.2 cm/year). rhGH therapy was initiated at the dose of 0.03 mg/kg/day. During the first year of therapy the height gain was +1.23 SDS and growth velocity was 7.2 cm/yr, respectively. Karyotype and SNP-array were normal. Next generation sequencing analysis showed a novel heterozygous variant c.3001A>T (p.Met1001Leu) of IGF1R gene, inherited from the father; this variant is considered like a variants of uncertain significance and could affect thyrosine kinase domain of IGF1R. We performed functional validation study to investigate the pathogenicity of this variant. Plasmids containing wild-type and mutant IGF1R were transfected into HEK293 cells. Immunoblot analyses indicated that the variant caused significant decreases phosphorylation of IGF1R with concomitant poor response to IGF-I stimulation ($p < 0.01$), thus supporting the pathogenic role of the variant.

Conclusions: Molecular characterization and functional analysis of two twins with short stature have led to the identification of a novel pathogenic variant of IGF1R gene, which can differently affect pre- and post-natal growth as well as phenotype in different individuals. Gene redundancy and epigenetic effects may play role in the phenotypic expression of the variant.

RFC11.5

Influence of sirtuin 1 and fibroblast growth factor 21 levels on IGF-1 concentration in children with short stature of different etiology

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Introduction: Short stature is one of the most common reasons for children presenting to an endocrinologist. In normal conditions, growth hormone (GH) stimulates the IGF-1 production in hepatocytes via the STAT5 signaling pathway. Approximately 40% of children diagnosed with idiopathic short stature (ISS), i.e. with normal GH secretion, have a reduced IGF-1 level for unknown reasons. Recently, it has been described that there are certain factors that reduce IGF-1 secretion by inhibiting STAT5. These include sirtuin 1 (SIRT1) and fibroblast growth factor 21 (FGF-21). The aim of the study was to assess the concentration of SIRT1 and FGF21 in children with ISS and to compare the results with those observed in children with GH deficiency (GHD) and healthy controls as well as to analyse the relationship between SIRT1 and FGF21 and height, GH secretion and IGF-1 and IGFBP3 concentrations in children.

Materials and Methods: The study group included 102 children with short stature (height SDS below -2.0). According to maximal GH concentrations (maxGH) in two different stimulation tests, children were qualified into GH deficiency (GHD) group – maxGH <10 ng/ml (n=40) or ISS group – maxGH≥10 ng/ml (n=62). The Control group consisted of healthy children with normal height (n=48). In each child SIRT1, FGF21, IGF-1 and IGFBP3 concentrations were determined.

Results: In the total group the median age was: 10.8 (8.4-12.7) years; there was no significant difference in age and sex between GHD, ISS and Control groups.

SIRT1 levels were similar in the ISS and GHD groups, but in both those groups significantly higher than in the Control group [median (25%-75%): 0.97 ng/ml (0.64- 2.0) vs 0.79 ng/ml (0.48-1.22) vs 0.36 ng/ml (0.14-0.38), p=0,000, respectively]. FGF21 levels did not differ between the groups. A significant negative correlation was found between SIRT1 and: height SDS (r=-0,44), IGF-1 (r =-0,21), and IGF-1/IGFBP3 molar ratio (r=-0,18).

Conclusions: In short stature children, regardless of GH secretion, SIRT1 concentrations are elevated. Since there are significant negative correlations between the concentration of SIRT1 and the level of IGF-1, IGF-1/IGFBP3 molar ratio and the degree of growth deficiency, it can be assumed that elevated SIRT1 levels are a mechanism that inhibits IGF-1 secretion in short stature children. FGF21 does not appear to have a significant role in inhibiting the intracellular GH signal for IGF-1 production in children with short stature.

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RFC11.6

Evaluation Of The Growth Hormone-Insulin like Growth Factor1 Axis And Serum Fibroblast Growth Factor 21 Levels As Related To Stature In Children And Adolescents With Coeliac Disease Adherent To Gluten Free Diet

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Background: Coeliac disease (CD) is a common cause of stunted growth. Despite adherence to gluten-free diet(GFD), short stature may persist in some patients with CD. Studies investigating the growth hormone (GH)-insulin like growth factor-1(IGF1)axis in children and adolescents with CD are scant and inconclusive. Fibroblast growth factor-21(FGF-21) is a181amino acid polypeptide that plays a role in growth, lipid and glucose metabolism. The inhibitory effects of FGF21 on GH action are direct, and may result from the reduced translocation of GH receptors from the cytoplasm to the cell membrane.Elevated serum FGF21levels are associated with short stature in children with malnutrition. Data regarding serumFGF21levels in patients with CD are currently unavailable.

Aims: To assess the current stature of patients with CD adherent to GFD, to determine the frequency of growth hormone (GH) deficiency and to investigate the associations of serum IGF1, IGF binding protein-3(IGFBP3) and FGF21levels with stature in patients with CD.

Patients and Methods: 141(79 females) consecutive patients withCD who were adherent to GFDfor at least two years were enrolled in the study. Demographic, clinical and biochemical data were retrieved from structured, electronic medical files. Standard methods were used for current anthropometric measurements and pubertal staging. Fasting blood samples for serumIGF1,IGFBP3 and FGF21 levels were drawn. Patients with height standard deviation (SD)1.5 SD below target height (TH) underwent GH stimulation tests (clonidine and L-dopa). Comparisons of clinical and laboratory data of patients with height SD within range of TH and those below TH were performed. Significance was granted for $p < 0.05$.

Results: The median age of the patients was11.3yr (range:3.0-18.0yr). Median duration of follow-up was4.6 yr (range:2.0-14.3 yr). Sixteen(11.3%) patients had short stature, i.e. height SD< -2 and 21(14.9 %) patients had body mass index SD<-2. Forty-eight (34.0%) patients were prepubertal. Of the12(8.5%)patients with height SD<1.5 SD of TH,3(2.1%) patients had GHD. Serum IGF1 SD and IGFBP3 SD were significantly higher in patients with height SD within TH than those with height SD below TH and without GHD (p=0.009 and 0.002; respectively). Serum FGF21 levels in patients with height SD within TH and those with height SD belowTH were not different(p=0.765). Serum FGF21 levels were not significantly correlated with any of the clinical and laboratory variables investigated in the study (p>0.05 for all).

Conclusions: The frequency of GHD in our cohort was 2.1%. The lower IGF1 and IGFBP3 levels in non-GHD patients below TH may suggest GH resistance. Serum FGF21 levels were not associated with stunted growth in our cohort.

Thyroid

RFC12.1

Macro-TSH IgG complex in a case of Congenital Hypothyroidism (CH)

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We present the case of a five-day female admitted to our Paediatric Unit due to TSH elevation (bTSH 303 mIU/L) on routine neonatal screening for congenital hypothyroidism (CH). The patient was born at 38 weeks' gestation by c-section presenting with adequate auxological parameters. Her mother suffered from Hashimoto's disease, already diagnosed before pregnancy, and requiring Levo-thyroxine therapy (L-T4). Blood tests performed at five days of life revealed the presence of an important TSH elevation (TSH 400 mIU/L) with FT4 values above the normal limit for age (fT4 2.61 ng/dL) and negative thyroid antibodies; the ultrasound showed an in-situ gland, with normal echotexture. Because of the discordant thyroid function test results, blood tests were repeated also evaluating the potential presence of immunoassay interferences. In particular, the detection of Polyethylene Glycol (PEG) thyrotropin precipitable percentage was performed, confirming the presence of monomeric TSH complex with autoimmune anti-TSH antibodies, mostly IgG, interfering with the immunoassay analytic procedure, which resulted into fictitiously elevated TSH values (macro-TSH) both in the patient and her mother, not previously referred. TSH measured after PEG precipitation was 36.2 mIU/L equal to 9% of total TSH (400 mIU/L), with normal fT4 and fT3 (respectively, 2.14 ng/dL and 3.30 pg/mL). Thyroid function reassessed after one week confirmed the persistence of macro-TSH (399 mIU/L) and increased TSH after PEG

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precipitation assay (44 mIU/L, 11% of total TSH). Hence L-T4 therapy was started at the dosage of 7,34 mcg/kg/day at thirteen days of life. Periodic blood tests showed a progressive improvement of TSH values leading to adjustment in L-T4 therapy. Macro-TSH interference at immunoassay assessment persisted, with a significant decrease of non-precipitable percentage (from 91% to 75% at 30 days after starting treatment).

This case suggests that, albeit rare, possible immunoassays interferences should be considered in presence of high serum TSH levels and inappropriately normal FT4 values before starting L-T4 therapy in a newborn suspected of CH. A careful maternal anamnestic data collection is of fundamental importance and in suspected cases mothers' macro-TSH should be controlled as well. The progressive reduction of the non-precipitable percentage during the follow-up suggests a possible transient condition, due to the IgG composition of the immunocomplexes responsible for the phenomenon, which could be easily derived from a trans-placental transmission. The child thyroid function will be revaluated after the age of two according to international guidelines.

RFC12.2

A novel frameshift mutation in Immunoglobulin Superfamily, Member 1 (IGSF1) causing central hypothyroidism, delayed puberty and GH deficiency

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Background: Central hypothyroidism is rare in children. It is often part of multiple pituitary hormone deficiency but can occur in isolation. Isolated central hypothyroidism may be due to mutations in TSHB, TRHR or IGSF1, involved in TRH signalling. We present an adolescent with a novel truncating variant of IGSF1, resulting in delayed puberty, central hypothyroidism and macroorchidism.

Case Presentation: A 15-year-old male was referred for pubertal delay, obesity and abnormal thyroid function tests (FT4 (6.5pmol/L [8.4-19.1], TSH 3.23mU/L [0.3-5.0]). He was born breech, birth weight 3.7kg (+0.32 SDS). At age 2, weight was 11kg (-1.38 SDS), height 85cm (-0.75 SDS), head circumference 52cm (+2.30 SDS). His medical history included raised ALT and liver steatosis. At presentation, his height was 166cm (-0.52 SDS), BMI 38.5kg/m2. On examination, Tanner staging was P1G1A1, 8ml testes. Initial investigations revealed LH 0.7IU/L, FSH 4.1IU/L, Testosterone 7.6nmol/L, IGF1 11.2ng/ml (13.5-66), prolactin 136 IU/L (90-300), AMH 28.1 (5.5-103). An LHRH-test showed a peak LH 11.2, FSH 12.8. Bone-age delayed 1 year. MRI showed a small pituitary gland. Levothyroxine was commenced and increased. Primed glucagon test showed undetectable GH but with suboptimal FT4 (7.3pmol/L). Later, primed insulin tolerance test (ITT) showed a low GH peak (4.21mcg/L). His growth and puberty progressed with quickly enlarging testes to 30ml. Sequencing of IGSF1 revealed a previously undescribed de novo hemizygous pathogenic variant c.3343C>T p.(Gln1115*) causing frameshift and premature stop codon.

The identified IGSF1 variant is not described in GnomAD. It locates to the 12th Ig-like loop, clustering with other frameshift mutations. The mutation likely leads to abnormal glycosylation and retention of shortened IGSF1 in the ER, resulting in ER-stress response and apoptosis in the pituitary contributing to pituitary hormone deficiency. Growth hormone deficiency (GHD) was evident on glucagon test and ITT, although difficult to interpret due to hypothyroidism and obesity. GHD may be transient given his normalising height and IGF1.

Conclusion: We describe a novel frameshift IGSF1 variant, resulting in most previously described features associated with IGSF1 deficiency, including central hypothyroidism, macroorchidism, macrocephaly, delayed adrenarche and puberty, GHD, obesity, fatty liver disease and higher than average birth weight. This case adds to genotype-phenotype correlations and for clinicians, highlights the importance of careful assessment for timely genetic diagnosis.

RFC12.3

Thyroid disorders in childhood cancer survivors treated with 131 I-MIBG, TKIs or immune checkpoint inhibitors: incidence, mechanisms and clinical management – systematic review

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Background: The thyroid gland is a common unintended target during and after cancer treatment in childhood cancer survivors. However, only a limited number of studies have assessed thyroid adverse events of newer or more selective anticancer drugs. The main objectives of this review are to provide an overview of thyroid disorders in children, treated with 131 I-metaiodobenzylguanidine (131 I-MIBG), tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs), to provide an understanding of the pathophysiological mechanisms behind the associated thyroid disorders, and to provide practical guidance regarding screening, follow-up and treatment options.

Methods: We performed a systematic review using Medline, Embase, Cochrane and clinicaltrials.org by means of the PRISMA guidelines.

Results: Fifty-four studies met the eligibility criteria for inclusion. The Table below summarizes the therapies with their mechanisms of actions. Hypothyroidism was the most frequent thyroid disorder with an incidence ranging from 35 to 81% for 131 I-MIBG. Thyrotoxicosis was usually a transient phase of thyroiditis, related to TKIs and ICIs. ICI-treated children were more sensitive for central hypothyroidism and 131 I-MIBG was associated with highest incidence of thyroid nodules. In general, time of onset was longer for 131 I-MIBG (years) compared with TKIs and ICIs (weeks to months).

Therapy	Target	Childhood cancers	Mechanism of action	Secondary effects
131 I-MIBG	Neural crest cells	Recurrent neuroblastoma and metastatic pheochromocytoma	Local radiation after dissociation of 131 I	Anemia, **hypothyroidism (35-82%), thyroid nodules (21-56%)**, sialadenitis, nausea
TKI	TK binding site of ATP	Chronic myeloid leukemia, Philadelphia positive acute lymphatic leukemia, unresectable or metastatic solid tumors and specific metastatic thyroid cancers	Inhibition of (de)phosphorylation of ATP and downstream pathways resulting in apoptosis and blockade of cell proliferation, differentiation, angiogenesis etc.	Hematologic toxicity, skin rashes, diarrhea, nausea, hepatotoxicity, **transient thyrotoxicosis (2%), central hypothyroidism (2%)**
ICI: anti-CTLA-4, anti-PD1 & anti-PD-L1	Immune checkpoint receptors or ligands	Melanoma, advanced solid tumors and refractory classic Hodgkin Lymphoma	Reactivation of anti-tumor immune responses by eliminating the inhibition of T cell activity	Immune-related adverse event: pneumonitis, colitis, hepatitis, neuropathies, **transient thyrotoxicosis (3%), central hypothyroidism (3-5%)**

Conclusion: Despite the limited data, thyroid disorders appear to occur frequently in childhood cancer survivors treated with 131 I-MIBG, TKIs or ICIs. Thyroid function monitoring is therefore recommended. We provide a practical guidance for surveillance of the thyroid function for the clinician taking care of childhood cancer survivors.

RFC12.4

Polyethylene glycol thyroid stimulating hormone (PEG-TSH) in real-life: a practical tool for solving a biochemical dilemma

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Background: The polyethylene glycol (PEG) method, which utilizes the addition of PEG to precipitate immunoglobulin fractions in order to measure free thyroid stimulating hormone (TSH), has been implemented as a tool for investigating incongruities in TSH measurement.

Aim of the Study: To investigate the practical application of PEG-TSH testing in pediatric scenarios with a discrepancy between elevated TSH and normal free thyroxine (FT4) levels.

Methods: The hospital's electronic laboratory database was queried for TSH tests performed between January 1st, 2015 and March 24th, 2023. Of those, PEG-TSH were identified and data of patients who underwent this assay was retrieved from medical records. Clinical and biochemical characteristics including PEG-TSH guided management were extracted.

Results: During the study period, 2949 TSH tests were performed in 891 children and adolescents for various indications. Of those, 61 (2.1%) were PEG-TSH results, performed in 38 patients (4.3%): 16 patients (42.1%) with congenital hypothyroidism (50% sublingual thyroid, 47% thyroid agenesis and 3% intact gland), 16 (42.1%) with subclinical hypothyroidism and 6 (15.8%) with Hashimoto thyroiditis. Patients were 1.3 months to 19 years old at testing with mean age of 7.1±5.3 years, older age characterized patients with Hashimoto thyroiditis ($p < 0.001$). Sex- and age-adjusted anthropometric parameters of patients were within the norms and did not differ between the groups: median height/length z-score of 0.34 [IQR -0.48, 0.91], and average BMI/weight-to-length ratio z-score of 0.18±0.85. All patients with congenital hypothyroidism were treated with L-thyroxine (3.41±0.96 mcg/kg/dy), while only 50% with Hashimoto (1.43±0.66 mcg/kg/dy) and no individuals with subclinical hypothyroidism were treated. Both TSH and PEG-TSH levels of patients with congenital hypothyroidism were higher than in the two other groups ($p = 0.021$ and $p = 0.009$, respectively), with no differences in FT4 levels between the groups. Spearman's correlation analysis revealed a strong association between TSH levels and PEG-TSH levels ($r = 0.871$, $p < 0.001$). Nearly 50% of PEG-TSH results guided the clinical decision of decreasing dose or not initiating L-thyroxine treatment.

Conclusion: Our study describes the real-life utilization of PEG-TSH assay in the spectrum of pediatric thyroid dysfunction. While use of PEG-TSH was infrequent, our findings support its value in avoiding unnecessary thyroid hormone treatment in equivocal cases. If the PEG-TSH level falls within the normal range, it may be suitable to manage the clinical condition based on the FT4 levels and age-appropriate clinical parameters.

RFC12.5

Application of Shear Wave Elastography (SWE) in the ultrasound evaluation of thyroid nodules in children and adolescents

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Introduction: Shear wave elastography (SWE) is an ultrasound diagnostic method used to measure tissue stiffness. Since the mechanical properties of tissue involved in the pathological process are changed, SWE might indicate regions of the examined tissue covered by the disease. It is well documented, that SWE helps differentiate benign and malignant nodules in thyroid gland in adults, however there are still few studies on application of SWE in thyroid diagnosis in children. The purpose of the study was to assess the application of SWE based on Young's modulus expressed in kPa in the management of thyroid nodules in children and adolescents.

Materials and Methods: 71 pediatric patients (49 girls and 22 boys) with 93 thyroid nodules were enrolled to the study and were qualified to SWE which followed fine needle aspiration biopsy.

Results: In 81 nodules the result of biopsy was benign (II according to Bethesda scale, cytological diagnosis: nodular goitre, parenchymal goitre, nodular colloid goitre or lymphocytic inflammation). In 11 cases the result was III according to Bethesda scale (AUS - Atypia of Undetermined Significance or FLUS - Follicular Lesion of Undetermined Significance in cytology) and 1 nodule was IV according to Bethesda scale (suspected follicular neoplasm - oxyphilic cell tumor). Benign nodules were located in 41% in left lobe, in 53% in right lobe and in 6 % in both lobes. In nodules qualified as III or IV according to Bethesda they were located in 42% in left lobe and in 58 % in right lobe. There were no significant differences between TSH and fT4 concentration between both groups. Patients with benign and suspected thyroid nodules were of comparable age. Mean SWE in benign nodules was lower than in nodules with III and IV according to Bethesda, however this difference was not statistically significant (44.77±18.07 kPa vs. 60.71±29.05 kPa, p=0.0559). Moreover there was a significant correlation between the Bethesda scale and SWE values.

Conclusion: Our results suggest that SWE is a viable diagnostic method however it still seems to need some adjustment for pediatric patients.

RFC12.6

Phenylbutyrate treatment of three patients with Monocarboxylate Transporter 8 deficiency

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Background: Monocarboxylate transporter 8 (MCT8) deficiency is a rare genetic disease that leads to severe global developmental delay. Thyroid hormone (TH) profile is characterized by high T3 and low T4 levels, with normal or elevated TSH. Recent studies have shown that the chemical chaperone phenylbutyrate (PB) restored mutant MCT8 function and increased TH content in a patient-derived cell model, making it a potential treatment for MCT8 deficiency.

Methods: We treated two monozygotic twins aged 14.5 years and one toddler aged 18 months with MCT8 deficiency due to P321L and V235L mutation in SLC16A2 gene, respectively, with accelerating doses of PB over 14 months. TH and related parameters were recorded. Serum metabolites of PB were monitored as a safety measure. Vital signs, anthropometric measurements and neuro-cognitive functions were evaluated. The biochemical effects of sodium PB (NaPB) in vitro were evaluated in MDCK1 cells stably expressing both mutations.

Results: NaPB restored the expression of the two mutants of MCT8 in stably transfected MDCK1 cells, but increased T3 transmembrane transport only in cells carrying the P321L mutation. PB treatment at high doses led to a significant improvement in TH levels, especially reduction in T3 and TSH and elevation in T4 levels. TH levels were correlated with PB doses. Total cholesterol levels were increased, without a change in sex-hormone binding protein levels. Body mass index SDS of the twins increased significantly, and the underweight toddler reached the third percentile in weight. Only minor neuro-cognitive improvements were observed during PB treatment in the twins, including reduction in hyperreflexia and mild improvement in gross motor and cognitive functions. The main adverse effects were gastrointestinal complains in the toddler and nausea and vomiting in the twins, associated with elevated liver enzymes, at the time of the highest dose of PB. Notably, maximal PB dose in the toddler was within the recommended range, and PB metabolites in the twins were measured below toxic levels. A full clinical and biochemical recovery was observed 7 to 10 days after treatment interruption.

Conclusions: In the first report of PB treatment in MCT8 deficiency, we found a significant improvement in TH profile, with minor neuro-developmental changes. Hepatotoxicity may represent a limiting factor in PB treatment of patients with MCT8 deficiency.

Pituitary, neuroendocrinology and puberty 2

RFC13.1

Are Glucagon-like peptide-1 (GLP-1) receptor agonists a new treatment option for hypothalamic obesity in the paediatric population: Preliminary experience from a tertiary paediatric endocrine centre

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Background: Hypothalamic obesity (HO), defined as abnormal weight gain due to physical hypothalamic destruction, for example due to suprasellar tumours, is characterised by significant hyperphagia, lack of satiety, and rapid weight gain in the first year of hypothalamic insult. HO is not usually responsive to caloric restriction or lifestyle modification, and no pharmacotherapies are specifically approved for treating HO. GLP-1 agonists, which suppress appetite via decreased gastric emptying and stimulation of hypothalamic satiety centres are licensed for obesity but their efficacy in HO is uncertain.

Case Series: We commenced six patients (50% female; aged 13-18 years) with HO secondary to suprasellar tumours on GLP-1 agonists (liraglutide or semaglutide). At initiation of therapy, mean BMI was 36.7kg/m^2 (±3.9) with mean BMI-SDS score of 3.24 ± 0.5. Complications of excess weight included obstructive sleep apnoea requiring overnight non-invasive ventilatory support in two patients and one patient had type 2 diabetes mellitus.

Case 1 (female, craniopharyngioma) commenced on liraglutide (maximum 3 mg daily) aged 13.4 years (treatment duration 15 months), lost 3.2% of bodyweight (BMI-SDS reduction -0.14) after 3 months, which was sustained at 6 months (8.3% weight loss; -0.44 BMI SDS-reduction) and 12 months (11.8% weight loss; -0.63 BMI-SDS reduction) respectively.

Case 2 (female, Rathke's cleft cyst) commenced on liraglutide (maximum 3mg daily) aged 12.6 years, and gained 13.8% of bodyweight (+0.08 BMI-SDS increase) after 12 months treatment. She was switched to semaglutide (maximum 2mg weekly) and her weight stabilised with only 0.61% weight gain after 12 months corresponding to a BMI-SDS reduction of -0.32.

Case 3 (male, craniopharyngioma) commenced on liraglutide (maximum 3 mg daily) aged 16.2 years (treatment duration 17 months) lost 4.1% of bodyweight (BMI-SDS reduction -0.24) after 3 months, which continued at 6 months (7.0% weight loss; -0.41 BMI SDS-reduction) and 12 months (8.6% weight loss; -0.63 BMI-SDS reduction) respectively.

Encouraged by the results from these patients, a further three patients (two with pituitary germ cell tumours; one with craniopharyngioma) have recently been commenced on GLP-1 therapy but auxological follow-up data is awaited. All six patients report reduction in appetite and pre-occupation with food.

Conclusion: Response to GLP-1 therapy in HO is variable but initial results are encouraging in our cohort. More data are required to evaluate its use for treating hypothalamic obesity and associated metabolic sequelae. Consideration is warranted as to whether weight stabilisation, rather than loss, reflects a successful treatment outcome in this challenging patient cohort.

RFC13.2

Arginine-stimulated copeptin is independent of GH secretion status

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Background: Copeptin is secreted in isomolar amounts along with arginine vasopressin peptide from the posterior pituitary. Its stability makes it a perfect candidate for the endocrine approach in the diagnosis of AVP deficiency. Arginine-stimulated copeptin is a possible alternative for the water deprivation test. We wondered whether basal and stimulated copeptin secretion is related to growth hormone secretion status or independent of it.

Design and Patients: This is a monocentric retrospective analysis of donated residual serum samples from 68 children and adolescents who underwent arginine or GHRH-arginine stimulation to test GH secretory capacity between 2018 and 2022.

Measurements: Copeptin was measured in baseline, 30-, and 60-min samples by BRAHMS Copeptin proAVP Kryptor immunofluorescence assay. GH was measured by in-house RIA calibrated against the WHO International Reference Preparation 98/574. Cut-offs for the diagnosis of GHD were 6.6 ng/ml for arginine (children, first test) and 15.9 ng/ml for GHRH-arginine (adolescents, retesting).

Results: According to the test results, there were 41 patients without GHD and 27 with GHD. The median baseline level of copeptin in the 41 patients without GHD was 5.6 (quartiles; 3.9 – 9.9) pmol/l, whereas it was 6.0 (3.1 – 9.0) pmol/l in patients with GHD (P=0.18). After 30 min, the median stimulated copeptin was 7.7 (5.3-11.2) pmol/l without GHD and 7.3 (4.3-11.3) pmol/l with GHD (P=0.49). After 60 min, the median stimulated copeptin was 7.8 (5.7-11.7) pmoil/l without GHD and 8.0 (4.9-11.4) pmol/l with GHD (P=0.67). In addition, there was no correlation between peak copeptin and peak GH concentrations.

Conclusions: The GH status of children does not appear to affect basal and arginine-stimulated serum copeptin concentrations.

RFC13.3

Treatment and outcome of the Dutch Childhood Craniopharyngioma Cohort study; first results after centralization of care

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Introduction: Childhood craniopharyngioma (cCP) has excellent survival, but quality of life may be severely hampered by hypothalamic dysfunction. We aimed to evaluate treatment and hypothalamic outcomes of a Dutch cCP cohort, and evaluate the effect of centralization of care.

Methods: A retrospective cohort study was performed, including cCP patients diagnosed between 2004-2021. Treatment characteristics and hypothalamic outcomes were evaluated and compared before and since centralization of care in May 2018.

Results: We included 87 cCP patients. Cyst drainage/fenestration was performed in 29.9%, limited resection in 27.6%, near total resection in 16.1%, and gross total resection (GTR) in 25.4%. Radiotherapy was given in 46.0%. After a median follow-up of 6.5 years, hypothalamic obesity (HO) was present in 24.7% and panhypopituitarism with diabetes insipidus in 71.3%. Higher BMI SDS at diagnosis and Muller grade II at last MRI of follow-up were associated to overweight/obesity. No association was found between extensiveness of resection and overweight/obesity at last moment of follow-up. When comparing before and after centralization of care, rates of GTR remained similar, but BMI outcomes changed; mean ΔBMI SDS 1 year after diagnosis from 1.12 (SD 1.15) to 0.81 (SD 1.24), and HO after 1 year decreased from 33.3% to 12.0% ($p = 0.067$), and after 2 years from 28.6% to 6.7% ($p = NS$).

Conclusion: In our nationwide cohort, GTR was performed in a relatively low percentage of patients and extensiveness of resection was no longer associated to HO at follow-up. A trend towards improvement of BMI is observed since centralization of care, which needs further exploration.

RFC13.4

Trio analyses of patients with congenital hypopituitarism reveals novel candidate genes

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Background: Congenital Hypopituitarism (CH) is a rare heterogeneous genetic disorder characterized by the deficiency of pituitary hormones. CH can be associated with extra pituitary phenotypes such as midline craniofacial malformations. To date, a minority of patients carry pathogenic variants in more than 30 genes, and thus more than 80% of cases remain unresolved.

Objective: To identify de novo pathogenic variants in novel CH genes in trios using whole-exome sequencing (WES).

Method: We selected 7 trios, performed a detailed phenotyping in the probands and parents, collected DNA and performed WES. Further analysis using VariantMaster, a bioinformatics tool (Santoni FA, 2014) was performed to detect de novo pathogenic variants.

Results: The hormonal deficiencies presented by the 7 probands were: GH (n=7), TSH (n=4), LH/FSH (n=6), ACTH (n=4) and Prolactin (n=1). Regarding the neuroimaging all patients had small anterior pituitaries, 3 had abnormalities in pituitary stalk and 5 had ectopic posterior pituitary. Extra pituitary phenotypes were present in 4 patients: ataxia, epilepsy and scoliosis in combination in one patients, micropenis and chryptorquidism in two patients, midline craniofacial malformations in two patients, and Joubert syndrome in one patient. In terms of genetics, we identified a homozygous pathogenic variant in POU1F1 (p.Arg291Trp) in a proband from a consanguineous family. Among the 6 remaining trios, we identified 5 de novo rare variants ($MAF < 0.0001$), in 5 novel genes in 3 patients. Genes were further filtered based on the type of the mutation, top expression in the pituitary and association with known human disorders leaving 4 putative candidate genes: MED13 (p.asn1986Ser); RASIP1 (p.Leu347Phe); ECPAS (p.Lys597Ile) and WBP11 (p.Leu223ArgfsTer6). WBP11, a gene involved in the major spliceosome complex, has been already associated with a variable human phenotype. Patients reported have delayed puberty, midline craniofacial malformations and proportionate short stature resembling CH and septo-optic dysplasia.

Conclusion: We identified 4 potentially pathogenic variants in new candidate genes for congenital hypopituitarism, one of them involved in the spliceosome machinery. We are currently following up to evaluate these genes in a larger population of singleton CH patients and performing studies to confirm the pathogenicity of these variants.

RFC13.5

Growth hormone and TSH deficiency after [177Lu] Lu-DOTATATE therapy for pediatric neuroblastoma; description of a first case

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Background: Neuroblastoma (NBL) is the most common extra cranial solid tumor in children. Endocrine adverse effects after treatment for NBL have been reported of which mainly caused by treatment with 131meta-iodobenzylguanidine ([131I]MIBG) or with alkylating agents and may consist of thyroid disorders, gonadal insufficiency or short stature.

Due to recent developments patients are increasingly treated with [177Lu]Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) targeting the somatostatin receptor that is overexpressed on neuroblastoma. However, the somatostatin receptor is also found on the cells of the anterior pituitary gland, where it regulates release of growth hormone (GH) and thyroid-stimulating hormone (TSH). Thus far no hormonal deficiencies have been reported after PRRT for NBL. We report a first case of GH and TSH deficiency after PRRT for refractory NBL.

Case: A 7 year old girl presented at the endocrine clinic with short stature. She had been treated for metastasized neuroblastoma at age 3 according to the DCOG-NBL2009 high risk protocol, including [131I]MIBG therapy, surgery and high dose chemotherapy with autologous stem cell transplantation (ASCT). Because of persistent metastatic disease she was treated with one cycle of 7400 MBq [177Lu]Lu-DOTATATE PRRT at age 4.

Following PRRT the girl underwent a second ASCT for persistent bone marrow suppression, and finished treatment with anti-GD2 immunotherapy. In the course of therapy, she had received numerous (over 20) blood transfusions. As a complication of treatment she developed stage 2 chronic kidney.

Additional endocrine testing revealed GH deficiency (IGF-1 < -2 SD with maximal peak in stimulation test to 14 mIU/L). GH treatment was started. Three months after GH therapy, TSH deficiency developed and thyroid hormone suppletion was started.

Discussion: Short stature after NBL treatment in this girl may be multifactorial including the high dose chemotherapy, [131I] MIBG therapy, and kidney failure. However, all these factors contributing to short stature do not result in GH deficiency. GH insufficiency has been suggested to occur in adults following treatment with PRRT. Although pituitary dysfunction caused by hyperferritinemia cannot be excluded, we hypothesize that the GH and TSH deficiency in this case are caused as a consequence of pituitary damage through binding of [177Lu]Lu-DOTATATE to the somatostatin receptors. Future studies are needed to confirm our findings.

RFC13.6

Pituitary size on volumetric MRI predicts the severity of the neuroendocrine phenotype in populations at risk

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Background: Hypopituitarism in children is a complex condition and its hierarchical evolution at different developmental windows is unpredictable. Magnetic resonance imaging (MRI) is helpful but largely a subjective assessment of anomalies of the hypothalamo-pituitary (H-P) structures. We aimed to test the utility of a quantitative measure of pituitary and stalk in predicting neuroendocrine phenotypes.

Patients and Methods: We recruited 62 patients (28F,34M) with H-P disorders (34 congenital, 28 acquired), followed for 8.0±4.0 years and aged 12.5±2.9 years. We graded neuroendocrine dysfunction by the endocrine morbidity score (EMS) ranging from 0 to 5 (no to 5 pituitary deficits).3T high-resolution volumetric MR brain sequences (T1,T2,CISS) were prospectively acquired to measure Regions of Interest (ROIs):1) Pituitary gland diameters [cranio-caudal (CC) and antero-posterior (AP) on sagittal T1/T2, transverse on coronal T1/T2] and volumes – both indirect (linear measurements) and direct (ROIs),2) Stalk diameters (upper, midpoint, lower on sagittal CISS). Imaging data were compared to those of 25 age- and gender-matched controls (13F,12M, aged 13.6±3.1 years).

Results: 36 had hypopituitarism (EMS≥2, Group1) and 26 had one or no pituitary deficits but may be at risk of evolving endocrinopathies (EMS0-1, Group2). Pituitary diameters [AP (6.3±2.4 vs 8.5±1.6 vs 9.0±1.9 mm, p=0.01) and transverse (10.34±2.8 vs 12.3±2.8 vs 13.6±2.3 mm p=0.01)], indirect volumes (155.6±128.4 mm^3 vs 214.2±80.1 vs 395.5±198.1 mm^3, <0.0001) and direct volumes (198.7±147.9 vs 349.2±81.4 vs 436.1±225.0 mm^3, p<0.001) were lower in Group 1 than in either Group 2 or control. The CC diameter was similar in Group 1 and 2 (4.0±1.6 mm vs 4.0±1.0) but both were lower than in controls (5.8-1.3 mm, p<0.0001). Direct pituitary volumes decreased with increasing EMS (EMS1 351.5±88.7,EMS2 295.6±133.1,EMS3 169.4±200.0,EMS4 130.2±75.7,EMS5 100.3±82.1, p=0.01). Upper, mid, and lower stalk diameters were similar between Group 1 and Group 2 (2.1,1.8,1.7 vs 2.6,2.0,1.7 mm) and did not correlate with increasing EMS. However, the prevalence of observed stalk abnormalities (absent/hypoplastic, interrupted, deviated, thick) increased with higher EMS (EMS0 30.0%,EMS1 46.7%,EMS2 62.5%,EMS3 90.0%,EMS4 87.5%,EMS5 100.0%, p=0.021).

Conclusions: Volumetric assessment of pituitary size may predict the degree of hypopituitarism, whilst linear measurement of pituitary height may be a useful screening tool to identify patients at risk. The degree of stalk slenderness is not additionally predictive, but a qualitative report of any stalk abnormality increases the likelihood of endocrinopathy.

Late Breaking

RFC14.1

Clinical characteristics of patients presented with primary adrenal insufficiency due to a p.R451W mutation in the CYP11A1 gene

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Background and objective: The first and rate-limiting step of steroidogenesis is the conversion of cholesterol to pregnanolone which is catalyzed by the P450scc side chain cleavage enzyme (encoded by CYP11A1 gene-SCC). Homozygous recessive mutations of the CYP11A1 gene cause a global steroid hormone deficiency thereby disorders of sexual development in 46, XY individuals with a variable phenotype depending on the mutation characteristics. About 60 cases of SCC deficiency due to CYP11A1 gene mutation have been reported so far. The most common mutation is the c.1351C>T (p.R451W) mutation, which has been detected in 12 cases. We, herein, present the clinical characteristics of 14 cases presented with adrenal insufficiency due to p.R451W mutation in the CYP 11A1 gene.

Design and Method: Data were retrospectively collected from tertiary pediatric endocrine centers using a standardized proforma. Family history, presenting age, clinical, biochemical, and hormonal characteristics, treatment options, and the follow-up characteristics obtained during their latest follow-up visits were recorded.

Results: 14 patients (M/F:7/7) from 10 consanguineous Turkish families were recruited. The mean age of the diagnosis was 3.8±2.4 (Range: 1.04-8.5 years). All of the male subjects were completely virilized with no sign of DSD. The main presenting complaints were signs and symptoms of primary adrenal insufficiency. However, despite having signs and symptoms 3 subjects were diagnosed when investigated due to the history of their affected siblings. While glucocorticoid deficiency (elevated ACTH, low cortisol) was present in all cases, none of the male cases had undervirilization excluding androgen deficiency. Mild mineralocorticoid (MC) deficiency was detected in 10/14 of the cases which were recovered in 2 subjects during follow-up. More strikingly, one patient with no MC deficiency at presentation had developed a salt-wasting adrenal crisis during acute illness. Although a deterioration was detected in height SDS, there was not a statistically significant difference between height SDS at presentation (-0.64±1.4), at the latest follow-up visit(-0.90±1.4), and target height SDS (-0.63±0.6).

Conclusion: In the present largest case series with a p.R451W mutation in the CYP11A1 gene our results confirmed a milder phenotype for all steroid hormones. Particularly lack of virilization defect in male subjects, and lack of salt-wasting crisis until a relatively late age of diagnosis suggested mild MC and androgen deficiency. Nevertheless, lack of MC deficiency at presentation does not exclude the risk of developing a salt-wasting adrenal crisis. Therefore special caution requires for patients with no MC replacement, particularly during acute illnesses.

RFC14.2

No Relationship Between Thyroid Function and ADHD – Results From a Nationwide Prospective Epidemiological Study and Mendelian Randomization

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Introduction: Limited research has focused on the potential connection between thyroid function and attention-deficit/hyperactivity disorder (ADHD), particularly beyond prenatal effects. The few studies addressing children and adolescents have important methodological shortcomings, mainly when seeking to establish causality. To clarify this relationship, a combined epidemiological and genetic approach was adopted to overcome the methodological limitations of each method.

Methods: The relationship between subclinical hypothyroidism and hyperthyroidism and the prospective risk of ADHD was investigated in German children and adolescents in a nationwide survey (KIGGS). To this end, a total of 4,432 adolescents were studied over a median follow-up period of 6 years. Data were subjected to a logistic regression approach, accounting for the so far most extensive set of covariates related to thyroid function and ADHD risk. The same approach was chosen to investigate the relationship between quartiles of thyroid stimulating hormone (TSH)

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and free thyroxine (fT4) levels and incident ADHD in euthyroid participants to test for a dose–response association. This analysis was complemented by Mendelian Randomization (MR), which is robust to inferential problems inherent to epidemiological studies. We utilized between 9 to 86 single nucleotide polymorphisms (SNPs) related to TSH and fT4 levels, hypothyroidism and hyperthyroidism, Hashimoto's thyroiditis, and Graves' disease as instrumental variables to clarify their causal relationship with ADHD based on data from 225,534 individuals (38,691 cases and 186,843 controls), employing a variety of conventional and robust MR methods.

Results: Neither the MR nor the epidemiological approach indicated a significant causal relationship between either type of thyroid dysfunction and ADHD, and this also applied to TSH and fT4 levels within the normal range.

Conclusions: Leveraging a combined epidemiological and genetic approach, which allows for reliable directional conclusions, our study found no compelling evidence supporting a relationship between normal range thyroid function, thyroid dysfunction, and ADHD. These findings discourage unnecessary diagnostics, thereby reducing the risk of misleading incidental findings that could divert attention from accurate diagnosis and appropriate treatment in patients with ADHD.

RFC14.3

Body composition in a pediatric population with type 1 diabetes mellitus - the importance of planned physical activity

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Introduction: Type 1 diabetes mellitus (T1DM) is associated with significantly higher cardiovascular disease mortality compared to the general population, even when glycated hemoglobin (HbA1c) is less than 7.0%. Inadequate body composition may increase the risk.

Aim and methods: To evaluate body composition of a group of pediatric patients with T1DM, from Portuguese Pediatric Endocrinology/Diabetic Clinic, using the bioimpedance system (InBodyÒ™). Demographic data, treatment regimens and glycemic control metrics were evaluated at the time of physical and body composition examination. Preschool (< 6 years) and recent diagnosed children (< 6 months) were excluded. Descriptive and analytical analysis, considering a type I error probability (α) of 0.05.

Results: A total of 78 patients, 53% female gender, were included. DM1 was diagnosed at a median of 4.9 (IQR 6.0) years and 86% were on treatment with Continuous Subcutaneous Insulin Infusion (CSII, 25% with automated closed loop model). Median HbA1c was 7.0% (IQR 1.1). Most of the sample had an adequate body mass index (BMI) SDS (60%) and 46% performed regular physical activity (PA) outside the school setting. The median percentage of body fat (PBF) was 18.9% (IQR 14.5), which was abnormal in 43%, with a visceral adiposity of 3 (IQR 5). Despite an adequate BMI, 19% had excessive PBF. Percent Body fat was statistically related to waist-to-hip ratio (r=0.61; p=0.001), visceral fat (r=0.88; p<0.001), BMI SDS (r=0.70; p<0.001), female gender (p<0.001) and PA performed outside school setting (p=0.007). Planned PA was statistically associated with lesser PBF (p=0.007), visceral fat (p=0.003) and waist-to-hip ratio (p=0.008) and higher muscle-to-fat ratio (p=0.008). Patients with CSII engaged more frequently in PA than patients with Multiple Daily Injections (p=0.032). No association was found between total daily insulin dose (U/kg) and visceral adiposity, PBF or planned physical activity. Glycemic control metrics (time in range, above or below range; variability coefficient index; glucose management indicator, HbA1c, mean glucose) did not differ neither in those with/without excessive PBF, nor with planned PA.

Discussion: We identified a large proportion of T1DM with excessive PBF, even in patients with normal BMI. PA outside the school setting was associated with a better body composition, including lower PBF and visceral adiposity. In relation to cardiovascular risk of T1DM, and considering the recognized benefit of physical activity, both in metabolic control and attaining glycemic control metrics, this study reinforces the importance of encouraging regular physical activity in this population.

RFC14.4

Evaluating the Effect of Recombinant Human Growth Hormone Treatment on Sleep-related Breathing Disorders in Toddlers with Prader–Willi Syndrome: a one-year retrospective cohort study

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Keywords: Sleep-Related Breathing Disorders, recombinant human Growth Hormone treatment, Prader–Willi syndrome, Toddlers.

Background: Recombinant human growth hormone (rhGH) therapy is beneficial for children with Prader–Willi syndrome (PWS) in improving short stature and metabolism, but the effect of early rhGH treatment on respiratory and sleep parameters for the PWS children under three years old remains elusive. Thus, this study aimed at investigating the impact of rhGH treatment on sleep-related breathing disorders (SRBDs) for toddlers with PWS.

Methods: We recruited 17 age-matched rhGH-treated PWS patients (rhGH group) and 17 none-rhGH-treated control (non-rhGH group) between October 2018 and January 2023. We collected data related to polysomnography-polygraphy (PSG) and serum level of insulin-like growth factor (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3).

Results: The mean age in the rhGH group was 20.76 ± 9.22 months which was similar with that of the non-rhGH group (25.23 ± 13.81 months). The demographic and anthropometric parameters were similar across the two groups after 52 weeks of treatment. Treatment with rhGH on toddlers did not exert adverse effects on the obstructive apnea-hypopnea index (OAHI), central apnea index (CAI), oxygen desaturation index (ODI), mean percutaneous oxygen saturation (SpO2), lowest SpO2, duration when SpO2 is lower than 90%, and proportion of the patients with SpO2 lower than 90%. The increased IGF-1 and IGFBP-3 did not worsen SRBDs.

Conclusion: Treatment with rhGH for 52 weeks on young toddlers with PWS showed no deleterious effects on SRBDs. This shed more light on the importance of initiating rhGH therapy early in PWS patients.

RFC14.5

Functional demonstration that variants in the C-terminal of IHH cause short stature and/brachdactyly

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Introduction: Variants in the N-terminal of the Indian-hedgehog gene (IHH) have been associated with Brachydactyly type-A1 (AD) and Acrocapitofemoral dysplasia (AR), only three of which have been functionally studied. However, heterozygous *IHH* variants, majority classified as variants of unknown significance (VUS) are being increasingly identified, not only in the N-terminal but also in the uncharacterized C-terminal, by NGS, in individuals with short stature and/or brachydactyly.

IHH plays a crucial role in endochondral bone development. It is synthesized as a precursor which is translocated to the endoplasmic reticulum and auto-cleaved into the active-secreted N-terminal peptide (IHH-N) and a C-terminal peptide (IHH-C), critical for self-cleavage.

Aims: To design a functional assay to determine the pathogenicity of *IHH* VUS and to determine whether variants localized in the C-terminal are pathogenic or not.

Methods: Eight *IHH* variants (3 IHH-N, 5 IHH-C) observed in short stature/brachydactyly individuals, 4 coding variants listed in gnomAD (2 IHH-N, 2 IHH-C) and 2 synonymous variants were introduced into pCMV6-IHH vector by site-directed mutagenesis and transiently transfected into HEK293T cells. Cultured media and cell lysates were collected and the expression of the different IHH peptides were analyzed by western blot.

Results: All 8 variants showed reduced IHH-N secretion (<50%) and decreased intracellular stability of both, IHH-N and IHH-C peptides compared to wildtype. All four gnomAD variants also showed significantly reduced IHH-N secretion whilst the synonymous variants behave as wildtype.

Conclusions: 1) All studied *IHH* variants, regardless of their localization in the N- or C-terminal significantly reduced the active IHH-N secretion. 2) The *IHH* variants can be re-classified to pathogenic variants. 3) Surprisingly, variants present at frequencies 0.0092-0.1% in gnomAD also showed significant reductions. 4) This study highlights the importance of performing functional studies to confirm the pathogenicity of VUS in short stature genes. 5) However, can IHH-associated short stature be considered as a monogenic disorder or a contributing factor to height deficit?

RFC14.6

Enhanced histones acetylation in children with obesity: relationship with insulin resistance and inflammation

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Introduction: Widespread changes occur in gene expression in obesity, contributing to metabolic and inflammatory abnormalities. Epigenetic mechanisms play a role in obesity by altering gene expression patterns, and connecting environmental factors to genetic alterations. Histone acetylation is a crucial epigenetic modification that impacts chromatin structure and regulates gene expression. Adipogenesis has been associated with gene-specific increases in histones H3 and H4 acetylation. A link between inflammation and histone modification has also been suggested. SIRT1, an enzyme involved in metabolic regulation, participates in histone deacetylation. This study aimed to investigate global histone acetylation in peripheral blood mononuclear cells (PBMCs) of children and adolescents with obesity, and its correlation with metabolic and inflammatory parameters.

Methods: The study included 60 children and adolescents, aged 11.3±2.3 years, comprising 30 subjects with obesity and 30 healthy controls. Detailed examinations were conducted, and anthropometric characteristics were recorded. Colorimetric methods were used to measure fasting plasma glucose (FPG) and lipid profile. Enzyme-linked immunosorbent assay (ELISA) was employed to assess insulin and TNF-α levels. PBMCs were isolated from fresh blood samples, and DNA and RNA were extracted. SIRT1 gene expression was measured using real-time PCR after preparing cDNA from RNA. Global histone acetylation was evaluated using an ELISA-based method with a specific antibody against acetylated H3 histone. Insulin resistance was determined by homeostatic model assessment of insulin resistance (HOMA-IR), and metabolic syndrome (MetS) was identified based on IDF criteria.

Results: anthropometric parameters, including weight z-score, BMI z-score, waist circumference, and blood pressure, were significantly higher in cases compared to controls. Additionally, glycaemic indices such as FPG, insulin, and HOMA-IR were significantly elevated in children with obesity. Histone acetylation was significantly higher in cases than in controls, and it was also remarkably increased in those with insulin resistance. SIRT1 gene expression was significantly reduced in children with obesity compared to the control group, and a marked inverse correlation was observed between histone acetylation and SIRT1 gene expression. Subjects with obesity also exhibited significantly higher TNF-α concentrations, which were positively correlated with the levels of histone acetylation.

In summary we showed for the first time that obesity in children and adolescents is accompanied by increased global histone acetylation, which is associated with insulin resistance and inflammation. Therefore, modulation of histone acetylation may be a potential interventional target for prevention of metabolic abnormalities associated with obesity.

Top 20 Posters

T1

Molecular and clinical studies in 84 patients with pseudohypoparathyroidism type 1B

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Context: Pseudohypoparathyroidism type 1B (PHP1B) caused by methylation defects of differentially methylated regions (DMRs) on the GNAS locus can be categorized into groups according to etiologies and methylation defect patterns of the DMRs. However, there are no reports evaluating the clinical differences in detail, such as diagnostic features at onset and Albright's hereditary osteodystrophy (AHO) features, among the groups.

Objective: To clarify the clinical characteristics in each group with different methylation defect patterns in four DMRs on the GNAS locus.

Design: Comprehensive molecular analyses consisting of methylation analysis, copy number analysis, and microsatellite analysis.

Patients and Methods: Eighty-four patients with PHP1B were included in this study. We classified them into three groups, namely, autosomal dominant inheritance-PHP1B (Group 1, G1), sporadic-PHP1B (G2), and atypical-PHP1B (G3), based on the methylation defect patterns in four DMRs on the GNAS locus and conducted epigenotype-phenotype analysis.

Results: G2 had youngest age at the time of diagnosis and highest serum intact PTH levels among the three groups. The most common symptoms at the time of diagnosis were tetany in G1 and G3, and seizures or loss of consciousness in G2. AHO features were most frequently observed in G2. There were no significant correlations between the average methylation ratios of seven CpG sites in the AB-DMR and hormonal and biochemical findings.

Conclusion: Epigenotype-phenotype analysis among PHP1B groups with different etiologies and different methylation defect patterns in four DMRs on the GNAS locus revealed differences in some clinical characteristics, including diagnostic features at onset and AHO features.

T2

Effects of tiratricol treatment withdrawal in MCT8 deficiency: ReTRIACt Trial

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We introduce the ReTRIACt Trial (NCT05579327) of tiratricol (Triac) for MCT8-deficiency, a rare X-linked disease resulting from disordered thyroid hormone transport and characterized by profound neurodevelopmental delay and features of chronic peripheral thyrotoxicosis. The ReTRIACt Trial aims to verify the effects of tiratricol observed in previous studies. It is a double-blind, randomized, multicenter, placebo-controlled study to evaluate the effects of tiratricol discontinuation in ≥16 evaluable male patients aged ≥4-years with confirmed MCT8-deficiency, maintained on a stable dose of tiratricol. Cohort A includes patients currently treated with tiratricol; Cohort B includes patients who are currently not receiving tiratricol. Patients within cohorts A and

B must demonstrate stable maintenance therapy with tiratricol within an open label tiratricol run in/titration phase prior to being randomized to receive placebo (tiratricol withdrawal) or continue tiratricol. Patients remain on either placebo or tiratricol for 30 days or until they reach a biochemical threshold (serum total triiodothyronine [T3] >ULN) for rescue. Patients resume open label unblinded tiratricol treatment either at the end of the 30-day period or on reaching the biochemical rescue threshold. The primary efficacy endpoint is the proportion of patients who meet the biochemical rescue threshold during the 30-day treatment period. Secondary endpoints include effect of tiratricol on serum thyroid hormone, sex hormone binding globulin, tiratricol concentrations, time to meeting biochemical rescue threshold, and cardiovascular parameters. Exploratory endpoints include sleep measurements and pharmacokinetic analysis. Due to the restricted mobility and known difficulties for MCT8 patients to travel to hospital, the study is conducted primarily in the domiciliary setting. The study requires only three visits to the hospital, with all remaining assessments being undertaken at home with the assistance of specialist domiciliary nurses and use of home-based clinical monitoring devices. The study is estimated to enroll patients in the second quarter of 2023. Given there is no registered therapy for MCT8-deficiency, the ReTRIACt Trial will aid in the regulatory process for approval of tiratricol for this disease.

T3

Prevalence of selected polymorphisms of Il7R, CD226, CAPSL and CLEC16A genes in children and adolescents with autoimmune thyroid diseases

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Introducion: Autoimmune thyroid diseases (AITDs): Hashimoto's thyroiditis (HT) and Graves' disease (GD) are common chronic autoimmune endocrine disorders in children. The mechanisms leading to the development of these diseases remain unknown, however scientific reports indicate that in addition to environmental factors, genetic background plays an important role. In our previous studies, we showed that some polymorphisms of the genes for IL2RA, FAIM2, IFIH1, PADI4 or CTLA-4 appeared more frequently in children and adolescents with autoimmune diseases like type 1 diabetes (T1D) and AITDs, which may be related to the occurrence and course of the disease. According to the literature, a number of other factors involved in immune mechanisms are known to potentially influence the development of autoimmune disease. The aim of this study was to assess the prevalence of selected single nucleotide polymorphisms (SNPs) of Il7R, CD226, CAPSL and CLEC16A genes in children and adolescents with autoimmune thyroid diseases. MATERIALS AND METHODS: We performed this study in the group of 56 HT patients (mean age, 15.2 ± 2.2 years) 124 GD patients (mean age, 16.5 ± 2 years) and a 156 healthy children as a control. We analyzed SNPs at the loci rs3194051, rs6897932 for IL7R gene, rs763361 for CD226 gene, rs1010601 for CAPSL gene and rs725613 for CLEC16A gene.

Results: We observed significant differences in allels IL7R (rs6897932) between HT boys and control group (C > T, p=0.028) and between all GD patients and healthy children (C > T, p= 0.035) as well as GD girls and controls (C > T, p=0.018). Moreover C/C genotype at rs6897932 of IL7R gene was statisticaly significant more frequent in all GD patients. In addition, the study revealed C/C genotype at the CAPSL locus (rs1010601) in HT boys to be statisticaly significant more frequent in comparison to control group. We observed no significant differences between AITD patients and a control group in other analysed SNPs (rs3194051 for IL7R, rs763361 for CD226 and rs725613 for CLEC16A). CONCLUSIONS: The presence of T allel in the IL7R (rs6897932) locus appears to have a potential protective effect against HT in boys, as well as GD in all children. Similarly, the presence of allel T in the CAPSL locus (rs1010601) seems to reduce the risk of HT development in all pediatric patients. Our observations need to be confirmed in studies on a larger group of pediatric patients.

T4

Functional characterization of novel MC4R gene variant in two unrelated patients with morbid obesity

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Background: The leptin-melanocortin pathway is pivotal in appetite and energy homeostasis. Pathogenic variants in genes involved in this pathway lead to severe early-onset monogenic obesity (MO). The MC4R gene plays a central role in the leptin-melanocortin, and variants predominantly heterozygous in this gene, are the most common cause of MO. We identified a novel heterozygous variant c.802T>C p.Tyr268His in the MC4R gene in two unrelated patients with morbid obesity and aimed to evaluate the functional impact of this novel variant on the pathogenicity of obesity.

Case 1: 17-year-old male Qatari patient with a birth weight of 4 Kg born to consanguineous parents was referred to our clinic for morbid obesity. He started to gain weight at the age of 2 years, and his current weight is 277 Kg and a height of 177 cm, with a BMI of 88.4 Kg/m^2. The patient presented with morbid obesity, hyperphagia, difficulty breathing, elevated liver enzymes (ALT: 85U/L(5-30U/L), AST: 12U/L(0-39U/L), ALP: 191U/L (52-171U/L).

Case 2: A 11-year-old female Jordanian patient with morbid obesity with a birth weight of 3.5 Kg. She started to gain weight since she was a few months old, and her current weight is 72.5 kg, BMI of 30.5 Kg/m2, BMI Z-score of 2.88, and BMI percentile of

99.8th percentile. She has a strong history of obesity; both her mother and father had gastric bypass surgery for morbid obesity. All her baseline investigations were normal.

Methods: HEK293 cells were transfected with plasmid DNA encoding either wildtype or mutant p.Tyr268His MC4R variant. Cyclic AMP (cAMP) generation and MC4R gene expression were evaluated with and without stimulation with forskolin. Additionally, the effect of the variant on the stability of the MC4R gene was assessed using in silico molecular modeling.

Results: HEK293 cells transfected with mutant *MC4R* p Tyr268His showed impaired ability to generate cAMP compared to cells transfected with wildtype MC4R receptor. The molecular modeling data of p.Tyr268His suggest the variant destabilizes the MC4R structure and affects the overall dynamics of the MC4R gene.

Conclusion: *In vitro* functional analysis and in silico molecular modeling showed the pathogenicity of the variant p.Tyr268His. The variant does not affect total protein expression; however, it is predicted to affect the post-translational localization of MC4R protein to the cell surface. This finding might help our patients to benefit from the novel therapeutic advances for monogenic forms of obesity.

T5

Clinical relevance of findings of the NGS panel for the pediatric patient with papillary thyroid carcinoma

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Background: In children, papillary thyroid cancer (PTC) is generally sporadic and may, less frequently, be part of an undiagnosed hereditary tumor predisposition syndrome (HTPS). Somatic molecular testing is useful to understand tumor etiology and behavior, predict prognosis, and possibly guide development of novel treatment strategies. RET/PTC fusions were found to be associated with an increased risk of invasive disease. The aims of our study were to analyze the findings of a next-generation sequencing (NGS) panel in a cohort of pediatric PTC according to age at presentation, recurrence risk, and response to treatment and to detect patients with HTPS.

Material and Methods: A retrospective descriptive study was conducted of 63 pediatric patients with PTC seen at a single center in whom a DNA-based NGS panel was performed targeting 54 thyroid cancer-related genes. Pathological molecular alterations were validated by DNA sanger sequencing in tissue and peripheral blood DNA samples to provide evidence of germline mutations. Recurrence risk was classified according to ATA-2015 as low (G1; n: 10), intermediate (G2; n: 13), and high (G3; n: 40).All patients were treated with total thyroidectomy and radioiodine. At the last follow-up, patients were classified as disease free (DF) or having persistent disease (PD). Mean (SD) follow-up was 4.48 (2.11) years.

Results: In 70% (44/63)of the samples, a pathogenic variant or gene fusion was detected: G1: 80%, G2: 54%, and G3: 63%. The most frequent alterations were RET-fusion (20%), ALK-fusions (14%), and *BRAF* (12 %). In 6/63 (9.5 %), pathological germline mutations were observed in genes associated with HTPS: DICER1 (n: 3), PTEN (n: 1), Lynch syndrome/ MSH6 (n: 2).

Chronological age was significantly lower in patients with gene fusions (median age 11.45 vs 13.7 years; p: 0.048). Mutations most frequently associated with PD were *RET/NCOA4* (RET/PTC3) (3/4;75%), *STRN/ALK* (4/8;50%), *BRAF* (4/8;50%), *RET-CCDC6* (RET-PTC1) (3/9;33%), *MSH6* (1/3;33%), and *DICER1* (1/5;20%). Overall, 43% of those with a positive NGS panel had PD versus 52% of those with a negative.

Fusions were more often found in G3 (21/29; 72%), but DF and PD were not related to fusions found.

Conclusions: Interestingly in our PTC cohort the NGS panel was highly specific to detect molecular alterations. Fusions were more frequent at a younger age and in the G3; however, it was not a determining factor to predict PTC outcome. Finally, detection of pathological germline mutations in genes involved in HTPS is a useful tool for genetic counselling.

T6

Granulosa cell tumors in girls: Preliminary results of a meta-analysis of new and published cases

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Background: Granulosa cell tumors (GCT) originate from sex cord/stromal tissue in the gonad. They are typically located in an ovary, but extra-gonadal localisation exists. These tumors are extremely rare in children and no systematic review has been published. The objective of this systematic review is to examine the following questions: What is the clinical picture of girls with a GCT? How are these patients treated and what is their prognosis?

Methods: To be included in the review, the article had to present a new case with GCT fulfilling the following criteria: female human fetus or a girl aged < 19 years with clinical information included a tumor containing granulosa cells.

The databases MEDLINE, Embase, Web of Science, and CINAHL were searched in November 2021. To find new cases, we asked pediatric endocrinologists in Sweden to report patients after informed consent had been secured. We also collected data from a Swedish paediatric reference pathology laboratory.

Results: The search identified 1,894 published references of which 35 were duplicates. We have screened 1,859 abstracts. We are in the process of reading 824 selected articles in full text to check for eligibility. Individual participant data has been extracted from 20 of the published reports for preliminary results. Nineteen new Swedish cases with a GCT were identified.

The preliminary analysis of 39 patients' data shows an average age of 7.3 years at the time of diagnosis (range: antenatal diagnosis up to 18 years of age). Symptoms at presentation were: prepubertal breast enlargement, vaginal discharge/bleeding, abdominal distension or pain, pubic hair growth, fever, constipation, swelling of vulva or cliteromegaly, hyperpigmentation of the skin, primary/secondary amenorrhea, headache, hirsutism and advanced linear growth.

The histopathological diagnosis was juvenile GCT in 76.9%, adult GCT in 12.8%, a mixed type of juvenile and adult GCT in 7.7% and another type of tumor containing granulosa cell component in 2.6% of the cases.

All patients received surgical treatment except one with a post-mortem GCT diagnoses. Adjuvant chemotherapy was administered in two cases.

Three patients (7.7%) died, two of them due to late discovery of the primary tumor and one secondary to local recurrence of the tumor with metastases 4 years after the primary diagnosis.

Conclusion: GCT can present in all pediatric ages and often, but far from always, with endocrine symptoms such as peripheral precautious puberty. Data from this systematic review will hopefully promote early recognition of this malignant disease.

T7

Variants in the Neurodevelopmental Gene Bone Morphogenic Protein/Retinoic Acid Inducible Neural-Specific 2 (BRINP2) are Associated with Severe Delayed Puberty

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Gonadotropin-releasing hormone (GnRH) is the master hormone regulating the reproductive axis and its pulsatile secretion is crucial for puberty onset and fertility. Disruption in GnRH neuron development or hypothalamic function can lead to absent or delayed puberty (DP) due to GnRH deficiency, with a phenotypic spectrum from severe delayed puberty to partial or complete Hypogonadotropic Hypogonadism (HH). HH can also be present as a shared trait with other neurodevelopmental disorders (NDDs).

The aim of our study was to identify novel genetic aetiology of severe DP by identifying variants in associated genes in our patient cohort; and ascertain the functional effects of identified variants of interest. Whole exome sequencing (WES) was performed on DNA samples from 180 probands with DP to identify potentially pathogenic rare coding variants in relevant gene pathways. Integrative analysis was performed on genomic data from human patients combined with transcriptomics analysis of rodent immortalized and primary GnRH neurons to determine novel regulators of GnRH neuronal development and function.

Bone morphogenetic protein/retinoic acid inducible neural-specific 2 (BRINP2) was identified as a candidate gene of interest as it was found to be significantly upregulated during GnRH neuronal development in these single cell transcriptomics analyses. Mutations in this gene have been previously associated with NDDs such as autistic spectrum disorder (ASD). Copy number variation in this gene is seen in multiple individuals from the Deciphering Developmental Disorders study with a phenotype including cryptorchidism and intellectual disability (https://www.deciphergenomics.org/gene/BRINP2/patient-overlap/cnvs).

BRINP2 is localised to the olfactory bulb, a key site during GnRH neuron migration. WES analysis identified four variants in BRINP2 (p.R726W, p.R649Q, p.I629V and p.D729N) in four unrelated probands with severely DP or partial HH, in combination with ASD or other NDD features. These four variants are all rare or ultra-rare and are predicted to be pathogenic by in silico tools including CADD, REVEL and SIFT. Protein expression of the four mutants was comparable to the reference protein.

BRINP2 has been shown to inhibit neuronal cell proliferation by negative regulation of cell cycle transition and Brinp2 knockout mice show hyperactive behaviour representative of human attention-deficit hyperactivity disorder, but pubertal timing has not been assessed. Thus, BRINP2 is a novel candidate for GnRH deficiency with NDD and we have investigated the role of BRINP2 in GnRH biology via wildtype and mutant protein sub-cellular localization, as well as tissue expression in mouse hypothalamic tissue across development.

T8

Design and Objectives of the Acorn Study: A Non-Interventional Study Evaluating Long-term Safety in Achondroplasia Patients Treated with Vosoritide

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Introduction: Achondroplasia is caused by a pathogenic mutation in the FGFR3 gene, leading to impaired endochondral bone growth and multiple medical complications. Vosoritide, a modified recombinant human C-type natriuretic peptide (rhCNP), was approved by the European Medicines Agency (EMA) in August 2021 for treating genetically confirmed achondroplasia in patients aged ≥2 years until closure of epiphyses. Acorn is the first treatment-based registry for achondroplasia, created to monitor long-term safety of vosoritide treatment in real world use.

Methods: Acorn is a multicenter, non-interventional post-authorisation safety study (PASS) requested by the EMA as part of the risk management plan (Category 3 per Risk Management Plan). The study aims to recruit approximately 330 patients into 2 cohorts: (1) incident users aged ≥ 2 to ≤ 8 years old, defined as those who either recently started, or plan to start treatment with vosoritide, and (2) prevalent users aged ≥ 2 years old who initiated treatment as part of the French expanded access program or vosoritide open-label clinical trial.

The primary objective is to evaluate the long-term impact of treatment on adverse bone-related safety events, such as fractures and slipped capital femoral epiphyses. Secondary objectives include evaluating the long-term impact of treatment on safety and disease-related outcomes, including achondroplasia-related complications/surgeries and changes in height and weight.

The study period is 10 years from the date of first patient enrolled. In addition, patients who complete (reach final adult height) or discontinue treatment during the study, will be followed up 2 years later.

Almost all vosoritide treated patients aged ≥ 2 years old to ≤ 8 years will be eligible for the study, leading to a more representative population of achondroplasia patients than in clinical trials. As an observational study, data collected will reflect standard clinical practice and real-life management and treatment use.

Results: The protocol was approved by the EMA in July 2023 and is registered on the EU post authorization study (PAS) register (EUPAS47514). In total, 8-10 countries and ~30 sites are involved; ethics submissions are ongoing. The first patient was enrolled in April 2023 and further data will be shared on the number, location and demographics of patients enrolled.

Conclusions: Vosoritide is the first approved medicinal treatment for children with achondroplasia. Acorn will collect important long-term, real-world data from patients across Europe, and will provide important insights into the impact of long-term treatment on safety, effectiveness and the use of vosoritide in context of other interventions.

T9

Early metabolic risk factors in children with 21 Hydroxylase Deficiency (21OHD): a case-control study

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Aims: The balance between hypo/hypercortisolism and hypo/hyperandrogenism is the main challenge in clinical management of patients with 21-hydroxylase deficiency (21OH-D). In adults, it has been established that both over and under-treatment might lead to the development cardiovascular risk factors. To date, only a few studies have addressed weather this risk begins in childhood. Aim of our study is to define the presence of early metabolic risk factors prevalence of obesity, body composition and blood pressure in children with 21-OHD in comparison to healthy controls.

Methods: 30 patients with 21-OHD (M/F=12/18), aged 11.4±3.7 years (range 6-18 years) were enrolled in the study. 30 healthy children, matched for age, sex and pubertal status were recruited as controls. At study entry, CAH patients and controls underwent a complete physical examination including measures of weight, waist and hip circumferences, blood pressure (BP), body composition by bioimpedance analysis (BIA), insulin and HOMA-IR.

Results: Compared with healthy controls, children with 21-OHD had increased weight (0.8±1.0vs0.4±0.8 SDS, p<0.001), BMI (0.6±0.7 vs -0.4±1.0, p<0.001), waist circumference (62.2±15.1 vs 58.4±6.0 cm, p=0.2), hip circumference (84.1±13 vs 67.4±10.7 cm, p<0.001), waist/hip ratio (0.88±0.06 vs 0.79±0.17, p<0.001), systolic BP (109.7±10.5 vs 99.7±10.0, p=0.0004), insulin (11.8±6.3 vs 6.6±5.9, p=0.0017) and HOMA-IR (1.8±1.2 vs 1.1±0.9, p=0.0091). BIA assessment revealed that 21-OHD children had a higher percentage of fat mass (FM 32.6±7.0 vs 21.4±2.0, p<0.001) and a lower percentage of lean mass (LM 67.4±7.0 vs 78.6±12.0, p<0.001). No difference was found between patients with 21-OHD salt wasting vs simple virilizing forms.

Conclusions: Preliminary results of our study suggested that 21OHD children have increased prevalence of early metabolic risk factors already in the first years of life, mainly characterized by a tendency toward overweight and obesity and abnormalities in body composition. These results highlight the importance of a careful metabolic evaluation and the need to identify early markers of metabolic risk in 21OHD children.

T10

Long term effects at 3-4 years of age of early intranasal oxytocin treatment in infants with Prader-Willi syndrome

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Introduction: The neuropeptide oxytocin (OT) plays an important role in modulating behaviour and social interactions. Prader-Willi syndrome (PWS) is a rare genetic neurodevelopmental disorder due to abnormal hypothalamic development including OT dysfunction that involves endocrine, nutritional and behavioural outcomes/features/trajectory. We previously showed in a phase I/II study (NCT02205034) that 18 infants with PWS, less than 6 months of age, who received an early short course (7 days) of intranasal OT treatment showed improved oral and social skills. We document here the long-term tolerance and effects of early intranasal OT treatment on the disease trajectory.

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Methods: We performed a cross sectional comparative study including 17 treated children (OT-exposed cohort) and compared them to 17 age-matched untreated children with PWS (unexposed cohort), at 3 to 4 years old. All PWS children were included in the French reference centre in the children hospital of Toulouse. We assessed social skills in the two cohorts with the Vineland adaptive behaviour scale, version II (VABS II). Behaviour was assessed with the childhood behaviour check list (CBCL), feeding skills including swallowing with questionnaire and videofluoroscopy of swallowing. Endocrine and metabolic issues were investigated and brain functional MRI (fMRI) was performed in the two cohorts.

Results: We reported here on the endocrine and metabolic data. No adverse event related to early OT treatment was reported. Circulating IGF-1 and HDL cholesterol were significantly higher in the OT-exposed cohort. We found a trend for a lower acylated ghrelin (AG) levels in the OT-exposed vs. unexposed cohort with normal AG values.

Conclusion: Early OT treatment is well tolerated up to 4 years and is likely to change the endocrine and metabolic trajectory of PWS. This study confirms the windows of opportunity for a short course of intranasal OT treatment in the first months of life.

T11

The serum steroid signature of PCOS hints at the involvement of novel pathways for excess androgen biosynthesis

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Context: Polycystic ovary syndrome (PCOS) is defined by androgen excess and ovarian dysfunction in the absence of a specific physiological diagnosis. The best clinical marker of androgen excess is hirsutism, while the best biochemical parameter is still a matter of debate. Current consensus guidelines recommend serum free testosterone as the most sensitive serum parameter to measure androgen excess. Recently, however, novel active androgens and androgen metabolic pathways have been discovered.

Objective: To assess the contribution of novel androgens and related steroid biosynthetic pathways to the serum steroid pool in PCOS women in comparison to healthy controls. Design: This is a case control study, wherein PCOS was diagnosed according to the AE-PCOS 2009 criteria. Serum steroid profiling was performed by liquid chromatography high-resolution mass spectrometry. Setting: Yeditepe University and associated clinics in Istanbul, Turkey, together with Bern University Hospital Inselspital, Bern, Switzerland. Participants: 42 PCOS women and 42 matched, healthy control women. Main outcome measures: Assessment of 34 steroids compartmentalized in four androgen related pathways: the classic androgen pathway, the backdoor pathway, the C11-oxy backdoor pathway, and the C11-oxy (11β-hydroxyandrostenedione) pathway.

Results: Metabolites of all four pathways were identified in healthy and PCOS women. Highest concentrations were found for progesterone in controls and androstenedione in PCOS. Lowest levels were found for 11-ketotestosterone in controls compared to PCOS, and for 20α-hydroxyprogesterone in PCOS compared to controls. PCOS also had higher serum testosterone levels compared to the controls. PCOS women had overall higher levels of steroid metabolites of all four androgen pathways compared to healthy controls. Conclusions: Novel alternative pathways contribute to the androgen production in healthy and PCOS women. Hyperandrogenism in PCOS is characterized by an overall increase of serum androgens in the classic, backdoor and C11-oxy pathways. While monogenetic disorders of steroid biosynthesis can be recognized by a specific pattern in the steroid profile, no diagnostic pattern or classifier was found in the serum for PCOS.

T12

Correlation between Metabolites of phthalate and Obese trends in Korean Children and Adolescents using Nationwide data

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The aim of this study was to investigate that exposure metabolites of phthalate one of the endocrine disruptors might be different in sex and might have influenced from obesity and insulin resistance in Korean children and adolescents. Nationwide data of 551 subjects aged 8-15 years (boys 281 and girls 270) who were included the study from 2010-2011. Subjects were grouped by sex and BMI percentile (normal: BMI<85p; overweight: 85p≤BMI<95p; obese: ≥95p). We examined anthropometric parameters of subjects and calculated body mass index. We estimated the amount of endocrine disruptors according to 24 hour recall record, metabolites of phthalates (MEP, MiBP, MnBP, MEHP, MiNP, MEOHP, MBzP, and MEHHP) from random urine and serologic parameters of fasting insulin, fasting glucose, and HOMA-IR. We clarified the correlation between metabolites of phthalate and obese trends using Pearson regression analysis. Urine level of MEOHP (μg/g cr

) was higher in boys (boys vs girls; 35.92 vs 30.46, p =0.0158). There were more food exposure of metabolites of phthalate (μg/day) in boys (DBP: boys vs girls; 10.72±3.45 vs 9.94±3.10, p=0.0058, DEHA: boys vs girls; 13.75±4.55 vs 12.52±3.95, p<0.01, DEHP: boys vs girls; 59.92±21.84 vs 54.97±18.67, p<0.01). In boys, urine level of MEOHP (μg/g cr) was inversely correlated with obese tendency (r: normal vs overweight vs obesity; -0.366 vs -0.478 vs -0.580, p<0.01). DEHP (μg/kg/day) was inversely correlated with obese tendency (r: normal vs overweight vs obesity; -0.621 vs -0.650 vs -0.723, p<0.01). In girls, u-MnBP was inversely correlated with obese tendency (r: normal vs overweight vs obesity; -0.371 vs -0.555 vs -0.847, p<0.01). u-MEOHP was inversely correlated with obese tendency (r: normal vs overweight vs obesity; -0.413 vs -0.686 vs -0.698, p<0.01). u-MEHHP was inversely correlated with obese tendency (r: normal vs overweight vs obesity; -0.379 vs -0.529 vs -0.826, p<0.01). In boys, u-MiBP, u-MEHP, u-MEOHP, BBP, DBP, DEHA, DEHP, and ΣDEHP were inversely correlated with fasting glucose, and HOMA-IR (p<0.01). In girls, u-MiBP, u-MEHHP, BBP, DBP, DEHA, DEHP, and ΣDEHP were inversely correlated with fasting insulin and HOMA-IR (p<0.01). In conclusion, metabolites of phthalates exposed via food ingestion were different in sex and body adiposity. Therefore we suggested that body adipose organ might interact with metabolites of phthalate in Korean children and adolescents.

T13

Single-nuclei RNA sequencing reveals potential mechanisms of ovarian insufficiency in 45,X Turner Syndrome

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Background: Turner syndrome (TS) arises from a complete or partial loss of one X chromosome (45,X) and is the most common genetic cause of primary ovarian insufficiency (POI) in women. Surprisingly little is understood about the pathogenesis of POI in TS beyond an acknowledged germ cell loss throughout the second trimester. Although X chromosome haploinsufficiency likely contributes, the variability in reproductive phenotype in 45,X TS suggests it is not the only explanation. We aimed to identify novel potential mechanisms of ovarian dysfunction in TS.

Methods: We performed focused single-nuclei RNA sequencing (snRNAseq) of 46,XX (n=2) and 45,X (n=2) fetal ovaries at 12-13 weeks post conception (peri-meiosis)(10x Genomics). Samples were obtained in collaboration with the Human Developmental Resource Bank (HDBR). Tissue karyotype was confirmed on skin biopsy and array.

Results: The 45,X ovary transcriptome is globally abnormal at single nuclei resolution. Within all oogonia snRNAseq cell subpopulations, the 45,X ovary had fewer germ cells than the 46,XX ovary. X chromosome inactivation dynamics were clearly disrupted in 45,X ovaries: 45,X germ cells expressed less *XIST* and *JPX* than 46,XX germ cells, although did express some *XACT* until the oogonia stage. A cluster of "synaptic oogonia" was absent from 45,X ovaries; genes differentially expressed in this cluster compared to shared clusters related to the synaptonemal complex, molecular chaperones (e.g., heat shock, CCT complex), and protein synthesis regulation. Key genes that were lower in the 45,X ovary include: 1) genes involved in intracellular protein regulation ("proteostasis"), including X-linked *HUWE1* and *RPS4X*, an X chromosome gene that escapes X-inactivation; 2) heat shock protein genes (*HIST1H2AA, HSP90AA1*) and histone methylases (*KDM1A, KDM3A*) in fetal germ cells; 3) genes involved in meiotic progression (*BUB1B*); and 4) genes related to mitochondrial energy production (*ATP11C; COX6C*). One key gene higher in 45,X ovary somatic cells was *NR4A1*, encoding an orphan nuclear receptor (NUR77) involved in development, inflammation, and steroidogenesis.

Conclusions: While failure of sex chromosome synapsis at meiotic recombination may be the primary defect in 45,X germ cells, these data suggest that the beginnings of meiotic failure in 45,X germ cells precede this. Aberrant ribosomal biosynthesis and proteostasis, possibly due to X chromosome haploinsufficiency or even a primary energy deficiency, may result in 45,X germ cell incompetence evident from the very earliest stages of germ cell development. Taken together, these data provide novel insights into potential mechanisms of ovarian insufficiency in Turner Syndrome and identify new therapeutic targets.

T14

Circulating Progranulin in Human Infants: Relation to Prenatal Growth and Early Postnatal Nutrition

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Background: Progranulin (PGRN) displays pleiotropic biological functions including on early embryogenesis, cell proliferation, lysosomal or neuronal functioning and wound repair, and has been proposed as a biomarker for metabolic diseases. Increased PGRN levels have been reported in type 2 diabetes, nonalcoholic fatty liver disease and in preeclampsia associated to placental dysfunction. However, the ontogeny of PGRN concentrations and the potential value of PGRN as indicator or metabolic disturbances in early life has not been explored so far. We longitudinally assessed PGRN concentrations in infants born appropriate- (AGA) or small-for-gestational-age (SGA), the latter being at risk for obesity and type 2 diabetes, especially if they experience an excessive postnatal catch-up in weight and are formula-fed (FF).

Methods: The study population consisted of 183 infants who were exclusively breast-fed [(BF), AGA, n=66; SGA, n=40] or FF (AGA, n=31; SGA, n=46) over the first 4 months of life. Assessments included auxology, fasting glucose, insulin, IGF-1, high-molecular-weight adiponectin, PGRN and body composition (by DXA), at birth, and at age 4 and 12 months.

Results: PGRN levels were low at birth and unaffected by prenatal growth. PGRN concentrations increased at 4 and 12 months, although to a lesser extent in SGA infants, and were unrelated to the mode of feeding. PGRN correlated with markers of adiposity, inflammation and insulin resistance in both AGA and SGA infants, especially in those FF.

Conclusion: The attenuated increase of PGRN levels in SGA infants over the first year of life, along with the association to markers of unhealthy metabolic profile, suggest a role of PGRN to the increased risk for metabolic syndrome in this population.

T15

Cognitive evaluation in children with 21 Hydroxylase Deficiency (21-OHD)

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Objective: The balance between hypocortisolism and hyperandrogenism in patients with classic congenital adrenal hyperplasia (CAH) treated with lifelong glucocorticoid (GC) is challenging. Glucocorticoid receptors are widely expressed in the brain; therefore it has been hypothesized that alterations in the exposure to glucocorticoids may affect cognitive ability in individuals with CAH. Only few studies have addressed this issue in children and results are scanty and conflicting. Aim of our study is to extensively evaluate cognitive function in an homogenous population of children with 21-OHD.

Methods: 24 children (M/F=15/9) with 21-OHD, aged 11±3.1 years, performed a cognitive evaluation through Wechsler Intelligence Scale-IV (WISC-IV), to obtain information about total QI, Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI), and Processing Speed Index (PSI). Additionally, an evaluation through NEPSY-II to also explore "attention and executive function" and "memory and learning".

Results: The average QI of 21-OHD patients (102±13.4) was in the normal range (90-110). At the same time, results of VCI, PRI, and PSI (109.9±13.6, 107.2±12.3, 95±13.4 respectively) were also normal. Interestingly, children with 21-OHD scored lower than normal range in WMI (88±15.9). Moreover the NESPY-II subtest narrative memory, revealed that males scored lower than females (6.8±4.1 vs 12.0±1.0, p=0.03) although results were still within the normal range.

Conclusion: Preliminary results of our study document that children with 21-OHD have normal QI. However, a mild impairment was found in working memory indexes suggesting that 21-OHD might be associated with cognitive alteration mainly involving memory function. Furthermore a greater impairment in narrative memory was found in males in comparison to females, thus raising issues about possible gender differences related to androgen exposure. Further studies on larger samples are needed in order to confirm these results and unravel pathogenesis of brain involvement in children with 21OHD CAH.

T16

Dose dependent risks of glucocorticoid treatment in classic CAH

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Introduction: In congenital adrenal hyperplasia (CAH), glucocorticoid (GC) treatment must perform two functions – to replace cortisol deficiency and to suppress the excess production of adrenal androgens. Unfortunately, androgen suppression usually requires supraphysiologic GC doses, which are associated with serious comorbidities. Our study examined the exposure or dose-dependent relationships between GCs and GC-related adverse events (GCRAEs) and comorbidities in the classic CAH population.

Methods: Using a cross-sectional analysis of an all-payer U.S. claims database from 2014-2021, we identified classic CAH patients using ICD codes and GC prescription data. Mean age was 42±16 years, 67% female. Participants were stratified by average daily GC dose, expressed in hydrocortisone equivalents (HCe): Low (10-20mg/d HCe, n=480), med (>20-30mg/d HCe, n=574) and high (>30mg/d HCe, n=965). Using an average adult BSA of 1.79mg/m2, the low dose group was designated as approximately physiologic dosing (5.6-11.2mg/m2/d). The low dose group was used as the reference and its GCRAE rates were compared against those of the medium and high dose groups using chi-squared tests.

Results: When evaluated by System Organ Class (SOC), trends were seen between increasing daily GC dose and increasing rates of GCRAEs for cardiovascular disorders, GI disorders, energy/sleep disorders, and infections. Significant differences were seen at the SOC level between the low (approximately physiologic) and high dose groups in cardiovascular disorders such as tachycardia, syncope/collapse, and cardiomegaly (p=0.0118), in energy/sleep disorders (specifically weakness) (p=0.0029), and infections such as pneumonia, sepsis, cellulitis, bronchitis (p=0.0062). When evaluated by individual disorder code, significant differences between the high and low dose groups included anxiety disorders (p=0.0196), hypertensive chronic kidney disease (p=0.0397), and abnormal weight gain (p=0.0003). Significant differences were seen between the approximately physiologic dose group and the medium dose group for bacterial infections NOS (p=0.0471), hypertensive chronic kidney disease (p=0.0157), and hyperglycemia (p=0.0312).

Conclusions: This study identified GCRAEs that displayed a dose-dependent relationship with GC exposure. As the average daily GC dose increased, so did the rates of CV disorders, GI disorders, energy/sleep disorders, and infections. In addition, rates of multiple GCRAEs were significantly increased in the groups on supraphysiologic dosing. Given the cumulative risks of lifelong exposure to supraphysiologic GC doses in classic CAH patients, this study highlights the need for steroid-sparing therapies in this population.

T17

Deterioration in polysomnographic evaluation after COVID-19 infection in patients with Prader-Willi-Syndrome

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Background: Patients with Prader-Willi-Syndrome (PWS) seem to be a risk-group for COVID-19 infection, due to their syndrome associated clinical features of hyperphagia and obesity, risk for central hypoventilation and obstructive sleep apnoea. Yet, little is known about the severity of infections and the long-term consequences in these patients. Therefore, we studied auxologic parameters and sleep laboratory examinations in PWS patients before and after COVID-19 infection.

Methods: 130 PWS patients were included in this study (mean age 10.8 years, range, 3.1-35.4). Of these, 83 participants (64%) had experienced a COVID-19 infection, and 73 caregivers answered our questionnaire. In 92/130 patients, polysomnographic data was available. In 57 patients with COVID-19 infection polysomnographic data were available before and after infection (35 female). Mean time between infection and post-COVID evaluation was 96.2 days (range, 5-402 days).

Results: None of our included patients had a severe course of COVID-19 infection and none were hospitalized. 6/73 (8.2%) had no symptoms, 56/73 (76.7%) mild symptoms, and 11/73 (15.1%) moderate symptoms. The control group of PWS patients without infection showed no differences in two adjacent polysomnographic evaluations. However, we found statistically significant differences in the COVID-19 group: statistically significant lower mean oxygen saturation (post 94.8% vs pre 95.7%, p=0.001), lower detected lowermost saturation (post 86.2% vs pre 87.3%, p=0.003), and a higher occurrence of hypopnea (post 13.9 vs 10.7, p=0.035). Moreover, we found a statistically significant reduction of time in optimal saturation range 95-100% (post 54.3% vs pre 73.8%, p=0.001), an increase in time in suboptimal saturation range 90-95% (post 45.5% vs 25.8%, p=0.001), and an increase in time in poor saturation range <90% (post 0.7% vs pre 0.2%, p=0.030). BMI-SDS for PWS showed no differences between the groups at any time. When applied, BMI-SDS for healthy German children was statistically significantly higher in the COVID group at follow-up after infection (post 0.56 vs pre 0.40, p=0.014). However, differences in BMI-SDS showed no influence on differences in polysomnographic evaluations in regression analyses.

Conclusion: PWS patients predominantly experienced mild symptoms during COVID-19 infection and none of them were hospitalized. However, on average three months after infection, differences in polysomnographic evaluations are still apparent, manifesting in lower oxygen saturations and more frequent hypopnoea. The infection caused weight-gain in the COVID-19-group, but this had no effect in regression analyses, ruling out an increased BMI-SDS as the cause. It remains unclear what mechanism caused this deterioration and if it will be persisting.

T18

Pubertal origin of growth retardation in Inborn Errors of Protein Metabolism: A longitudinal cohort study

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Background: Inherited amino-acid metabolism disorders (IAAMDs) require lifelong restriction of natural dietary proteins. Nutritional amino-acid mixtures (AMM) free of the poorly metabolised amino-acids by the enzyme block, improve nutrition. An adequate protein intake is crucial to ensure normal body development, notably during puberty. We aimed to: 1/ describe growth and puberty in IAAMDs 2/ investigate associations linking height, IGF1 and IGFBP3 with AAM and plasma amino-acids.

Methods: Retrospective longitudinal study of 213 patients with urea cycle disorders (UCD,n=77), organic aciduria (OA,n=89), maple syrup urine disease (MSUD,n=34), or tyrosinaemia type 1 (n=13). We collected growth parameters, pubertal status, dietary intake, IGF1 and IGFBP3 concentrations throughout growth.

Findings: Overall final height (n=69) was below target height: -0·9(1·4) vs. -0·1(0·9)SD, p<0·0001. Final Height was≤-2SD in 25% patients. Height≤-2SD was more frequent during puberty than during early-infancy or pre-puberty : 23·5% vs. 6·9%, p=0·0017; and vs. 10·7%, p<0·0001. Pubertal delay was frequent (26·7%) and more common in males: 43·8) vs. 17·0), p=0·0056. BMI Z-score and protein intake (g/kg/day) were not different between patients with vs. without pubertal delay : 0·5(1·5) vs. 0·5(1·6), p=0·94 and 0·7(0·2) vs. 0·8(0·4), p=0·33 respectively.

Overall height(SD) correlated positively with isoleucine concentration: β, 0·008; 95%CI, 0·003 to 0·012; p=0·001, and negatively with AAM: β, -1·228; 95%CI, -1·716 to 0·741; p<0·0001. In OA, height was lower during puberty in patients with vs. without AAM: -1.75(1.30) vs. -0.33(1.55)SD, p=0.0004, and median(IQR) isoleucine and valine concentrations(μmol/L) were lower in patients with vs. without AAM supplementation: 40(23) vs. 60(25) (p=0.0179) and 138(92) vs. 191(63) (p=0.0142), respectively. In UCD and MSUD, height (SD) correlated negatively with protein intake : -0.008; 95%CI, -0.015 to 0.001; p=0.0309; and β, -0.001; 95%CI, -0.018 to 0.003; p=0.0080, respectively, and not with AAM.

During puberty, mean IGF1 was -0.7(1.4)SD and mean IGFBP3 was -0.2(1)SD. IGF1 correlated with tryptophan and not with isoleucine. IGFBP3 did not correlate with plasma amino-acid.

Interpretation: In IAAMDs growth retardation worsen during puberty which was delayed. The mechanism might involve AAM use and lower isoleucine concentration, independently of the IGF1 pathway. We recommend close monitoring of diet during puberty.

T19

Pre-treatment Blood Transcriptome Predicts Growth Response to Somapacitan Treatment in Children Born Small for Gestational Age

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Treating short stature in children born small for gestational age (SGA) requires daily growth hormone (GH) injections that are burdensome for patients and caregivers. Results from REAL5 (ongoing randomised, multinational, open-label, controlled, dose-finding phase 2 trial; NCT03878446) indicate that somapacitan (0.24 mg/kg/week) has an efficacy, safety, and tolerability profile similar to daily GH (0.067 mg/kg/day) after 52 weeks of treatment in children born SGA. Predicting GH treatment response from gene expression has the potential to improve clinical management of short stature. Here, we investigate the prediction of growth response based on baseline blood transcriptome in children born SGA treated with either daily GH or somapacitan in the REAL5 study.

62 GH-treatment-naïve, prepubertal children born SGA were randomized (1:1:1:1:1) to receive somapacitan (0.16, 0.20 or 0.24 mg/kg/week) or daily GH (0.035 or 0.067 mg/kg/day) for 52 weeks. 44 consented to a baseline blood transcriptome profile [n=9, 10, and 10 in somapacitan 0.16, 0.20 and 0.24 mg/kg/week arms; n=6 and 9 in daily GH 0.035 and 0.067 mg/kg/day arms]. Children were categorised based on treatment response: the upper and lower quartiles of height velocity (HV; cm/year) were defined as good and poor responders, respectively.

Differential expression analysis identified genes associated with HV in a continuous manner across all arms separately. Boruta was used to identify which of the top 100 genes, ranked by false discovery-rate corrected p-values, were informative in distinguishing good from poor responders. Random forest classifier was used to predict good/poor responders vs. remaining three quartiles, across all doses, using expression from these genes. Performance of the classification models was assessed using out of box area under the curve (OOB AUC) and error rate (ER).

Growth response prediction from baseline (pre-treatment) blood transcriptome was strong following treatment with either daily GH (OOB AUC: 0.97-1.00; ER: 0-5.3%) or somapacitan (0.91-0.93; 13.5-14%). Genes predictive of growth response to daily GH in children with GH deficiency (GHD) and Turner syndrome (Stevens et al. 2021, Pharmacogenomics J.) had strong predictive value in children born SGA with either daily GH (OOB AUC: 0.81-0.90; ER: 15.8-21%) or somapacitan (0.84-0.88; 21-24%) treatment.

We demonstrate pre-treatment blood transcriptome predicts first-year growth response for somapacitan in children born SGA. However, growth response was less predictive than equivalent prediction in children with GHD. This may reflect a greater heterogeneity of the short stature SGA study population.

T20

Hyperparathyroidism is associated with inferior event free survival in lymphatic childhood malignancies in a single center retrospective analysis

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Introduction: Vitamin D status is investigated as a modifier for the risk and course of multiple malignant diseases. Findings point towards a detrimental role of low vitamin D levels for event free and overall survival (EFS/OS). However, vitamin D deficiency is often associated with secondary hyperparathyroidism, which may influence EFS/OS in childhood malignancies.

Methods: Real world data from 1547 cases (873 male) of childhood malignancies (397 lymphatic) from a single center tertiary university hospital were analyzed. Laboratory data sets with relevance to calcium homeostasis including plasma parathyroid hormone (PTH) and serum 25-OH-vitamin D (25OHD) from 5/2005 – 7/2021 were obtained and filtered for the highest PTH and lowest 25OHD of each patient during the entire observation period.

Data on relapse, secondary malignancies and mortality were obtained via chart review; from the national German registry (Kinderkrebsregister) and from the international ALL-BFM study. Data were stratified for the presence/non-presence of hyperparathyroidism (PTH > 65 pg/ml) and the presence/non-presence of a vitamin D deficiency (<30 nmol/L) and EFS/OS of the entire cohort and six disease specific groups was analyzed.

Results: In lymphatic malignancies hyperparathyroidism was associated with inferior EFS (Hazard Ratio (HR) 2.25 [1.38 – 3.66]; OS: HR 1.85 [0.71 – 4.80]), whereas deficient vitamin D levels did not associate with inferior EFS/OS.

In the entire cohort and for the other diagnostic strata neither hyperparathyroidism nor vitamin deficiency was associated with inferior EFS/OS.

Conclusion: In childhood lymphatic malignancies, hyperparathyroidism at any time during follow-up is associated with inferior EFS and may mediate the discussed effects of low vitamin D. Further prospective and mechanistic studies on this subject are urgently needed.

Poster Category 1

Adrenals and HPA Axis

P1-1

Circulating miRNA profile in adrenarche

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The physiology of adrenarche, i.e. the development of the zona reticularis of the adrenal cortex, is mostly unknow. Some genes of steroidogenic enzymes need to be down- (HSD3B2) while others upregulated (e.g. CYB5) to enhance androgen production in zona reticularis, but it is not known how this is regulated. Micro RNAs (miRNAs) are small non-coding RNAs that can affect gene expression at posttranscriptional level. We hypothesized that miRNAs might be involved in regulating adrenarche and investigated circulating miRNA profiles in a case-control setting before and during adrenarche. Subjects were selected from prepubertal participants of the Finnish PANIC study, and they had been examined longitudinally at ages 6-8 and 9-11 years. Children in the case group (n = 34) had adrenarche at age 9-11 years, while controls (n = 24) had no signs of adrenarche at that age. Adrenarche was defined either by clinical criteria as having at least one clinical sign of adrenarche (pubarche, axillary hair, adult-type body odor, oily hair/skin, acne/comedones) or by biochemical criteria as having serum DHEAS concentration > 1 μmol/L. Circulating small RNAs were extracted from serum with spin-column purification, miRNA libraries were prepared and indexed using QIAGEN kits with 200 bp size selection and sequenced using the Illumina NovaSeq 6000

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system with S1 flow cell channel and 72 bp read length. Mapping and calculations of read counts were performed with QIAGENs' online tool, and differential expression analyses were performed with edgeR and DESeq2 packages. We found that at age 6-8 years (before adrenarche), a total of 3 miRNAs were up- and 5 downregulated in children who later developed signs of adrenarche at age 9-11 years. At adrenarche, 5 miRNAs were up- and 16 downregulated. Most promising candidates include miR-1-3p (upregulated before clinical adrenarche; fold change 1.98), miR-203a-3p (upregulated during adrenarche; fold change 1.48), and miR-20b-5p, miR-486-5p, and miR-16-5p (all downregulated during adrenarche; fold change -1.81, -1.61, and -1.49, respectively). These findings suggest that miRNAs might have a role in adrenarche, and that they could serve as biomarkers. Ongoing functional testing of the effects of these identified candidate miRNAs on steroid hormone biosynthesis might reveal novel mechanistic insights for the regulation of adrenocortical development and steroid production.

P1-2

Metabolic effects of cortisol insufficiency are sex-depended in a zebrafish model of 21-hydroxylase deficiency

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Background: Patients with 21-hydroxylase deficiency (21OHD) require life-long glucocorticoid (GC) replacement and have high prevalence of metabolic disease. Our previous work using a zebrafish model of 21OHD (*cyp21a2-/-*) showed that cortisol-deficient adults were fertile and had normal external sex characteristics, however, they had large body size and increased subcutaneous and visceral fat deposition compared to wild-types. Unlike human 21OHD, they did not present hyperandrogenism. We analysed the liver transcriptome of *cyp21a2-/-* fish in order to better understand the role of cortisol in the developing metabolic phenotype and to gain insights into the mechanisms leading to metabolic disease in 21OHD.

Methods: We collected adult livers from an established GC-deficient zebrafish model (*cyp21a2-/-*) using 18 months old male and female wild-types and mutants (n=6 in each group). We conducted RNA extraction and paired-end sequencing, followed by transcriptomic analysis of differentially expressed genes (DEGs) and Gene Set Enrichment Analysis (GSEA).

Results: Regardless of genotype, females had significantly larger livers compared to males (weight to length ratio, $p<0.001$). Principal component analysis showed that sex had a higher impact on differential gene expression than GC-deficiency. There were 4195 DEGs between males and females in wild-type and 3889 in mutant fish, with 1946 DEGs shared between the two groups (independent of the mutation). For both wild-type and mutant fish, GSEA showed upregulation of ATP metabolism and small molecule catabolism in males compared to females, while translation and ribosome organisation were suppressed. Regarding the effects of GC-deficiency, in both males and females GSEA showed downregulation of oxidative phosphorylation and ATP metabolism and upregulation of ribosome organisation and translation in *cyp21a2-/-* compared to wild-type fish. However, wide dysregulations of lipid metabolic pathways were only found in mutant males, while in females the predominant feature was the upregulation of processes involved in organogenesis in *cyp21a2-/-* mutants compared to wild-types.

Conclusion: Our findings indicate that sex has higher impact than GC-deficiency on the regulation of metabolic processes in the adult zebrafish liver, energy homeostasis being significantly upregulated in males and reproduction and organogenesis in females. There were clear sex-depended effects of cortisol deficiency on the liver transcriptome, with a more marked impact on lipid metabolism in males. These findings suggest a complex interplay between GCs and sex hormones in the regulation of metabolism and energy homeostasis. They also highlight the benefit of using zebrafish lines of differentially impaired steroidogenesis for translational research in congenital adrenal hyperplasia.

P1-3

Acute Adrenal Insufficiency Related Adverse Events In Children With Congenital Adrenal Hyperplasia (CAH): Changes During The Period 2019-2022 In I-CAH

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Background: In 2019, the International CAH Registry (I-CAH) performed a benchmarking exercise of acute adrenal insufficiency related adverse events including adrenal crises (AC) and sick day episodes (SDE).

Methods: In 2022, I-CAH data on children aged <18 years at first visit with 21-hydroxylase deficiency CAH from 35 centres in 19 countries were analysed to examine the current occurrence of SDE and AC and compare it to the data that had been collected up to 2019 when 34 centres had participated in this exercise.

Results: In 2022, a total of 510 children with a median of 10 children (range 1, 58) per centre had 2,461 visits evaluated over a 3-yr period (2019-2022). The median patient age at the time of the visits was 8.3yrs (range 0, 20.6). The median duration of follow up per patient was 1.9yrs (0.1, 3.0) with a median of 2.4 visits (0.7, 20.6) per patient year. In 2022, of the 2,461 visits in 510 children, a total of 464 SDE were reported in 402 visits (16%) from 207 children (41%). Of the 464 SDE, reported management included an increase in oral glucocorticoids in 389 episodes (84%) and parenteral hydrocortisone in 68 episodes (15%); 280 episodes (60%) were self-managed in the community. The median SDE per patient per visit in 2019 and 2022 were 1 (0, 4) and 0 (0, 2), respectively. The median AC per patient per visit were 0 (0, 1) in both 2019 and 2022. The percentage of AC to total SDE in 2019 and 2022 were 4% and 6.5%, respectively. Infectious illness remained the most frequent precipitating event, reported in 69% (321 of 464 SDE) in 2022 and 72% (1,105 of 1,544 SDE) in 2019. Comparing the 19 centres that participated in both 2019 and 2022, the median SDE per patient year per centre in 2019 and 2022 was 0.4 (0, 6) and 0 (0, 2.5), respectively in 2022 (p=0.01). Of these 19 centres, 11 (58%) showed a reduction in SDE per patient year in 2022 compared to 2019 in 3 centres (16%) the SDE rate had increased and in 5 (26%) it remained unchanged.

Conclusions: The current study shows that the rate of reported SDE has fallen in 2022 compared to 2019. There is a need to continue widening participation whilst exploring the underlying factors that have led to a change in the rate of reported SDE.

P1-4

Major importance of genetic background in cortisol metabolism: Salivary diurnal glucocorticoid profiles in monozygotic twins with intra-twin birthweight-differences

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Objective: Although low birthweight (bw) and unfavourable intrauterine conditions have been associated with metabolic sequelae in later life, little is known about their impact on glucocorticoid metabolism. We studied monozygotic twins with intra-twin bw-differences from birth to adolescence to analyse the long-term impact of bw and catch-up growth on glucocorticoid metabolism.

Methods: 46 monozygotic prepubertal twin-pairs with bw-difference of <1SDS (concordant; n=29, 13 female) and ≥1SDS (discordant; n=17, 6 female) were recruited. At a mean age of 6.9 yrs saliva samples were collected (at 7 am/waking, 1 pm, 6 pm and 9 pm/before bed) and analysed with liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Results: Cortisol and cortisone concentrations showed statistically significant or highly significant intra-twin correlations in all twin pairs at 3/4 (cortisol), respectively 4/4 (cortisone) time points. Graphic evaluation of the diurnal cortisol patterns for each twin pair showed a distinct alignment in all groups. However, significant differences were found in the discordant group: the formerly smaller twins showed lower cortisone concentrations at 6 pm (2.77 vs 3.88 nmol/L, p=0.033) and statistically significant higher 11-deoxycortisone concentrations at 7 am (0.34 vs 0.13 nmol/L, p=0.042). Other time points showed no intra-twin differences. Analyses of the change of intra-twin differences over the day by mixed linear modelling showed no intra-twin differences in diurnal patterns. Regression analyses of intra-twin differences (smaller twin - larger twin) at 7 am showed a statistically significant influence for catch-up growth, indicating lower cortisol concentrations in smaller twins with more catch-up growth (adj.R^2=0.159, p=0.014, ß=-3.71). Regarding 7 am cortisone concentration, regression analyses showed that intra-twin differences were statistically significantly influenced by being in the concordant or discordant group, with lower cortisone concentrations in the formerly smaller twins of the discordant group (adj.R^2=0.121, p=0.012, ß=-5.74).

Conclusion: In monozygotic twins with intra-twin bw-differences, we found only few statistically significant differences regarding single time points and no differences regarding diurnal patterns. Additionally, a moderate influence on intra-twin differences in morning cortisol concentrations for intra-twin catch-up growth was found, as well as a weak influence on morning cortisone concentrations for being in the concordant or discordant group. However, we found statistically significant intra-twin correlations for cortisol and cortisone over the day in all groups and a pronounced graphic alignment of cortisol diurnal patterns in the individual twin pairs. We therefore suggest a major importance of the genetic background in cortisol metabolism.

P1-5

Glucose profiles of children with classical congenital adrenal hyperplasia: lesson from continuous glucose monitoring

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Background: While the risk for hypoglycemia during acute illness is well described in children with classical congenital adrenal hyperplasia (CAH), there is little evidence for the prevalence of asymptomatic hypoglycemia in CAH. We explored the glucose profile of children with classical CAH by the use of continuous glucose monitoring (CGM).

Methods: We conducted an observational study in children aged 1-6 years with a diagnosis of classical CAH receiving hydrocortisone and fludrocortisone replacement therapy. Participants underwent two 14-days continuous glucose monitoring (CGM) sessions. Data were analyzed according to three day-time lags (7am-4pm; 4pm-10pm; 10pm-7am) that corresponds to the timing of assumption of the hydrocortisone dose.

Results: Eleven participants (3.01.8 y) completed at least one CGM session. Hydrocortisone mean dose was 13.7mg/m^2/d (12.4, 15) in the CGM cohort with three daily administration and a daily percentage distribution of the dose of 35%-30%-35% among the three assumptions (7am, 4pm, 10pm). Morning plasma

Delta-4-Androsenedione, testosterone were measured at the enrolment and resulted suppressed (<0.26nmol/L and <0.13nmol/L, respectively) with 17-OH progesterone meeting the therapeutic target (0.48nmol/L[0.43,3.65]).

We analyzed 20.6 patient-days from the whole CGM cohort for a total of 226 days of monitoring.

The percentage of time of sensor glucose values <70mg/dL was higher during the 10pm-7am and the 7am-4pm time slots than in the late afternoon period [17% [7,54] and 15%[6.8,24] vs 2%[1.1,16.7] during the periods 7am-4pm and 4pm-10pm respectively (p=0.006 and p=0.003)].

Conclusion: CGM demonstrated a disrupted daily glucose pattern in children with CAH. Children without CAH in the same age group displays less than 1% of sensor glucose readings <70mg/dL in the absence of values lower than 54mg/dL. As a contrary, herein we observed that both during nighttime and morning/early afternoon, children with CAH spend ~15% of the time at a glucose value lower than 70mg/dL in sharp contrast with what observed in the late afternoon and in their healthy peers whose time in mild hypoglycemia in about 6 minutes per day.

P1-6

A retrospective analysis of children and youth with congenital adrenal hyperplasia treated with hydrocortisone modified-release hard capsules

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Context: Children with congenital adrenal hyperplasia (CAH) require hydrocortisone replacement from birth. The highest ACTH driven endogenous production of androgens happens in the early morning. To achieve a good therapy control, immediate release hydrocortisone is given early in the morning or late at night. In year 2021 the hydrocortisone modified-release hard capsule (Efmody®) was approved by the European medicine agency and from September 2021 it is licenced in Germany for therapy in children aged 12 years and older with adrenal insufficieny. Due to the modified-release of hydrocortisone, a peak concentration of Cortisol is achieved in the early morning by taking the highest daily dose of the medication at bedtime.

Objective: To investigate growth, pubertal development, safety and long-term disease control in children and youth with CAH treated with hydrocortisone modified-release hard capsules and monitored through 17-OHP saliva profiles.

Methods: A retrospective and descriptive analysis of CAH-patients treated in a one-centre outpatient clinic. Analysis of weight, length, blood pressure, dose of hydrocortisone before and after start of treatment with hydrocortisone modified-release hard capsules, as well as therapy control by 17-OHP saliva sampling and incidence of adrenal crisis.

Results: Forty-five children with CAH (20 females) are treated with the modified-release hard capsules since September 2021. Median age of treated children is 12.2 years (12,24 +/-4,73 years). Mean dose relation of immediate release hydrocortisone/ hydrocortisone modified-release hard capsule at changeover to Efmody® was 0.96 +/- 0.11. Height was analysed according parental target height (z-scores). Further, weight, blood pressure, pubertal development and skeletal age was analysed. No increase of adrenal crisis was observed despite a lot of illnesses calling for stress dosing. This was done with immediate release hydrocortisone or a combination of Efmody® and immediate release hydrocortisone.

Conclusion: Hydrocortisone modified-release hard capsules, approved for the therapy of adrenal insufficiency in children older than 12 years of age is a safe therapy in children. There was no increase in adrenal crisis observed.

P1-7

The process of knowledge-making with a patient encounter – from education to negotiation of the way of treatment in patients with congenital adrenal hyperplasia (CAH)

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Introduction: CAH is a chronic inherited disease which needs the treatment for the whole life. This situation forms the necessity of a proper patient- doctor relations: not only compliance, but rather informed cooperation. The neonatal screening for CAH allowing the early diagnosis and treatment and availability of internet sources of professional knowledge is the new challenge in the way of education of patients. In Poland there is still observed the dominance of the paternalistic model in physician-patient relationships and a low level of social trust in physicians.

Material and Methods: An interdisciplinary project on CAH, integrating social sciences (anthropology) and medicine (pediatric endocrinology). The data was analyzed basing on (1) in-depth interviews (IDI) with parents of children with CAH, and with (2) endocrinologists who take medical care of CAH patients; and additionally (3) qualitative analysis of the Polish closed Facebook (FB) group dedicated to CAH (currently 792 members, the group has been operating since 2013; anthropologist conducted the observation with the consent of the group members). The collected material was coded. This process employed an inductive approach using thematic analysis.

The Results: Nowadays patients become more and more aware of their rights and possibilities of medical treatments, among others thanks to Internet. We can observe self-education of patients also based on professional materials. We Identified 4 areas of negotiating medical decisions in the case of CAH: 1. Number of hydrocortisone doses: patients increasingly declare the will to give more than 3 doses of hydrocortisone daily; 2. Technological novelty: the readiness to use a cortisol pump. 3. Genital reconstruction surgery: timing and a need of more individual approach; 4. Emergency Hydrocortison Injection Kit availability.

Conclusions: CAH is one of this chronic diseases in which the treatment takes place at home and parents/ patients become a professionals in this particular topic thanks to the continuous observations of potential symptoms and necessity of making decisions concerning the evaluation of patients condition and current treatment. Thus, they are armed with a specific type of knowledge that the doctor cannot ignore. Additionally it is overlapped by FB group activities what gives the tools allowing the generalization of parents experience and knowledge and can influence the approach to the patient by professionals. The FB group becomes the important social actor processing experience of patients and experts knowledge and forms a new patient type, who could became a partner in better therapy and implementation of new solutions.

P1-8

Congenital Adrenal Hyperplasia (CAH): Situation and Possibility to Develop a Newborn Screening in Indonesia -- An Exploratory Study

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Introduction: Indonesia, an archipelago with approximately 17,000 islands and 34 provinces has around 4.8 million babies born annually, yet only 2-3% undergo newborn screening (NBS) resulting in high preventable disease burdens. Currently, the country only has 1 newborn screening project which will be relaunched and aimed to cover 30-40% of babies. Health policy plays a huge role in determining the day-to-day lives of children, families, and health professionals and researchers hope this study will encourage all stakeholders to prioritize and engage with NBS.

Aim: Understand the lived experiences of patients and families with late and early diagnosis of CAH in Indonesia; raise awareness of the importance of NBS amongst policymakers, health professionals, and the public; and support advocacy efforts to expand and scale the program in Indonesia.

Methods: This qualitative study involved 40 interviews of parents of CAH patients across Indonesia to understand their experiences with CAH (informed consent, voluntary participation). The data analysis was conducted through thematic analysis. Ethics was secured from the Faculty of Medicine, Universitas Indonesia.

Results: Families with a late diagnosis of CAH have had negative experiences and challenges compared to patients with an early diagnosis (through NBS). Parents highlighted challenges with gender misalignment, forcing them to consider changing the identification of their child once CAH was diagnosed later in life. The lack of educational and monetary resources was consistently highlighted as a major challenge. Parents living in remote areas had trouble obtaining medication due to transportation costs, resulting in children having to skip doses for periods at a time. Educational resources free of medical jargon were highly valued. Parents wanted the opportunity to learn more about CAH, however, access to simplified resources was difficult. Parents' concerns extended broadly and included their child's interpersonal relationships, self-esteem, and overall well-being.

Conclusion: The study findings demonstrate an urgent need to expand and scale NBS for CAH in Indonesia. NBS provides the opportunity for early intervention, leading to enhanced child outcomes. Further, developing educational resources with limited medical jargon, increasing affordable access to essential medication, and equipping families with psychological support to manage CAH are crucial in increasing the quality of life for children and parents. This study provides initial insights into challenges associated with late diagnosis of CAH; further research in this area can be considered critical. NBS possesses the potential to prevent devastating outcomes for children and families.

P1-9

The @MATES4Kids Movement: Reducing Preventable Mortality Associated with Congenital Adrenal Hyperplasia (CAH) by 30% by 2030

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Background: Children living with paediatric endocrine conditions in resource-poor countries experience inequitable rates of preventable mortality and morbidity. Reducing preventable mortality will help member states committed to delivering on the United Nations' Sustainable Development Goals 3.2.1, 3.2.2 and 3.4.

CLAN (Caring & Living As Neighbours) has been improving health outcomes for children living with CAH in resource poor countries since 2004, through a rights-based, community development approach focusing collaborative action on five pillars: 1. Affordable access to medicines and equipment; 2. Education, research and advocacy; 3. Optimal medical management; 4. Family support groups; and 5. Reducing financial burdens on families. CLAN founded the @MATES4Kids movement in 2021, bringing together a broad range of individuals and organisations committed to practical actions to reduce preventable mortality from CAH. @MATES4Kids' objectives are to: rapidly scale action on pillar 1 by improving access to essential medicines; strengthen CAH Communities; and increase Newborn Screening.

Aim: To engage paediatric endocrinologists from the six World Health Organisation (WHO) regions (African, Americas, Eastern Mediterranean, European, South East Asian and Western Pacific) in the @MATES4Kids movement.

Methods: In 2022, @MATES4Kids elevated this issue to WHO, proposing a strategic approach to improving access to hydrocortisone and fludrocortisone tablets. An inaugural CAH@MATES4Kids Meeting co-chaired by CLAN and GPED (Global Pediatric Endocrinology and Diabetes) convened at IMPE (International Meeting of Pediatric Endocrinology) 2023, allowing interested stakeholders to share experiences, identify priorities and agree future strategies.

Results: IMPE 2023 facilitated communication between global and regional paediatric endocrine societies and CAH@MATES4Kids agreed an implementation plan for strategic action in the six WHO regions utilising the Knowledge To Action Framework. Tools developed to aid identification of priorities, guide implementation, monitor progress and evaluate outcomes include: CLAN Snapshot Survey; CAH Health Needs Assessment; CAH Equity Scorecard; Child Health Equity Checklist Count (CHECC) Scorecard and @MATES4Kids Monitoring Indicators. Champions for each WHO Region and a Community of Practice will facilitate a Continuous Quality Improvement approach to critical action with an agreed timeline. Drug / monetary donations from Direct Relief, GPED, CARES Foundation, the international CAH Community and CLAN have already supported CAH Communities in Ukraine, Sri Lanka and Zimbabwe.

Discussion: Reducing preventable mortality associated with CAH will require innovative, sustained, multistakeholder and multidisciplinary efforts. Paediatric endocrinologists can play a key role advancing this agenda on the road to 2030.

P1-10

Endocrinological, genetic and immunological features of a long-term survivor with MIRAGE syndrome

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MIRAGE syndrome is characterized by myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes and enteropathy. It was established in 2016 as a new syndromic disorder caused by a gain-of-function mutation in the *SAMD9* gene, which encodes a protein that suppresses cell proliferation. Due to the poor life prognosis, there are few reports on the long-term survival. Therefore, we herein report the clinical course of a 24-year-old male patient with particular focus on endocrinological, genetic and immunological abnormalities. At birth, he had extreme skin pigmentation, hypospadias and a bipartite scrotum. During the neonatal period, he had granulocytopenia, which improved spontaneously after blood transfusion, and cerebral hemorrhaging. At 7 days old, hydrocortisone replacement therapy was started due to adrenal crisis. At 12 years old, allergic purpura developed. At present, he now also has psychomotor retardation, short stature, epilepsy, colon dilation and immature pubertal development. He had been hospitalized 2-3 times annually for adrenal crisis associated with viral or bacterial infections, but the frequency decreased from 20 years old. In 2016, a genetic test revealed a heterozygous Asp769Asn variant in the *SAMD9* gene, leading to the diagnosis of MIRAGE syndrome. At 24 years old, we examined his endocrinological condition and re-evaluated his genetic and immunological features. Primary adrenal insufficiency and hypergonadotropic hypogonadism were confirmed on the CRH test, insulin tolerance test and LHRH test. In contrast, GH secretion, the thyroid function, and glucose metabolism were normal. On a genetic re-evaluation using leukocyte-derived DNA, the heterozygous Asp769Asn variant was confirmed as before with an allele frequency of 47%, which suggested the absence of monosomy 7 or UPD7. A rare variant, Cys420Arg, was simultaneously detected with an allele frequency of 35%. This variant was present in 2% at 3 years old and 17% at 18 years old. Expression experiments revealed that Cys420Arg is a loss-of-function variant that mitigates the exaggerated antiproliferative effect of Asp769Asn. However, an immunological re-evaluation revealed that his immunological condition had deteriorated in some cell populations. Namely, decreased plasmacytoid dendritic cells (pDCs) and transitional B cells were observed. T-cell receptor excision circles were not detected, a finding compatible with the decrease in recent thymic emigrant cells (RTEs; CD3+4+45RA+31+). While the frequency of contraction of infectious diseases decreased, while that of a reversion variant in the *SAMD9* gene increased, his immunological condition deteriorated. His further follow-up will help clarify the long-term prognosis of MIRAGE syndrome.

P1-11

Girls with Premature Adrenarche but not SGA Reach Their Target Height

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Introduction: Premature adrenarche (PA) is the most common cause of premature pubic and axillary hair growth before the age of 8 in girls. At the time of diagnosis, the height and bone age of the cases with premature adrenarche were determined to be higher than their peers. The long-term effects of advanced bone age on the final length of the cases are controversial. In this study, it is aimed to share the long-term follow-up data of the cases diagnosed with premature adrenarche.

Method: 143 patients followed by the Pediatric Endocrine Clinic between 1994-2022 with pubic and/or axillary hair were included in the study.

Results: Out of 143 cases, 132 were diagnosed with PA, 6 with non-classical congenital adrenal hyperplasia, 2 with adrenocortical carcinoma, 2 with rapidly progressive puberty, and 1 with growth hormone excess. The mean height SDS of the patients with PA was 0.59 ±1.06. Their target height SDS was -0.25±0.87, median bone age was 8.36(IQR:1.02), and median estimated adult height SDS was -0.27(IQR:1.55). The mean difference between bone age and chronological age was 0.73±1.05years. 12.7% of the cases were SGA. HOMA-IR was higher than 2.21 in 25.8%. 34.8%(n:46) of premature adrenarche cases reached the final height. The mean final height SDS was 0.15±1.01. In the cases who reached the final, the mean final height SDS-target heightSDS was 0.34±0.78, and the mean final height SDS-PAH SDS was 0.38±1.05. A significant correlation was found between the first height SDS-target height SDS and the final height SDS-target height SDS in paired t-test(p=0.002). It was observed that the subjects whose height was above the target at the time of presentation completed their growth with a height above their target, although their SDS decreased significantly until the final. The difference between the final height and target height SDS of the patients with SGA was significantly lower than that of those without. The mean final height SDS-target height SDS of the subjects with SGA was -0.06±0.46 and their mean final heightSDS was below the target.

Conclusion: As a result, it became clear that even though the cases of premature adrenarche had advanced bone age at the time of diagnosis, it was observed that they completed their final height above their target height. However, it was shown that this was not valid in cases with a history of SGA birth, and they were below their targets.

P1-12

Growth and Metabolic Syndrome (MetS) Criteria in children with Classic Congenital Adrenal Hyperplasia (CAH) treated with corticosteroids (CS) versus normal obese children

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Introduction: Management of CAH presents unique challenges distinct from other forms of adrenal insufficiency. Higher doses of glucocorticoids are required to suppress adrenal androgen synthesis, which can lead to overtreatment. Steroid-associated adverse events (SAAE) include hypertension, hyperglycemia, and diabetes, overweight and obesity and short stature.

Aim: The goal of this study was to assess the occurrence of steroid-associated growth and metabolic adverse events (SAAE) in children with CAH on treatment with CS since early infancy and to compare them with another high-risk group (obese children BMISDS > 2).

Methods: Data of 30 children with CAH was analysed retrospectively. They received hydrocortisone (n = 11) or prednisolone (n= 19) and fludrocortisone (0.1: 0.15 mg OD) since early infancy. The mean hydrocortisone dose = 22.5 +/- 7 mg/m2. The growth data was recorded and the different metabolic criteria including impaired fasting glucose (IFG), high LDL and cholesterol, lower HD and high blood pressure for age and sex were studied over this period and compared with the data for 66 age-matched obese non-nephrotic children.

Results: Comparison between the CAH group treated for an average of 5 years with CS and age matched obese children showed that short stature (HtSDS < -2) and high LDL occurred more significantly the CAH group. Impaired fasting glucose and low HDL occurred more in the obese group. Hypertension was detected in 2/30 (6.7%) of the CAH group vs 12.1% in the obese group. (Table 1)

Conclusion: Children with classic CAH on CS treatment for > 5 years had high rate of obesity and overweight (60%0 and short stature (23.3%). In addition, some of them have higher occurrence of metabolic criteria including high LDL and triglyceride and blood pressure. These patients shall be monitored closely for abnormal growth (weight and height) as well as for abnormal metabolic criteria.

Table 1. Metabolic risk factors among CAH children on CS therapy for > 5 years vs age matched obese children.

Variables	**CAH on CS for >5 yr**	**Obese 6-12 yr**	**P value**
Number	30	66	
Age	6.7 +/- 2.3	7.8 +/- 2.5	
Overweight and obese	60%	100%	
Short stature HtSDS <-2	23.3% *	6%	.0139
IFG>5.6 mmol/L	0%	16.7%*	.01732
LDL > 2.7 mmol/L	26.7%*	7.5%	.0114
HDL < 1.03 mmol/L	3.3%	21.2%	.17068
TG >1.7 mmol/L	16.66%	7.5%	.17702
Cholesterol > 4.5 mmol/L	10%	21.2%	.18352
Hypertension BP >95th centile for age and sex	6.66%	12.1%	.41794

P1-13

Epidemiology and causes of primary adrenal insufficiency in children: A population-based study

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Objective: Incidence and causes of primary adrenal insufficiency (PAI) have not been comprehensively studied in children. Our objective was to describe the epidemiology and to assess national causes of PAI in children.

Design: A national population-based descriptive study of PAI in patients aged 0-20 years.

Methods: Diagnoses referring to adrenal insufficiency in children born in 1996-2016 were collected from the national health care register. Patients with PAI and the causes of the disease were identified by studying patient records. Incidence rates were calculated in relation to the person-years in the national population of same age.

Results: Of the 97 patients with PAI, 36% were female. The incidence of PAI was highest during the first year of life: 3.4/100,000 person-years (in females 2.7/100,000 and in males 4.0/100,000). At 1-15 years of age, the total incidence of PAI was 0.4/100,000, in females 0.3/100,000, and in males 0.6/100,000 person-years. Cumulative incidence was 10/100,000 persons at the age of 15 years and 13/100,000 persons at 20 years of age. Congenital adrenal hyperplasia was the cause in 57% of all patients and in 88% of patients diagnosed before age of one year. Other causes among the 97 patients included autoimmune disease (29%), adrenoleukodystrophy (6%), and other genetic causes (6%). From the age of five years, most of the new cases of PAI, and after the age of eight years 95% of new cases of PAI were due to autoimmune disease.

Conclusion: After the first-year peak, the incidence of PAI is relatively constant through ages of 1-15 years. One out of 10,000 children are diagnosed with PAI before the age of 15 years. PAI during the first four years of life is most likely due to CAH but autoimmune disease is the most prevalent cause later in childhood.

P1-14

Use of Aromatase inhibitors to improve height outcomes in children with Congenital Adrenal Hyperplasia due to 21 hydroxylase deficiency

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Keywords: Congenital Adrenal Hyperplasia, Advanced bone age, Aromatase inhibitors, Predicted Adult Height

Introduction: Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) is characterized by cortisol and mineralocorticoid deficiency with excess adrenal androgen production. Standard treatment includes glucocorticoid and mineralocorticoid replacement. Slightly supraphysiological glucocorticoid replacement aims to reduce androgen load to maintain adequate growth, but adult height is often reduced due to the aromatisation of excess androgens into oestrogens causing growth acceleration with early epiphysial fusion at the growth plate. Aromatase inhibitors (AI) are a potential adjunct treatment in CAH to improve compromised predicted adult height (PAH) in the presence of significantly advanced bone age.

Aim: To describe growth-related parameters in five CAH patients with significantly advanced bone age, treated with non-steroidal AI, Anastrozole or Letrozole in addition to standard of care.

Results: Five male patients had genetically confirmed non-salt-wasting CAH diagnosed between two and six years of age. Bone age (BA) was advanced by 9.3 Standard Deviations (SD) (range 4.2-17.4) compared to chronological age at diagnosis. AI was started as an adjunct therapy at the age of 9.6, 7.25, 5, 3.5, 5years for the patients A, B, C, D and E in addition to gonadotropin releasing hormone analogue therapy to suppress biochemically confirmed central precocious puberty. Patients received AI for a mean period of 40.25 months (range 26-52). Mean BA was+6 SD (range 3.6-11.3) after 24 months of treatment. The mean BA improvement was 3.5 SD and the PAH has improved by 10-16cm for more than 24 months of treatment. Throughout the treatment period, bone mineral density, liver function and lipid profile remained normal.

Conclusions: AI may help as an adjuvant therapy in improving PAH by delaying bone maturation in children with CAH due to 21-OHD in the presence of significantly advanced BA without significant short term adverse effects. Larger multi-centre studies are required to validate the efficacy and safety, including evaluation of long-term adverse effects.

P1-200

Evaluation of chromatin remodeling factors ATRX and DAXX and telomeres in pediatric adrenocortical tumors

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Background: Impairment of the chromatin remodeling factors ATRX and DAXX and telomeres abnormality play a role in cancer biology, influencing the clinical outcomes. However, their roles in adrenal tumorigenesis require broader investigation.

Aim: To evaluate ATRX and DAXX genotype and expression, telomere length, and the alternative lengthening of telomeres (ALT), as well as their clinical significance, in primary adrenocortical tumors ACT samples from pediatric patients.

Methods: 106 children with ACT (72% girls, median age 1.8 years), and their primary tumor samples were included. Tumor ATRX, DAXX, and TERT genotypes were assessed by whole exome sequencing (Illumina) and their relative gene expression by qPCR. ATRX and DAXX protein expression were evaluated by IHC. Telomere length was assessed by qPCR, and ALT by FISH. Patients' progression-free (PFS) and overall survival (OS) were calculated using Kaplan-Meier curves and log rank. A significance level of $\alpha=0.05$ and 95% confidence intervals were used.

Results: Age at diagnosis below four years was associated with a better prognosis, while advanced disease and classification as carcinoma by the Wieneke score were associated with a worse prognosis. *ATRX* was mutated in 44.5%, and *TERT* in 37% of the tumors evaluated, which were all carriers of the p53 p.R337H germline mutation. *ATRX* mutations were not associated with *ATRX* gene expression, and none of the samples expressed *TERT*. Compared to control normal adrenals, *ATRX* gene expression was decreased ($p<0.01$), while *DAXX* gene expression was increased ($p<0.01$) in pediatric ACT. ATRX protein expression was lost in most samples (95.6%), being positive in two mutant samples. DAXX protein expression was lost in a minority (22.2%). There was a weak negative correlation between *ATRX* ($\rho=-0.35$; $p=0.008$) and *DAXX* ($\rho=-0{,}3$; $p=0.023$) gene expression and telomere length. ALT was present in 27.3% of ACT. *ATRX* and *TERT* mutations were not associated with telomere length nor with ALT. Patients whose tumors were concomitantly mutant for *ATRX* and *TERT* (n=4) had reduced PFS ($p=0.006$) and OS ($p=0.003$). There was no association between gene/protein expression, telomere length, or ALT and PFS or OS.

Conclusion: Abnormal ATRX and DAXX gene and protein expression are frequent in the pediatric ACT and influence the telomere length, but not the patients' clinical outcome. However, the co-occurrence of somatic mutations in *ATRX* and *TERT* is strongly associated with the unfavorable prognosis of these patients.

P1-201

Molecular characterization of TNXA/TNXB chimeras in cases carrying deletion of the CYP21A2 gene: High incidence of chimeras identified

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Introduction: CAH-X syndrome refers to a subset of Congenital adrenal hyperplasia (CAH) patients who display the hypermobility phenotype of Ehlers–Danlos syndrome (hEDS) due to the monoallelic/biallelic presence of a *CYP21A2* deletion extending into the *TNXB* gene (chimeric *TNXA/TNXB* gene). To date, three different *TNXA/TNXB* chimeras have been described, CH-1 (presence of a TNXA-derived 120bp deletion in exon 35 of the *TNXB* gene), CH-2 (presence of p.Cys4058Trp in the *TNXB* gene) and CH-3 (presence of one or more of the three variants cluster: p.Arg4073His, p.Asp4172Asn and p.Ser4175Asn in the *TNXB* gene). Herein, we present the molecular investigation of *TNXA/TNXB* chimeras in subjects carrying deletion of *CYP21A2* gene in a period of 7 years (2017-2023).

Patients and Methods: Amongst 805 individuals referred for genetic analysis of the CYP21A2 gene, twenty-two cases (16 CAH patients and 6 CAH heterozygotes) harbored deletion of the CYP21A2 gene in monoallelic or biallelic constellation. These twenty-two cases were further analyzed for the presence of *TNXA/TNXB* chimeras. The CYP779f/Tena32F PCR primers were employed to amplify a 8.5kb PCR product that was then subjected to nested PCR and bidirectional sequencing. MLPA analysis was also employed to detect the CH-1 chimera (MLPA kit P050-CAH).

Results: Chimeras were identified in 50% (11/22) of cases studied. In CAH patients, chimeras were found in 37.5% of cases particularly: CH-1 chimera in 12.5% (2/16) and CH-2 chimera in 25% (4/16). CH-3 chimera was not identified in CAH patients. In one CAH patient harboring homozygous deletion of the *CYP21A2* gene CH-2 chimera was found also in homozygosity. In heterozygotes for *CYP21A2* gene deletion chimeras were identified in 88.3% of cases with CH-1 chimera present in 66.7% (4/6) and CH-3 chimera in 16.7% (1/6) of cases. CH-2 chimera was not identified in any heterozygote.

Discussion: *TNXA/TNXB* chimeras were identified in 50% of tested cases carrying deletion of *CYP21A2* gene underlying the necessity for further clinical evaluation of these individuals. The genetic diagnosis of CAH-X is necessary to provide proper genetic counseling and clinical management of CAH patients preventing long-term symptoms of EDS. Furthermore, heterozygotes carrying *TNXA/TNXB* chimeras should also be monitored to provide the proper genetic counseling and prognosis since they may present with a varied EDS phenotype than monoallelic/biallelic CAH-X patients.

P1-202

Increased adiposity and insulin resistance negatively affect growth in pre-pubertal heterozygote carriers of 21-Hydroxylase deficiency

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Introduction: 21-Hydroxylase deficiency (21-OHD) is the archetype of congenital adrenal hyperplasia (CAH). Deficiency of 21-Hydroxylase results in an impairment of cortisol synthesis, which is critical in stressful conditions when higher output is required to restore homeostasis. In addition, an increased androgen production, might results in undesirable manifestations of hyperandrogenism, as menstrual abnormalities, infertility and cosmetic annoyances and growth impairments. Interestingly, heterozygote carriers (HZ) carriers may occasionally manifest some of such conditions.

Objective: Therefore, we aimed to explore physical growth in pre-pubertal children with HZ evaluated by performing an ACTH stimulation test.

Methods: Retrospective data from hospital records of 54 diagnosed pre-pubertal children with heterozygous 21-hydroxylase deficiency and with available clinical data of final height-SDS were analyzed. Anthropometric and laboratory tests including indexes of insulin resistances (HOMA-IR and Triglycerides/HDL ratio values) and bone age were analyzed. Height-SDS changes over time were calculated as delta-height-SDS (final height-SDS - pre-pubertal height-SDS). Thus, the population was divided into terciles according to h delta-height-SDS (1st tertile:<-0.748; 2ndtertile: between -0.748 and 0.001; 3rd tertile >0.001). The main differences across the tertile groups were investigated by Kruskall-Wallis test.

Results: The three tertile groups were similar in terms of age at baseline (8.0, 8.5 and 8.1, years respectively), gender (M/F 3/15, 6/12 and 4/14 respectively) and height-SDS at baseline. Interestingly, Weight-SDS and BMI-SDS and indexes of insulin resistances progressively decreased across the three tertile groups at baseline, showing higher values in the first tertile. Height gain during puberty progressively increased across the three tertiles at baseline, showing higher values in the third tertiles.

Conclusions: In pre-pubertal children with HZ, high values of BMI-SDS, weight-SDS and insulin resistances are related to an impaired height-SDS variation during growth and to a worse height gain during puberty.

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Adrenal insufficiency due to bioinactive ACTH caused by novel POMC variants

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Introduction: Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive disease characterized by ACTH-resistant isolated cortisol deficiency. FGD usually presents with hypoglycemia, convulsions, prolonged jaundice, and marked skin hyperpigmentation in the early period of life. Several defects in MC2R, MRAP, MCM4, NNT, and TXNRD2 genes are related to FGD. In all these situations, plasma ACTH is high. By contrast, all reported cases of glucocorticoid deficiency due to mutations in the gene encoding proopiomelanocortin (POMC), the precursor protein from which ACTH is derived, had low or undetectable plasma ACTH. Patients with POMC defects generally present early-onset obesity, hyperphagia, red hair, hypopigmentation and ACTH deficiency. Only 3 cases of POMC gene mutations characterized by a bioinactive ACTH, mimicking FGD, have been so far described in literature.

Case Report: We report the case of a boy who presented at the age of 2 years with a history of recurrent hypoglycemia. Biochemical evaluation revealed high ACTH levels (815 pg/ml, nv 10-130 pg/ml) and undetectable cortisol (&lt;0,16 mcg/dl, nv 4,3-22,4 mcg/dl) leading to a diagnosis of primary adrenal insufficiency (PAI). Skin and mucosae were not hyperpigmented and the patient had red hair. Treatment with glucocorticoids and mineralcorticoids was started with resolution of symptoms. During the follow-up he also developed epilepsy, mild psychomotor delay and obesity with hyperphagia.

Several genes known to cause FGD, adrenal hypoplasia or metabolic and syndromic diseases associated with PAI resulted to be normal. An extensive work-up excluded acquired conditions of PAI. In order to reach a definitive diagnosis, whole exome sequencing (WES) was performed. Three variants in POMC gene were identified: the p.R145C variant (inherited from the mother), already described in two children with glucocorticoid deficiency; p.R137C and p.K136N (inherited from the father), which are novel variants never described in the literature.

Conclusions: We report a unique case of hypocortisolism, obesity and hyperphagia caused by secretion of bioinactive ACTH molecule due to novel mutation of POMC gene. This case expands our knowledge on genetic conditions responsible of AI in children and highlights how POMC mutations should be considered in children with otherwise unexplained PAI, in particular when associated with early-onset obesity and hyperphagia. PAI in children and young people often has a genetic basis and establishing the specific etiology can influence management and treatment.

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Longitudinal Changes in Serum DLK1 Concentrations During Minipuberty in Healthy Infant Girls; Association to Changes in Linear Growth and Fat Mass

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Background: Growth in infancy is considered primarily to be regulated by nutrition and insulin, whereas less is known about the influence of IGF-I, reproductive hormones and other factors of importance. Recently, paternally inherited genetic defects of DLK1 (Delta-like 1 homolog) were found in girls with central precocious puberty (CPP) with a metabolic phenotype. In addition, low maternal serum DLK1 concentrations were significantly lower in pregnant women who delivered an SGA newborn compared to controls. Knowledge about circulating DLK1 during minipuberty and the association to changes in linear growth and body composition needs further clarification.

Objective: To evaluate longitudinal changes in serum DLK1 concentrations during female minipuberty compared to changes in linear growth body mass index (BMI) and fat mass.

Method: In a prospective, longitudinal study (The COPENHAGEN Minipuberty Study, ClinicalTrials.gov ID: NCT02784184) between 2016 to 2018, we examined 233 healthy term children born AGA (114 females), at birth and up to six times within the first year of life. Length was measured in supine position to the nearest 0.5 cm with a baby length measuring mat (ADE Germany GmbH & Co, Hamburg, Germany). Weight was measured on an electronical calibrated scale (Babyscale, Solotop Oy, Finland) to the nearest 0.005 kg. Body fat percentage was calculated by Slaughter's equation using triceps and subscapular skinfolds. At each visit a blood sample (n=206) were attempted in all female infants and then analysed for DLK1, growth factors and reproductive hormone. Serum DLK1 was assessed by an immunoassay (ELISA) (Immuno-Biological Laboratories, Inc (IBL-America), Minneapolis, USA) with a detection limit of 336 pg/ml.

Results: Serum DLK1 in girls was detectable in all longitudinal samples (100% > LOD) with an overall mean (SD) concentration of 17.4 ng/ml (3.5) (n =43) within the first month of life, followed by a log-linear decline through the first year of life. At 12 months of age, the mean (SD) DLK1 concentration was 9.5 ng/ml (2.4) (n=26). We did not find a correlation between mean DLK1 level (SDS) for each individual and the mean BMI SDS (Pearson Correlation coefficient -0.01, p=0.9).

Conclusion: Serum DLK1 declined significantly during the first year of life in healthy infant girls born AGA. In our initial analyses, we did not find any significant correlation between DLK1 and BMI in infant girls.

P1-205

Effects of hyperandrogenism on psychological perception and quality of life in patients with non-classical congenital adrenal hyperplasia

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Background: Non-classical congenital adrenal hyperplasia (NCCAH) is a hyperandrogenic disorder affecting negatively the psychological health and the quality of life (QoL) of patients.

Aim: To evaluate the psychological health and QoL in female NCCAH patients in comparison to female age-matched healthy controls.

Participants and Methods: A total of sixty-eight females, aged 10-27 years, were enrolled in this study, including thirty-four patients with NCCAH (mean age 16.2±3.4 years) and thirty-four healthy controls (mean age 15.0±3.1 years). Data was collected on anthropometry, clinical features of hyperandrogenism (hirsutism, acne, hair loss) and menstrual irregularities. Hormonal and metabolic markers were assessed. A validated World Health Organization (WHO) Brief quality-of-life questionnaire-26 was used for the assessment of physical (D1) and psychological (D2) health, social relationships (D3) and environment (D4). Psychological assessment was evaluated using the EDI-3 standardized questionnaire.

Results: Hirsutism and acne were more common in NCCAH girls compared to healthy controls (80.5% vs. 19.5%, p<0.0001 and 80% vs. 20%, p<0.001, respectively). No significant difference was found in the rate of menstrual disorders between groups. The estimated mean Ferriman-Gallwey score was higher in NCCAH girls (18.7±5.3vs7.7±8.3,p<0.001)beingcorrelatedwithAndrostendione and 17OHProgesterone levels (r=0.519, p<0.001 and r=0.424, p<0.001, respectively). Overweight/obesity presence was determined in 17.7% of all participants without a significant difference between the groups. Androstendione (15.4±6.7 vs. 9.8±5.3, p<0.001) and basal levels of 17OHProgesterone (2.2 ±1.3 vs. 0.8±0.6, p<0.001) were significantly higher in NCCAH females. Androstendione levels correlated with the presence of acne (r=0.369, p=0.002), hair loss (r=0.370, p=0.002) and hirsutism (r=0.289, p=0.017). 17OHProgesterone basal levels correlated with hirsutism (r=0.450, p<0.001), acne (r=0.491, p<0.001) and psychological health (r=0.355, p=0.003). Analyzing the WHOBrief QoL questionnaire the NCCAH girls showed significantly lower physical and psychological health scores compared to healthy females (50.5±11 vs. 62.9±11.5 for D1, 57.6±11.5 vs. 68.7±10.5 for D2, p<0.001). The psychological status correlated negatively with the presence of hirsutism (r=-0.306 p=0.012), acne (r=-0.333, p=0.006) and hair loss (r=-0.333, p=0.006). The EDI-3 survey showed that NCCAH patients had significantly low assessment score results on 8 of all used psychological scales compared to controls - interpersonal alienation, interoceptive deficits, emotional dysregulation, low self-esteem, affective problems composite, general psychological maladjustment, ineffectiveness and overcontrol (p<0.05 for all).

Conclusion: The hyperandrogenic NCCAH girls have impaired QoL and psychological health. Therefore, early diagnosis and management are important for the prevention of psychological consequences.

P1-206

Adrenal insufficiency is not a common cause of hypoglycemia in children

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Background: Hypoglycemia etiology in children is heterogeneous and varies by age. Both growth hormone (GH) and cortisol deficiencies may present with hypoglycemia; the latter may result in an adrenal crisis that may be fatal.

Objectives: To evaluate responses of cortisol and GH to spontaneous hypoglycemia in infants and children, and to assess the rate of true cortisol deficiency in children, defined as cortisol<500 nmol/l.

Study Design: This retrospective study included 127 children (0-18 years old) who presented with hypoglycemia during 1992-2022, and who had a serum laboratory glucose level ≤50 mg%.

Results: Cortisol <500 nmol/l was detected in critical samples of 50% (n=64) of the patients, and cortisol <270 nmol/L in 12.2% (n=29). A normal cortisol response to Synacthen stimulation was observed in 93.7% (n=119). Compared to the rest of the cohort, among children with cortisol levels <500 nmol/L, the median GH level in the critical samples was higher (6.0 vs. 3.4 ng/ml, p<0.037), and insulin was detected more frequently (59.6% vs. 35.6%, p<0.011). No other biochemical or clinical differences were observed between these groups.

A critical sample cortisol level was associated with fast test nadir cortisol (R=0.574; p<0.001) and Synacthen stimulated cortisol (R=0.448; p=0.004), but not with age (R=-0.009; p=0.922) or with glucose (R=0.025; p=0.802), insulin (R=-0.122; p=0.206) or GH (R=-0.163; p=0.088) levels measured in critical samples. Critical sample GH levels were inversely related to age (R=-0.322; p<0.001) and measured glucose (R=-0.431; p<0.001), but not to critical sample cortisol or height-SDS (R=0.021; p=0.836).

True cortisol deficiency was diagnosed in 4.3% (n= 8). Four had multiple pituitary deficiency. The other diagnoses were: primary adrenal insufficiency (n=1), IGF1 receptor mutation (n=1), fructose 1,6 diphosphatase deficiency (n=1) and transient hyperinsulinism (n=1).

Conclusions: While an insufficient cortisol response to hypoglycemia is common among children, true cortisol deficiency is uncommon. As no one clinical parameter can diagnose cortisol deficiency, a Synacthen stimulation test should be performed to rule out adrenal insufficiency.

P1-207

Health-Related Quality of Life in Children with Congenital Adrenal Hyperplasia: A Systematic Review and Meta-Analysis

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Introduction: Congenital adrenal hyperplasia (CAH) is a lifelong condition associated with long term medical and psychosocial issues, which can adversely affect Quality of Life (QoL). There is paucity of high-grade evidence on health-related QoL in children and adolescents with CAH, with available studies being limited by small study samples. We conducted a systematic-review(SR) and meta-analysis(MA) to assess factors associated with health-related QoL among children and adolescent with CAH worldwide, and compare self-reported and parent-reported QoL of children/ adolescents with CAH with healthy children/adolescents.

Method: This study was registered prospectively in the PROSPERO International-prospective-register-of-systematic-reviews (reg no: CRD42022313389). Google-scholar, PubMed, LILACS, Cochrane and Scopus databases were searched up to 03/05/2022, using a pre-defined search strategy and MESH terms, to identify original studies describing/assessing self-reported/parent-reported health-related QoL in patients with CAH ≤21 years. Studies comparing QoL of children/ adolescents with CAH with healthy controls using standardised validated questionnaires were included in MA. Methodological quality of studies were assessed by the Newcastle-Ottawa quality-assessment Scale (NOS), and heterogeneity by I2 statistics.

Results: A total of 1308 publications were screened, from which ten studies (CAH n= 593) were eligible for the SR (NOS scores ranging from 3-7/9), while six studies were eligible for the MA, and they showed moderate-considerable heterogeneity.

MA showed that compared to healthy controls, children and adolescents with CAH (n= 227) had lower parent-reported QoL in their overall psychosocial health (MD-9.9[-12.6,7.3],P=<0.001)), as well as in all three individual psychosocial domains: school domain ((MD-7.4[-12.2, -2.5], P=0.003); emotional domain (MD-5.6[-10.2, -0.9], P=0.02) and social domain (MD-4.3[-8.1, -0.5], P =0.03); while self-reported QoL in children/ adolescents with CAH was lower in school domain only (MD-8.5[-15.9, -1.2], p=0.02). Children/ adolescents did not show any difference to healthy controls in parent- and self-reported health-related physical QoL. Factors associated with lower overall QoL among children/adolescents with CAH included: poor disease control, poor compliance to medication, higher number of hospital admissions, greater virilization, and presence of hyperpigmentation, hypertension and urinary incontinence.

Conclusion: Children/ adolescents with CAH had impaired overall psychosocial QoL from parenteral perceptive, and impaired QoL in school domain from self-report, while their physical QoL was similar to healthy children. Factors associated with lower QoL included poor disease-control, and disease/treatment-related complications. Further research is needed to determine if better disease-control and increased psychosocial support could help improve QoL in children with CAH.

P1-208

Genotype-Specific Cortisol Reserve in a Cohort of Subjects with Non-Classic Congenital Adrenal Hyperplasia (NCCAH)

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Background: Recent guidelines suggest that NCCAH subjects stop their glucocorticoid therapy after achieving adult height. However, these guidelines do not differentiate between genotype groups within the NCCAH population.

Aim: Compare ACTH stimulated cortisol and 17-hydroxyprogesterone (17OHP) levels, and the rate of partial cortisol insufficiency in NCCAH subjects carrying one mild and one severe (mild/severe) mutation vs. subjects with bi-allelic mild (mild/mild) mutations.

Methods: A retrospective evaluation of the medical records of 122 patients who presented with postnatal virilization and were diagnosed with NCCAH. Patients with postnatal virilization (mainly precocious adrenarche) underwent the standard intravenous 0.25 mg/m^2 ACTH stimulation test. Those with stimulated 17OHP level above 40 nmol/L were screened for the nine most frequent CYP21A2 gene mutations followed by Multiplex Ligation-dependent Probe Amplification (MLPA). A stimulated cortisol level below 500 nmol/L was defined as partial cortisol defficiency.

Results: The NCCAH patients (n=122) were subdivided according to their genotype into three groups: 77 carried the mild/mild genotype, mainly homozygous for pV281L mutation; 29 were compound heterozygous for one mild and one severe mutation, mainly p.V281L/ p. I2Splice and 16 were heterozygous for p.V281L, and therefore were excluded from the statistical evaluation. Stimulated cortisol levels were significantly lower in the mild/severe than in the mild/mild group (mean±sd, 480± 90 vs 570 ±125 nmol/L, p<0.001). The mild/severe group exhibited a significantly higher rate of partial cortisol insufficiency (21/28, 75% vs 28/71, 39%, p= 0.004). Peak 17OHP was significantly higher in the mild/severe group (198± 92 vs 118 ± 50 nmol/L, p<0.001). A cutoff 17OHP level of 170 nmol/L is suggested to differentiate between groups.

Conclusion: The high rate of partial adrenal insufficiency in the mild/severe group underscores the need to carefully consider the value of glucocorticoid therapy cessation and the importance of stress coverage in this group.

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Successful transition in Congenital Adrenal Hyperplasia - A single centre experience over 20 years

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Introduction: Transition medicine aims at the coordinated transfer of young patients with a chronic disease from paediatric to adult specialist care. The present study reflects 20 years of experience in transitioning patients with congenital adrenal hyperplasia (CAH) in a single centre university setting.

Methods: The endocrine transition clinic was established in 2002 and offers joint consultations with a paediatric and an adult endocrinologist for patients and their families. Data obtained at the transition clinic were evaluated retrospectively from 2002 to 2005 and 2008 to present (2006 and 2007 not considered due to incomplete data acquisition).

Results: 59 patients (29 m) with CAH were transferred from the paediatric to the adult endocrine department during the stated time period. Median age was 18.4 years (17.6 -23.6). The main

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underlying enzyme defect was 21-hydroxlase deficiency (21-OHD, 90% of cases). 38 patients (23 m) presented with classic 21-OHD with salt wasting (sw), 7 (1 m) with the simple virilising (sv) form and 8 (3 m) with non-classic (nc) 21-OHD. Rarer enzyme deficiencies were found in 6 cases: 2 sisters with 17α-OHD, 2 siblings with P450-oxidoreductase-deficiency, 1 male patient with 3ß-hydroxsteroid-dehydrogenase-deficiency and 1 female patient with 11ß-OHD. At present 34 patients (57.6%, 20 m) are still seen at the adult clinic, 1 patient (1.7%, m) moved abroad and 24 patients (40.7%, 8 m) were lost to follow-up (13 sw 21-OHD, 6 sv 21-OHD, 5 nc 21-OHD). 37 patients (62.7%) attended the adult clinic for > 2 years after transfer, 17 patients (28.8%) for > 10 years. 6 patients (10.2%) were transferred within the last two years. In the group of patients lost to follow-up, median time of continued visits at the adult clinic was 16.3 months (0 – 195.2). Defining a successful transfer as 2 or more visits in the adult endocrine department after initial consultation in the transition clinic, transfer was efficient in 85 % of the cases.

Conclusion: A seamless transfer from paediatric to adult medical care is essential for adolescents with CAH. It requires continuous joint support from both sides during the transition period. Successful transition remains challenging and necessitates adequate funding. Further investigations are needed to establish predictive parameters for a sustainable transition process.

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Change of Thyroid Volume in the Treatment of Congenital Primary Hypothyroidism

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Objectives: In congenital primary hypothyroidism, the effect of treatment on thyroid volume is not known. In this study, the change in thyroid volume according to etiology and its effect on treatment discontinuation rates in the treatment of congenital primary hypothyroidism were investigated.

Materials and Methods: The clinical features and thyroid ultrasonography findings at the time of diagnosis and at the age of three years of 207 patients with congenital primary hypothyroidism were evaluated.

Results: At diagnosis, the thyroid of the patients was 64.3% (n:133) normal, 16.9% (n:35) hyperplastic, 10.1% (n:21) agenetic, 4.8% (n:10) hypoplastic, 2.4% (n:5) ectopic, 1.4% (n:3) hemiagenetic. However, at the age of three, the thyroids of the patients were 75.8% (n:157) normal, 8.2% (n:17) hyperplastic, 10.1% (n:21) agenetic, 1.9% (n:4) hypoplastic, %2,4 (n:5) ectopic, 1.4% (n:3) hemiagenesic. There was no significant difference in thyroid volumes of patients with normal thyroid volume at the time of diagnosis with treatment (p:0.305), and the rate of discontinuation of treatment at the age of three was 78.6%. The median thyroid volume of patients with hyperplastic thyroid at diagnosis decreased by 3.54 SDS with treatment (p:0.0001) and the rate of discontinuation of treatment at the age of three was 85%. The rate of discontinuation of treatment was not different between those whose thyroid volume returned to normal and those whose hyperplasia continued (p: 0.430). An increase in thyroid volume SDS (median 1.12 SDS) was observed in all patients with hypoplasia at diagnosis (p:0.005). After 3 years of treatment, 70% of patients who were hypoplastic at diagnosis had normal thyroid size and the success rate of treatmentdiscontinuation was 50%.

Conclusion: In our study, in which the effect of congenital hypothyroidism treatment on thyroid volume was evaluated for the first time, it was found that the effect of treatment on thyroid volume varied according to thyroid pathology. While there was no significant change in thyroid volume SDS with treatment in patients with normal thyroid gland at diagnosis, a significant decrease was observed in patients with thyroid gland hyperplasia at diagnosis, and a significant increase in patients with hypoplasic thyroid gland at diagnosis. In conclussion, in patients with congenital primary hypothyroidism, even if the thyroid gland is hyperplastic or hypoplastic, there may be an improvement in volume over time and drug discontinuation may be possible.

P1-211

Salivary 11-oxygenated 19-carbon steroids in children with congenital adrenal hyperplasia and Addison's disease compared to healthy children

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Background: 11-oxygenated 19-carbon (11oxC19) steroids, 11ketotestosterone (11KT) and 11βhydroxyandrostenedione (11OHA4) are adrenally derived steroids that rise in congenital adrenal hyperplasia (CAH). Increased 11oxC19 concentrations are associated with markers of poor control of CAH. To date, 11oxC19 concentrations have not been measured in patients with Addison's disease (AD).

Methods: Children with primary adrenal insufficiency provided saliva samples at 9am, then 2-hourly throughout the day using Salivettes®. Children did not eat, drink or brush their teeth an hour prior to sampling. Salivary cortisol, cortisone, 17OHP, T, A4, 11KT and 11OHA4 were analysed. Results were compared to healthy controls matched for age and sex.

Results: 26 (15M), aged 2–18 years [21 with CAH (hydrocortisone dose 5.6-15.7mg/m2/day), 4 with AD (hydrocortisone dose 10.3-25mg/m^2/day)] participated. One child, aged 2 years, could not provide samples. Salivary cortisol showed hydrocortisone

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Table 1. Table showing salivary steroid hormone concentrations compared to healthy controls matched for age and sex

Salivary steroid	CAH (n=21)	Addison's disease (n=4)
Cortisol	High*	High*
Cortisone	No difference (NS)	No difference (NS)
T	Increased (p=0.03)	Slightly increased (NS)
A4	Increased (p=0.03)	Increased (p=0.03)
11KT	Increased (p=0.03)	Decreased (p=0.03)
11OHA4	Increased (p<0.01)	No difference (NS)

* Likely contaminated with hydrocortisone NS: non-significant on Wilcoxon matched pairs signed rank test

contamination. Median salivary cortisone, in all groups, did not differ from healthy children. Salivary 17OHP was significantly higher in CAH compared to AD, p<0.001.

Of 24 samples 11KT was undetectable in 2 children with AD. No healthy children had undetectable concentrations of 11KT. Salivary 11OHA4 concentrations were similar (undetectable in 20/24(83.3%) samples in AD and 16/25(64%) samples in healthy children).

Discussion: Saliva samples are preferable for home monitoring of patients with CAH and AD, and multiple hormones can be measured on single samples. Salivary cortisol is unreliable in patients treated taking hydrocortisone, while salivary cortisone is more reliable. Salivary 11oxC19 steroids, T and A4 are elevated in CAH. The place of 11oxC19 steroids in monitoring of children with CAH, and optimal range for good control, are yet to be determined.

Children with AD have significantly lower salivary 11KT and slightly increased salivary T compared to healthy children. Increased salivary T would be unexpected in AD as the HPG axis is not thought to be affected. Both T and 11KT are potent activators of the androgen receptor. It is possible that loss of negative feedback from 11KT may lead to increased free salivary testosterone.

P1-212

Features of allel variants of congenital adrenal hyperplasia in kazakhstan children of different ethnic groups

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Background: More than 90% of cases of congenital adrenal hyperplasia (CAH) are associated with the occurrence of mutations in the CYP21A2 gene encoding 21-hydroxylase. The level of residual activity of 21-hydroxylase determines the clinical form and severity of the disease.

Aim: To study the distribution of allelic variants of CAH due to 21-hydroxylase deficiency in different ethnic groups of Kazakhstani children.

Material and Methods: We studied DNA isolated from the blood of children with the classic form of CAH. The cohort of patients consisted of 50 patients from 7 regions of Kazakhstan. Of these: 35 (70.0%) Kazakhs, 8 (16.0%) Russians, 2 (4.0%) Turks, 2 (4.0%) Ukrainians, 2 (4%) Uzbeks, 1 (2 %) Uighur. The following set of mutations was used: Δ8bp, Q318X, R356W, E6 cluster (I236N, V237E, M239K), F306+t, I2splice, I172N, P30L, V281L, P453S.

Results: We studied 50 children with CAH from unrelated marriages with mutations in the CYP21A2 gene. Detection of homo-heterozygous mutations on both alleles was achieved in 41 out of 50 patients, which was 82.0%. In five cases (10.0%), a mutation was found in one allele; in 2 (8.0%) patients, none of the 12 common mutations was found. In general, frequent 12 mutations of the CYP21A2 gene were identified in 87 alleles (87.0%), of which in 30.0% of cases a homozygous genotype was detected, in 70% - heterozygous. The most frequent I172N and I2splice mutations in Kazakhs occurred in 37.7% and 26.7%, respectively (Table 1). Russian children have frequent mutations - I2splice, I172N and E6 cluster. In other nationalities, I2splice and Δ8bp are the most frequent.

Conclusions: It was shown for the first time that in Kazakhstan, in children from different nationalities with CAH due to 21-hydroxylase deficiency, the most common mutations are I172N and I2splice.

Table 1. Distribution of allelic variants in different ethnic groups

	Allelic variant frequency, %								
Ethnic group (number of chromosomes)	Δ8bp	I2spl	I172N	Q318X	R356W	E6 cluster	P30L	V281L	F305+t
Kazakhs (61)	7 11,5%	16 26,2%	23 37,7%	6 9,8%	3 4,9%	3 4,9%	1 1,6%	1 1,6%	1 1,6%
Russians (16)	0	10 62,5%	2 12,5%	1 6,3%	0	2 12,5%	1 6,3%	0	0
Other (10)	3 30%	5 50%	0	0	0	0	1 10%	0	1 10%

P1-399

Transcriptome profiling evaluation of pediatric adrenocortical tumors (pACT) reveals a favorable-prognosis transcription signature and potential therapeutic targets

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Aim: To uncover a feasible tumor expression prognostic signature and potential therapeutic targets for children with pACT.

Methods: Tumor RNAseq from 53 pACT children (70% girls, median age: 1.7yrs) was performed (Illumina). Using a robust, state-of-the-art, differential gene expression analysis pipeline, differentially expressed genes (DEGs: adjusted $p<0.05$ and $|\log2\ \text{fold-change}|>1$) were identified (DESeq2). We investigated the DEGs between known favorable disease-progression associated features at diagnosis: age<4yrs, localized disease (IPACTR stages I+II), diagnosis of adenomas (Wieneke score <2), and pACT-2 tumor methylation signature, and which of these DEGs overlapped within these features. DEG-sets enrichment of gene ontology biological process and pathway over-representation were analyzed ($p<0.005$). Patients' progression-free (PFS) and overall survival (OS) were calculated (Kaplan-Meier curves and log-rank).

Results: Favorable progression was observed in patients diagnosed <4yrs of age [n=45 (85%), 5yr-PFS=97% and 5yr-OS=100%, both $p<0.0001$], with localized disease [n=41 (73%), 5yr-OS=94%, p=0.03], with adenomas [n=24 (45%) 5yr-PFS and 5y-OS both 100%, p=0.04 and p=0.03, respectively], and with pACT-2 methylation signature [n=38 (88%), 5yr-PFS=96% and 5yr-OS=100%, both $p<0.0001$]. The down-regulated DEG-set (down_DEG-set, n=79) from younger children's pACT was enriched for calcium-ion regulation of exocytosis and sphingolipid biosynthesis, and the up_DEG-set (n=15) for immune and inflammatory response. Localized disease down_DEG-set (n=48) was involved in immune cell differentiation, and the up_DEG-set (n=7) in MAPK cascade, response to metal-ion, carbohydrate metabolism, and negative regulation of hippo signaling. The down_DEG-set from adenomas (n=22) over-represented fructose and mannose metabolism, glycolysis/gluconeogenesis, and mitophagy; and the up_DEG-set (n=115) over-represented immune and inflammatory response, mesenchymal stem cell differentiation, negative regulation of epithelial cell apoptotic process, PI3K-Akt and JAK-STAT. The pACT-2 down_DEG-set (n=202) was enriched for fructose, mannose, and pentose phosphate pathways, glycolysis/gluconeogenesis, extracellular matrix-receptor interaction, and HIF-1 signaling; and the up_DEG-set (n=202) for NK-cell mediated cytotoxicity, and TGF-beta receptor pathways. Overlapping the DEGs within all evaluated favorable features revealed the differential expression (down-regulation) of one single transcript, which was also up-regulated in the carcinomas: a long intergenic non-coding RNA (lincRNA), not-yet described in adrenocortical tumorigeneses but involved in the regulation of multiple tumors and Wnt signaling pathway, whose increased expression was associated with reduced PFS (p=0.04) and OS (p=0.007) of our patients.

Conclusion: Our data reveal that tumor deregulation of energy metabolism and immune/inflammatory response mainly compromise the prognosis of children with ACT, and uncovers a lincRNA as a novel potential target for precision therapy and precise prognostic management of children with ACT.

P1-400

11-oxygenated androgens as biomarkers in congenital adrenal hyperplasia: reference intervals for children

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Background: Patients with congenital adrenal hyperplasia (CAH) might suffer from hyperandrogenism. For diagnosing and treatment monitoring, usually levels of androstenedione (A4) and testosterone (T) are measured in blood. More recently, adrenal-specific 11-oxygenated androgens such as 11- hydroxyandrostenedione (11OHA4), 11-ketoandrostenedione (11KA4), 11-hydroxytestosterone (11OHT), and 11-ketotestosterone (11KT) were introduced as promising biomarkers, but are not yet implemented for routine clinical care and reference intervals for children are lacking. We aim to quantify dehydroepiandrosterone (DHEA), A4, T, dihydrotestosterone (DHT), 11OHA4, 11KA4, 11OHT, and 11KT in healthy children to gain more insight into the natural course of these androgens. Moreover, we want to establish reference values for prepubertal and pubertal children to facilitate the interpretation of these androgen concentrations in CAH patients.

Methods: A sensitive two-dimensional liquid-chromatography tandem mass spectrometry assay was developed for the quantification of eight androgens (DHEA, A4, T, DHT, 11OHA4, 11KA4, 11OHT, and 11KT) and validated for clinical use. This included measurement of these androgens in a cohort of 256 healthy children (aged 0-17), which were divided into two groups based on age: a prepubertal cohort (n=133; 94 boys, 39 girls) with boys up to 10 and girls up to 9 years old, and a pubertal group (n=123; 52 boys, 71 girls) with boys over 11 and girls over 10 years old. In addition, the androgen concentrations of ten untreated paediatric CAH patients were measured and compared to the concordant reference cohort.

Results: We estimated age-adjusted median values for eight-steroids and computed reference intervals for the (11-oxygenated) androgens using a non-parametric (if n = ≥120) or transformed parametric (if n= <120) method (2.5 – 9.7 percentile). Concentrations of the 11-oxygenated androgens and DHEA started to rise around the age of 6 to 7 without sex differences. Untreated CAH patients have significantly higher concentrations of all androgens compared to the reference group.

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Conclusions: The levels of adrenal-specific 11-oxygenated androgens show an age-dependent, but not sex-dependent, increase, which is most likely due to the onset of adrenarche. The 11-oxygenated androgens might be used as (additional) biomarkers to diagnose and monitor treatment of CAH patients, as conventional biomarkers show high variability. The reference intervals computed in this study facilitate the interpretation of (11-oxygenated) androgen measurements in these patients.

P1-401

Impact of Newborn Screening for Congenital Adrenal Hyperplasia (CAH) on Adult Height: Data from the CAH Registry of the German Society for Pediatric and Adolescent Endocrinology and Diabetology (DGPAED)

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Objective: The treatment of children with classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CAH) is a challenge since both undertreatment and overtreatment with glucocorticoids can affect growth. Numerous reports in the literature have shown that the linear growth of individuals with CAH is affected and adult height is compromised. However, most of these data were obtained in the era before CAH newborn screening.

Design: We analyzed the height outcomes of patients with classical 21-hydroxylase deficiency diagnosed before and after the establishment of newborn screening.

Patients and Methods: We identified 619 patients with classical CAH (239 male, 380 female) and complete data sets regarding the information on newborn screening, phenotype, near adult height (NAH), and parental target height (TH). The median age of the patients at NAH was 15.9 years. The data was derived from 37 pediatric endocrinology centers that enter their data in the electronic registry of the German Society for Pediatric and Adolescent Endocrinology and Diabetology (DGPAED). To assess the effects of newborn screening, we used a linear regression model adjusted/ stratified for sex and phenotype. We excluded patients who had been treated with prednisolone/ dexamethasone. Therefore, the final group consisted of 600 patients with classical CAH. Newborn screening was performed in 107 (17.3%) patients. Corrected NAH was calculated as the difference between NAH and TH. Descriptive analyses and linear regression models were implemented with SAS 9.4.

Across all CAH patients, the corrected NAH (mean; 95% confidence interval) was lower in patients with CAH and newborn screening (-0.25 SDS; -0.44 - -0.06) than in patients without newborn screening (-0.44 SDS; -0.53 - -0.36) (p=0.069). The screening had no effect on cNAH in female patients (n=373), but cNAH was significantly lower (p=0.033) in male patients (n=227) with screening than without screening (-0.35 SDS, -0.62 - -0.07 vs. -0.69 SDS, -0.83 – -0.54). After stratifying for CAH phenotype, screening does not affect the cNAH of patients with SW-CAH (n=410), whereas patients with SV-CAH (n=190) had a significantly better cNAH (p=0.034) with screening 0.15 SDS (-0.28 – 0.59) than without screening (-0.35 SDS; -0.52 - -0.18).

Conclusions: Our data show that CAH newborn screening and subsequent early treatment are important factors for height outcomes in children with classical CAH. In particular, adult height was significantly improved by newborn screening in patients with SV-CAH and in male CAH patients.

P1-402

Micronodular bilateral adrenal hyperplasia: about 2 cases in early childhood

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Background: Micronodular bilateral adrenal hyperplasia (MiBAH) is a rare cause of adrenal Cushing syndrome (CS) that may be subdivided in two main entities: primary pigmented nodular adrenocortical disease (PPNAD) and isolated micronodular adrenocortical disease (i-MAD). The most common presentation of MiBAH is familial PPNAD as part of Carney complex (CNC). The underlying genetic defect in most forms of PPNAD is inactivating germline mutations of the PRKAR1A gene encoding the regulatory subunit type I-alpha (RIalpha) of protein kinase A (PKA).

Case Reports: Patient 1 presented at the age of 2 years and 4 months with rapid weight gain, centripetal obesity, moon facies, hypertension, decreased linear growth, muscle weakness and irritability. Biochemical evaluation confirmed hypercortisolemia with an elevated 24-h urinary free cortisol (UFC), and absent diurnal variation. He failed to suppress to 1 mg overnight dexamethasone. ACTH remained undetectable. The adrenal glands appeared as normal on computed tomography scan. The patient underwent bilateral adrenalectomy and pathological findings were micronodular cortical hyperplasia without pigmentation, consistent with i-MAD. Genetic testing showed a duplication on chromosome 19p that includes the PRKACA gene, which encodes the catalytic subunit alpha (Ca) of PKA. Testicular ultrasound showed tumors which were mixed Leydig cells primarily with a few abnormal Sertoli cells.

Patient 2 presented at the age of 4 years with rapid weight gain, hirsutism, facial swelling, decreased energy. Hypercortisolemia was confirmed with elevated UFC, salivary free cortisol levels, undetectable ACTH. Adrenal imaging revealed an isolated nodule of 6 mm on the right adrenal gland. The patient was screened for manifestations of CNC. High values of IGF1 (429 μg/l) with pituitary MRI showing micronodules were observed. The patient underwent bilateral adrenalectomy with pigmented and nodular adrenals at laparoscopy and well delineated pigmented micronodules at pathological examination. No molecular defect has been identified so far.

Conclusion: To our knowledge, Patient#1 is the first case describing Leydig cell tumors in association with i-MAD due to defects of the PRKACA gene. The diagnosis of patients with MiBAH is challenging as the adrenal glands can be normal on imaging studies and the knowledge of any associated lesions is useful in making the diagnosis. PRKAR1A and PRKACA are among the genes that need to be tested in these situations. The exact biology of how the PRKACA duplications lead to tumor formation remains unknown but it is most likely linked to an increase in PKA signaling, just like PRKAR1A defects in CNC

P1-403

Pediatric Cushing's disease due to somatic USP8 mutations

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Objective: Somatic mutations in the USP8 gene were discovered as the most common genetic defects in corticotropinomas with a frequency of 30 to 60% in adult patients. With regard to pediatric patients, establishing prevalence of USP8 mutations is still challenging due to the rarity of CD incidence in childhood.

Aim: To determine the frequency of somatic genetic drivers of CD in a cohort of pediatric patients.

Patients and Methods: We studied 14 pediatric patients with CD who underwent surgical treatment between 2016 and 2020 and whose formalin fixed paraffin embedded corticotroph tumors and blood samples for DNA extraction were available. Germline and tumor whole-exome sequencing was performed in all of them.

Results: We identified three different somatic USP8 mutations in 3 out of 14 patients, resulting in a frequency of 21%. One variant was previously described as pathogenic, the other two novel variants were found to be likely pathogenic. We did not identify any other significant somatic or germline defects.

The median of age of diagnosis in patients with USP8 mutations was 15.2 years and 13.5 years in patients without mutations. No significant differences in basal plasma ACTH or serum cortisol levels between groups were found (p=0.6 and p=0.88 respectively).

In the group of patients with USP8 mutations, one patient had a macroadenoma, tumor size of the second patient was 9 mm, of the third patient – 5 mm. In the group of patients without USP8 mutations, only one patient had tumor size more than 8 mm. Not a statistical difference but tendency was found (p=0.038, significant p=0.02 after the Bonferroni correction).

All patients with USP8 mutations achieved remission after first transsphenoidal surgery (TSS). In the group of patients without USP8 mutations, remission after first TSS was reported in 6 patients out of 11. The other five patients who did not achieve remission underwent second TSS. Four of these patients entered biochemical remission. The last patient underwent radiation treatment after the second TSS, which led to biochemical remission in one year. Follow-up time after achieved remission was from 1 to 6 years, recurrence of CD was not detected.

Conclusions: We report an estimate of the contribution of somatic genetic defects underlying CD and its genotype-phenotype correlation in a single pediatric cohort. Further research is required to unveil molecular abnormalities in CD which can be useful in designing strategies for clinical screening, prognosis of post-treatment outcome and lead to novel therapeutic targets.

P1-404

Nephrocalcinosis: an emerging issue in children with Congenital Adrenal Hyperplasia

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Hypercalcemia and nephrocalcinosis (NC) are rare findings associated with congenital adrenal hyperplasia (CAH), whose pathogenetic mechanisms are still unclear.

In this study we aimed to investigate the prevalence of NC in a cohort of Italian children affected with classical form of CAH, and to correlate its association with metabolic control of the disease.

Subjects and Methods: This is a multicenter one year-perspective study involving five Italian Pediatric Endocrinology Centers. The study population included 52 subjects (35 males) with molecular diagnosis of CAH evaluated at three different time-points: T0, T1 (+ 6 months), T2 (+12 months). At each follow-up visit, ACTH, 17-hydroxyprogesterone (17-OHP), Δ4-androstenedione, dehydroepiandrosterone sulfate (DHEAS) serum levels, and Ca/Cr ratio in urine were measured. A renal ultrasound was also performed. A multivariate statistical approach using principal component analysis (PCA) was performed to study possible hidden patterns of associations/correlations between variables, and to assess the trend of them during the time.

Results: The prevalence of NC was 17.3% (9 subjects) at T0, 13.5% (7 subjects) at T1 and 11.5% (6 subjects) at T2. A statistically significant difference was found for 17-OHP [T0: 11.1 (3.0~25.1), T1: 7.1 (1.8~19.9), T2: 5.9 (2.0~20.0), $p<0.005$] and for Δ4-androstenedione [T0: 0.9 (0.3~2.5), T1: 0.3 (0.3~1.1), T2: 0.5 (0.3~1.5), $p<0.05$] which both decreased over the follow up time. No statistically significant difference was found in the mean values of the Ca/Cr ratio [T0: 0.08 (0.05~0.16), T1: 0.11 (0.05~0.17), T2: 0.09 (0.06~0.18)], and ACTH [T0: 58.5(16.0~195.5), T1: 57.7 (14.6~187.5), T2: 35.0 (16.0~116.2)], even if for the latter a downward trend was observed.

PCA highlighted two strong correlation patterns among 17-OHP, Δ4-androstenedione and ACTH, and among DHEAS and Ca/Cr. Interestingly, a trend over time was observed along the negative directions of PC1 and PC2, moving from the first time point (T0) to the end point (T2). In these directions, the loading plot revealed a decrease of the 17-OHP, Δ4-androstenedione and ACTH variables amount, so these results suggested that these variables decrease during the follow up.

Conclusions: NC represents an important issue related to CAH. The decrease of 17-OHP, Δ4-androstenedione and ACTH levels, matched with the decrease in the NC prevalence during the follow up, could suggest that an accurate metabolic control of the disease is pivotal to prevent this complication. More studies are needed to clarify pathogenesis and to detect risk factors.

P1-405

Multicenter study on clinical, biochemical and ultrasonographic characteristics, therapeutic management and outcome of TART in males with congenital adrenal hyperplasia

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Objectives: 1. To describe the clinical, biochemical and testicular ultrasonographic features in a population of males with congenital adrenal hyperplasia (CAH) and Testicular Adrenal Rest Tumor (TART). 2. To identify factors related to the onset of TART. 3. To evaluate the therapeutic management and outcome of TART.

Methods: Males with classic and non-classic 21β-hydroxylase-deficient CAH, diagnosed with TART, followed at 7 national and international pediatric endocrinology centers, were retrospectively evaluated. Data acquired at the diagnosis of CAH, in the first two years of life, at the diagnosis of TART, and during assessments following the finding of TART were analyzed; these included: genotype; age at diagnosis of CAH and TART; clinical and auxological data; levels of 17-hydroxy progesterone (17-OHP), ACTH, delta4-androstenedione, testosterone; hydrocortisone dosage; dexamethasone therapy (yes/no and dosage); spermiogram; location, size, resolution, recurrence of TART. Poor disease control was defined as altered levels of ACTH, 17-OHP, and delta4-androstenedione.

Results: Forty-three patients were recruited, 95.3% with salt wasting (SW), 2.3% with simple virilizing form and 2.3% with non-classic CAH. The mean age at diagnosis of TART was 16.2±4.3 years. In 88.3% of cases, TART was bilateral and localized to the paramediastinal level. Palpable mass was found in 14% of cases, testicular pain in 2.3%. In the 4 patients who underwent spermiogram, 75% had azoospermia.

In 83.7% of cases, poor disease control was documented before the diagnosis of TART. The finding and duration of poor disease control, as well as ACTH and adrenal steroid levels, did not correlate with age at onset, size, and resolution of TART.

TART resolution was documented in 53.5% of cases. A positive correlation was documented between TART resolution and dexamethasone dosage (r=0.636; p=0.002), but not with duration of dexamethasone therapy (r= -0.159; p=0.369). Univariate regression analysis confirmed the association between TART resolution and dexamethasone dosage (p=0.019). Genotype, clinical and biochemical data at diagnosis of CAH and in early life did not correlate with age of TART onset, resolution rate and number of recurrences.

Conclusions: In this study, one of the largest case series of CAH males with TART is described. Poor disease control would not appear to significantly influence the onset of TART, therefore it is conceivable that other factors may affect its onset. Dexamethasone dosage seems to be the only factor able to positively influence the regression of TART.

P1-406

Congenital adrenal hyperplasia due to 11 β-hydroxylase deficiency: Clinical, Biochemical and Genetic characteristics

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Background: Congenital adrenal hyperplasia (CAH), resulting from mutations in *CYP11B1* (gene encoding 11β-hydroxylase), is a rare autosomal recessive disorder due to an impairment of the last steroidogenesis step. Consequences are a decreased cortisol secretion, elevated plasma levels of ACTH, and accumulation of steroid precursors responsible of hyperandrogenism and hypertension. It is the second most frequent cause of CAH after 21-Hydroxylase deficiency. Its incidence is estimated at 1:100 000 live births in non-consanguineous populations but may be as high as 1: 5000 in some specific populations.

Study Aim: To estimate the prevalence, clinical and hormonal features, genetic findings and outcomes of patients with 11β-hydroxylase deficiency (11β-OHD) in our population.

Methods: Clinical and hormonal data were collected from the medical records of patients attending two centers in Algeria between 2007 and 2023. Genetic analysis of *CYP11B1* was performed using Sanger sequencing after obtaining written informed consent from patients and parents.

Results: From a cohort of 290 patients with classic CAH, 11β-OHD was confirmed in 29 (10%) patients from 18 families with a high level of consanguinity (82.75%), M:F ratio 1:1.23.

Molecular studies revealed different mutations in *CYP11B1*. The most frequent mutations in our population were: mutation c.650delinsTT (p.(Ser271Ilefs*42))(3 families, 8 patients). c.1136G>T (1 family,3 patients) and c.1066c>T (p.Gln356*) (3 families). One patient had a short intragenic inversion in *CYP11B1*.

Age at diagnosis ranged from 20 days to 13 years. Male patients were diagnosed later than female patients (Mean age in boys 40.5 +/- 46 Months vs 16.7 +/-21.4 Months in girls). All males presented with pseudo-precocious puberty while females presented with virilization (Prader score 3-5), leading to wrong sex assignment at birth in 5 patients. Sex reassignment was refused by the parents of three patients.

Hypertension was observed in 13 patients at a median age 4 years ([1.5-13.8 years]. One of the males presented TART (Age 9 years).

Biochemistry showed mildly elevated 17OHprogesterone (Mean 43.81 nmol/l+/-39.35) and Δ4-androstenedione (mean 9.66 nmol/l +/-10.76 ; while 11-deoxycortisol was very high when measured (N=20 : Mean 234 nmol/l+/- 150.27)

Conclusion: 11β-OHD appears more frequent in Algeria than reported elsewhere. The spectrum of genetic mutations is wider than in 3βHSD, c.650 delG insTT being the most common mutation. With late diagnosis, patient outcomes show a high prevalence of hypertension. Since 11β-OHD cannot be detected on CAH screening, timely diagnosis relies on careful neonatal examination, and early detection of advanced growth and sexual development.

P1-407

17OHP levels to diagnose Non-Classic Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency (NC-CAH) in children with precocious pubarche

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Background: Basal 17OHP levels to indicate an ACTH-stimulation test and post-ACTH 17OHP cut-off levels diagnosing NC-CAH vary among different guidelines.

Objective: To establish the performance of basal and post-ACTH 17OHP concentrations for the NC-CAH diagnosis in children with precocious pubarche (PP).

Methods: Clinical, biochemical, and molecular analysis from 202 PP patients submitted to ACTH stimulation test (1997-2021). 17OHP was measured by RIA and *CYP21A2* genotype was confirmed by allelic-specific PCR and direct sequencing. ROC curves were generated for basal 17OHP and post-ACTH 17OHP and sensitivity (S), specificity (E), and likelihood ratio (LH) levels were calculated to determine their performance in diagnosing NC-CAH.

Results: NC-CAH was confirmed in 35 patients while 167 were diagnosed with isolated PP and were considered as the control group. *CYP21A2* analysis of was performed in 30 patients with NC-CAH, confirming the diagnosis in all, and in 22 controls, definitively excluding the disease. In this first tier of analysis, the only significant clinical difference was higher growth velocity in NC-CAH (33.3%) than in the controls (4.5%; p=0.02). Basal 17OHP concentration showed an area under the curve (AUC) of 0.94 (95% CI, 0.84-0.99) and the cut-off point with the best diagnostic combination was 170 ng/dL (S:97%, E:72%, LH+ 3.5). The post-ACTH 17OHP had an AUC of 1.0 (CI 95%) and a plasma concentration of 1,104 ng/dL and showed excellent diagnostic accuracy (S:100%, E: 100%). Adopting this post-ACTH 17OHP concentration as the cut-off point for diagnosing NC-CAH, a second tier of analysis was performed evaluating basal 17OHP in all patients with PP (202). The AUC was 0.97 (95% CI, 0.95-0.99), and the concentration of the basal 17OHP with the best diagnostic accuracy was confirmed to be 170 ng/dL (S:94%, E: 90 %, LH+ 9.9). Interestingly, all patients with basal 17OHP greater than 502 ng/dL had the diagnosis of NC-CAH confirmed (S:63%, E:100%), and would not require an ACTH-stimulation test. On the other hand, a basal 17OHP lower than 86 ng/dL excluded NC-CAH in all patients (S:100%, E: 70%).

Conclusion: In our cohort, basal and post-ACTH 17OHP levels presented an excellent diagnostic performance in patients with PP. A basal 17OHP concentration of 170 ng/dL and a post-ACTH level of 1,104 ng/dL represent the best cut-off values to, respectively, indicate the ACTH stimulation test and confirm the diagnosis of NC-CAH in these patients. Moreover, a basal 17OHP greater than 502 ng/dL confirmed NC-CAH.

P1-408

Primary Adrenal Insufficiency in Children: Genetic and Clinical Characterization of a Large Cohort in Thailand

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Background: Primary adrenal insufficiency (PAI) is a rare but life-threatening condition. Its diagnosis is frequently delayed due to its nonspecific and diverse symptoms. The etiology of PAI is heterogeneous and varies among populations.

Objective: The objective of this study was to characterize the clinical and hormonal phenotypes of Thai children with PAI and to determine the underlying genetic defects.

Method: Thai children aged 0-18 years with PAI, who were treated at King Chulalongkorn Memorial Hospital, Bangkok, Thailand between 1999 and 2019, were recruited. Clinical, biochemical, hormonal data, and treatment regimens were collected. Mutation detection was performed using various molecular techniques, including PCR Sanger sequencing of a specific gene for patients with a clinical clue to an underlying gene, whole-exome sequencing for patients with nonspecific clinical profiles, and long-read sequencing with allele-specific PCR for patients with markedly elevated 17-hydroxy progesterone (17-OHP) levels suggesting 21-hydroxylase deficiency (21-OHD) and mutations in CYP21A2.

Results: During the 21-year period, 112 patients with PAI were recruited. The most common manifestations were hyperpigmentation (76%), salt-losing crisis (60%), and ambiguous genitalia (59%). Classic 21-OHD CAH was the most common cause of PAI (86/112; 77%). The female-to-male sex ratio in CAH was 2.4:1, suggesting missed or delayed diagnosis in affected males. The median age at diagnosis was 25 days in salt-wasting form and 2.5 years in simple virilizers. Mutations were successfully identified in 60% (67/112) of patients. Of the 94 patients with CAH, 86 (91.5%) had 21-OHD. Using long-read sequencing, we were able to identify mutations in CYP21A1P/CYP21A2 of all 46 patients with 21-OHD. Chimeric genes were identified in 34.7% (16/46) of patients, and large gene deletions were detected in 30% (14/46) of tested alleles. For rare monogenic causes of PAI, mutations were identified in 90% of tested patients, which were NR0B1 (6/26, 23%), ABCD1 (4/26, 15%), StAR (3/26, 12%), CYP17A1 (3/26, 12%), CYP11B1 (2/26, 8%), and CYP11A1 (1/26, 4%). Two novel mutations were identified, including p.Asn482Tyr and p.Ser98Leu in the CYP11A1 gene.

Conclusion: This study characterized the phenotypic and genotypic spectra of Thai children with PAI. Comprehensive genetic testing elucidates the etiologies of most PAI patients. Long-read sequencing with allele-specific PCR is a new combined technique that could identify 100% of CYP21A2 variants. Excluding CAH, NR0B1 mutations are the most common genetic cause of rare forms of PAI in the Thai population.

P1-409

Hydrocortisone (HC) versus Prednisone(P) Therapy in treating Children with Classic Congenital Adrenal Hyperplasia (CAH): Impact on statural growth weight gain and metabolic criteria

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Introduction: Debate still exists about the safety of long-term use of prednisone (P) versus hydrocortisone (HC) for treating children with congenital adrenal hyperplasia -21OH D (CAH).

Aim: To investigate the linear growth and weigh gain as well as metabolic component in children with CAH who were treated with either HC or P since early infancy for 5 years or more.

Methods: Data of 30 children with CAH was analysed retrospectively. They received P (n = 22) or HC (n = 8) in addition to fludrocortisone for 5 years or more. Those on HC were taking 15.2 +/- 3.7 mg /m^2 daily and those on P were taking 21 +/- 5 mg/m^2 HC equivalent dose. The growth data and blood pressure (BP) were recorded each clinic visit. Metabolic data included measuring fasting blood glucose, triglycerides, cholesterol, LDL and HDL.

Results: After 5 years of treatment with P or HC the HtSDS, BMI and BP did not differ significantly between the two groups.

Table 1.

Anthropometric and biochemical data of children with CAH : Those taking prednisone (P) vs hydrocortisone (HC)

	Obese	Over WT	HtSD <-2	High SBP	High DBP	High 17OHP	High TG	High Chole
P (n =22)	7/22	6/22	6/22	0	1/22	8/22	0	3/22
HC (n= 8)	1/8	4/8	1/8	1/8	1/8	2/8	1/8	0
p value	0.5	0.8	0.4	0.6	0.44	0.58	0.6	0.27

Six out of the 22 children on P therapy had short stature (HtSDS <-2) while 1 out the 8 children on HC had short stature (Table 1).

Fasting glucose, insulin and HOMA-IR vales did not differ between the two groups. However, high cholesterol was detected in 3/22 of those treated with P and low HDL was detected in 1/22 of those treated with P but none of the HC treated group. LDL was significantly higher in the P treated group versus the HC group.

Obesity (OB) and overweight (OW) occurred both in the P (32% and 27.3% respectively) and in HC groups (12.5 % and 50% respectively). Hypertension was detected in 1 patient on P and another on HC treatment.

Conclusion: A single daily dose of P was comparable to twice daily HC dose in achieving control of children with CAH. Increased occurrence of overweight and obesity was significant in both groups. There was slightly higher LDL and cholesterol level in the P treated group vs HC treated group.

P1-410

Patient education for management of sick day episodes in adrenal insufficiency: A systematic review of structured education and online patient resources

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Background: Management of adrenal insufficiency (AI) during sick-day episodes require adjustment of oral glucocorticoid therapy or administration of intramuscular injection to prevent adrenal crisis. Education of families of a young person with AI on management during sick day episode is therefore critical.

Aim: To critically appraise patient education of sick-day episode management of adrenal insufficiency by conducting

- A systematic review of structured education.
- A systematic search of online educational resources available on Google and YouTube.

Methods: A systematic search was conducted in four databases(Medline, Embase, Web of Science, CINAHL). Systematic searches of Google and YouTube resources were then conducted. The readability of the web-page resources identified from Google was then assessed using the Flesch-Kinkaid reading ease score.

Results: Systematic search of the literature identified three publications that reported structured education for AI, all of whom involved adult patients. All were delivered face to face. Two were delivered by endocrinologists/nurses(single 2-hour small group training and a single 3-hour educational meeting) and one by pharmacists(three-step programme taught over 3 consecutive days). All provided the opportunity to practise injections. All programmes led to improved knowledge and patient satisfaction. A total of 16 resources were identified via Google and 17 via YouTube. 9/16(56%) identified via Google were developed by health care providers/researchers. Most of YouTube resources were developed by patient groups (6/17, 35%) or individual patients(5/17, 29%). Fifteen of the 16(94%) web-pages provided information about symptoms of an adrenal crisis; 7/16(44%) discussed how to manage oral sick-day dosing, 3(19%) discussed how to self-inject hydrocortisone. Almost half of eligible web-pages (7/16, 44%) were given a Flesch-Kinkaid score of 30-50 which translates as "difficult to read". Eleven out of the 17 videos(65%) included information about the symptoms of an adrenal crisis; 6/17(35%) discussed how to manage oral sick day dosing, 1(6%) discussed how to self-inject hydrocortisone.

Conclusion: Evidence of a structured educational programme for patients diagnosed with AI in the published literature is limited, are none for paediatric patients and their families. Most educational resources obtained through a systematic search of Google or YouTube did not address several clinically important points. The readability of almost half of the resources available on google were aimed at those with tertiary university education or higher. There is a need to understand the educational needs of families and young people with AI to co-develop accessible educational resources.

Bone, growth plate and mineral metabolism

P1-16

Low bone mineral density in children with Cerebral Palsy and its risk factors: finding a way to prevent secondary osteoporosis

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Introduction: Children with cerebral palsy (CP) has an increased risk of bone fragility, low areal bone mineral density (aBMD) and low trauma fractures leading to increased pain experience, decreased mobility and lower quality of life.

Purpose: The aim of this study was to determine the prevalence of low BMD among children with cerebral palsy in Denmark across the spectrum of gross motor function scale (GMFCS) of I-V and identify possible risk factors of low aBMD.

Methods: A cross sectional study of 81 children and adolescents in the out-patient clinic of Herlev Hospital, Department of pediatrics. Mean age was 8.9 years (2,3- 17,5 years), 64 participants was GMFCS I-II (77%) and hence slightly decreased mobility and 18 was GMFCS III-V (23%) indicating severe decreased mobility. Participants had aBMD evaluated by Dual-energy X-ray absorptiometry scan (DXA-scan) whole body less head (WBLH). Further assessment included bone age, Bone Health Index, anthropometrics, full examination including tanner stage and blood test for biomarkers.

Results: This study interestingly demonstrated that children and adolescents with cerebral palsy has decreased aBMD across all levels of physical mobility. Participants with GMFCS I-II had a BMD z-score of -0.01 and participants with GMFCS III-V a BMD z-score of -1.03 (p= 0.002). Further we found aBMD to be related to level of physical activity (hours of weight bearing activity) (p=0.003), vitamin D level (P=0,005), tube feeding (P<0.001) and being underweight (p=0.003). We found that children who participated in leisure activities had a significantly higher aBMD compared to children who did not regardless of their GMFCS score (p=0.004).

Perspective: This study shows that bone fragility is present even in children with only slightly decreased physical mobility and highlights the importance of predicting children at risk in a clinical setting to prevent development of secondary osteoporosis in a longer term among children with impaired mobility.

P1-17

Dual-X-ray-Absorptiometry (DXA) bone parameters in children with Achondroplasia

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Achondroplasia is the most common skeletal dysplasia caused by a gain of function of the fibroblast growth factor receptor 3(FGFR3) that impairs endochondral ossification, exiting in short stature and altered bone microarchitecture. Although fractures and reduced bone mineralization are not comorbidities frequently reported, specific normative DXA data are lacking.

Aim of the study was to assess bone density parameters in an Achondroplasia cohort.

Fifty-seven patients (Female-F=27, Male-M=30) with Achondroplasia were evaluated at the mean age of 11.1±3.8years by DXA(Lunar Prodigy and Lunar iDXA, GE) for bone mineral density(BMD,g/cm2 and Z-score) at the lumbar spine(LS) and total body less head(TBLH). Lumbar bone mineral apparent density(BMAD g/cm3 and Z-score) was calculated based on Crabtree-2017. The delta between LS-BMD Z-score and LS-BMAD Z-score was obtained. Height, weight, body mass index-BMI were recorded and expressed as SDS according to Merker-2018 references. Based on Tanner stage, 35 were prepubertal(61.4%) and 22 post-pubertal(38.6%); 38 patients underwent surgery for foramen magnum stenosis-FMS(66.7%).

Overall mean height and BMI were 0.37±0.29 SDS and -0.08±0.31 SDS, respectively. Mean LS-BMD was 0.673±0.030 g/cm2 and -1.41±0.18 Z-score, mean TBLH-BMD was -2.18±0.13 Z-score and mean BMAD 0.247±0.010 g/cm3 and -0.99±0.28 Z-score. M and F differed for BMI-SDS(-0.69±2.85vs0.60±1.38;p=0.04), LS-BMD (0.627±0.140vs0.720±0.24;p=0.09) and LS-BMAD(0.229±0.05vs0.265±0.08;p=0.04), while prepubertal and postpubertal differed for age (p<0.0001), LS-BMD (0.825±0.241vs0.588±0.102;p<0.0001) and LS-BMAD (0.276±0.09vs0.231±0.08;p=0.04). A significant delta between LS-BMD Z-score and LS-BMAD Z-score was found in the post-pubertal group(p=0,03). Height-SDS was lower (-0.28±2.63vs-0.775±1.61,p=0.01) and BMI-SDS higher (0.440±1.62vs-1.107±1.62;p=0.0175) in patients that underwent FMS but no differences in DXA bone parameters were found by comparing subjects who underwent or not FMS. In multivariable analyses,TBLH BMD Z-score was predicted by BMI-SDS(coeff 0.188, p=0.01) and FMS (coeff. -0.524,p=0.053) after adjustment for age, gender, pubertal status and FMS (R2 0.152,p=0.02), while LS-BMD Z-score and BMAD Z-score only by BMI-SDS(coeff 0.257,p=0.0008; R2 0.223,p=0.04 and coeff 0.296,p=0.0227; model not significant, respectively). Height-SDS was not a predictor of DXA bone parameters.

Preliminary data show that children and adolescent with Achondroplasia display low BMD values for age and sex at the TBLH, low normal values at the LS and normal LSBMAD Z-score values based on references for the general pediatric population; although specific normative data for Achondroplasia are warranted, the use of BMAD is suggested.

P1-18

Bone mineral density in children and adolescents with Cystic Fibrosis: a follow-up study

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Background: Adults with CF show a higher rate of osteoporosis compared to healthy adults. Achieving proper bone mass is a process starting in childhood. We aimed to evaluate the prevalence of decreased bone mineral density (BMD), changes during puberty and risk factors for low BMD in children and adolescences with CF in a large Dutch cohort.

Patients and Methods: A retrospective observational cohort study was performed in 106 children with CF aged 8-18. Anthropometry, DEXA scan results and endocrine data were collected. BMD z-scores were adjusted for height. At risk and low BMD scores were defined as z-scores ≤ -1 and ≤ -2 respectively. We analyzed if BMD was associated with BMI-SDS, serum vitamin D values, lung function (FEV1%predicted) and presence of cystic fibrosis related diabetes (CFRD). Sixty-five of 106 patients underwent a second DXA-scan during follow-up.

Results: At the initial scan overall prevalence of low BMD values was 5.7% for lumbar spine (LS) and 3.8% for total body less head (TBLH). Mean adjusted BMD z-scores were normal (0.05 ± 1.13 and 0.14 ± 1.08 for LS and TBLH respectively). The children were well-nourished, but the range was remarkable (median (range) BMI-SDS -0.12 (-3.33 to +2.46), and had normal mean FEV1%predicted values (91.3 ± 15.6).

After a mean follow-up time of 2.37 ± 0.54 yrs, significant decreases in both mean adjusted LS and TBLH BMD z-scores were found (-0.23 ± 0.67 and -0.72 ± 0.54 respectively). Female gender ($\beta = 0.445$, $p = 0.001$) and new onset of CFRD ($\beta = -0.429$, $p = 0.003$) were significant predictors for the change in adjusted TBLH BMD z-score in a multivariate model. FEV1%pred values at baseline were associated to adjusted TBLH BMD z-scores univariately ($\beta = -0.009$, $p = 0.037$). The change in BMI-SDS was a significant predictor for the change in adjusted LS BMD z-scores ($\beta = 0.313$, $p = 0.005$).

Conclusion: Although overall most children with CF have normal BMD, a significant decrease in BMD over time is seen, already during childhood and especially in boys and in those with newly onset CFRD. Optimizing nutritional status, especially in children with decreased lung function, remains important to prevent bone loss.

P1-19

Bone mineral density development in children with chronic non-bacterial osteomyelitis treated with zoledronate

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Introduction: Chronic non-bacterial osteomyelitis (CNO) is a sterile inflammatory disease of the skeleton characterized by local pain and swelling. If first line treatment (non-steroidal anti-inflammatory drugs) fails, bisphosphonates are recommended. There are no randomized controlled studies so far that would clarify the zoledronate efficiency, and also no study systematically exploring the effect on bone mineral density (BMD).

Methods: We have applied standardized protocol in our center since 2021. All patients with CNO undergo whole body magnetic resonance imaging (WBMR) and bone densitometry using dual energy x-ray absorptiometry (DXA) and peripheral quantitative computerized tomography (QCT) before and one year after the start of treatment with intravenous zoledronate. The doses were 0.025 mg/kg and 0.05 mg/kg body weight at first and second application, respectively, six months apart. Patients with other coincident diseases affecting the skeleton were excluded from this analysis.

Results: There were 23 children with CNO who started the protocol, of whom 15 finished the first year so far. Their mean age at first zoledronate application was 11.3 years (range 5-18 years). The repeated bone densitometry at year 1 was available in 12/15 (DXA) and 10/15 (pQCT) children, respectively. At study start, both mean lumbar spine areal BMD Z-score as well as mean trabecular volumetric BMD Z-score were normal (-0.4±1.1; p=0.22 and -0.5±1.1; p=0.13, respectively). Whereas lumbar spine areal BMD Z-score significantly increased after two doses of zoledronate (-0.4±1.1 vs. 0.8±1.4; p=0.033), trabecular volumetric BMD Z-score did not change (-0.5±1.1 vs. 0.04±2.0; p=0.43).

Conclusion: Zoledronate treatment of children with CNO leads to increase in lumbar spine areal BMD already after the first two applications. Whereas the rheumatologist's main focus is pain relief, diminished swelling and regression of the skeletal lesions on WBMR, potential side effect such as increased BMD and related osteopetrosis-like bone fractures shouldn't escape the attention.

P1-20

Non-Osteogenesis Imperfecta Primary Osteoporosis in Children: Clinical and Genetic Features

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Keywords: children, primary osteoporosis, next-generation sequencing

Background: Primary osteoporosis (POP) is a rare bone fragility disorder of childhood and is mainly related to osteogenesis imperfecta (OI). However, patients without clinical OI features with recurrent long bone and/or vertebral fractures who comply with the osteoporosis criteria are considered to have non-OI POP. Diagnosis and classification of non-OI POP rely mostly on genetic testing.

Objective: To characterize the clinical findings and familial relationships of children with POP without OI features and to determine the molecular aetiology.

Participants and Method: The clinical and genetic characteristics of 25 patients (17 male, 68%) from 22 families who were followed up with the diagnosis of non-OI POP whose next-generation sequencing analyses were performed were reviewed

Results: The most common complaints at presentation were recurrent fractures (n=17, 68%) followed by backache (n=6, 24%), and short stature (n=1, 4%). Two patients had no complaints. Both were screened after their siblings were diagnosed with osteoporosis (one because of monochorionic twins, the second since both siblings have a history of congenital cataracts). Parental consanguinity was present in 8 (31%) patients. Fifteen (58%) patients had a family history of osteoporosis or recurrent fractures, one had hearing loss and four had nephrolithiasis. Physical examination findings were; extremity deformities (n= 4, 16%), scoliosis/kyphosis (n=8, 32%), chest deformity (n= 2, 10%) and joint laxity (n=7, 28%). Vertebral compression/fracture was observed in 12 (48%) patients on X-ray. After initial screening and exclusion of systemic diseases causing osteoporosis, hearing test, renal ultrasonography (nephrolithiasis: n=2), echocardiography (mitral regurgitation: n=2), and ophthalmologic examination (cataract, glaucoma: n=2) were performed. A gene panel including 22 genes for POP/OI with next-generation sequencing analysis identified molecular aetiology in 32% of the patients (n=3, *LRP5* heterozygous; n=2, *PLOD2* heterozygous; n=1, *SLC9A3R1* heterozygous; n=1, *IFITM5* heterozygous; n=1, *SP7* homozygous). All patients underwent oral vitamin D and calcium supplementation. Bisphosphonate treatment was initiated in 12 (48%) patients due to vertebral compression fractures and/or recurrent long bone fractures. After a mean treatment of 4.4±4.1 years, DXA L1-4 Z Scores improved significantly (-2.4±1.0 vs. -0.6±1.1, $p<0.0001$).

Conclusion: Childhood non-OI POP is a heterogeneous group of disorders diagnosed based on excluding systemic diseases and vitamin D deficiency. However, only a third of them can be explained by known genes associated with osteoporosis and, further genetic and metabolic mechanisms need to be explored for these patients

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P1-21

Serum osteocalcin, sclerostin and lipocalin-2 levels in adolescent boys with obesity over 12 week sprint interval training

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Aim: to examine the effects of supervised cycling sprint interval training (SIT) on serum osteocalcin, lipocalin-2 and sclerostin levels, and bone mineral characteristics among obese adolescent boys.

Methods and Subjects: untrained adolescent obese boys (n=14) aged 13.4 ± 0.3 were assigned to either a 12-week SIT group (3 sessions/week) or a non-exercising control group (n=14) who continued with their habitual everyday life. Serum osteocalcin, lipocalin-2 and sclerostin concentrations and bone mineral values were assessed before and after intervention.

Results: after 12-week intervention, where 14 boys in both groups ended the study, serum osteokine levels were not changed ($p > 0.05$) after 12 weeks period between the groups, while whole body bone mineral content and lower limbs bone mineral density increased in SIT group ($p < 0.05$) with no differences between the groups. Change in body mass index was negatively correlated with the change in osteocalcin ($r = -0.57$; $p = 0.034$) and positively with the change in lipocalin-2 levels ($r = 0.57$; $p = 0.035$) in SIT group.

Conclusions: supervised 12-week SIT intervention did not change osteocalcin, lipocalin-2 and sclerostin levels, but improved bone mineral characteristics in adolescent boys with obesity.

P1-22

Fibroblast growth factor receptor-3 (FGFR3) mutation frequency in 17 Albanian children who were clinically to have Achondro – Hypochondroiplasia

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Keywords: Achondroplasia, Hypochondroplasia, Dwarfism, Fibroblast growth factor receptor-3.

Introduction: Achondroplasia (ACH) and hypochondroplasia (HCH) are the two most common forms of short-limb dwarfism. They are autosomal dominant diseases characterized by a rhizomelic shortening of the limbs, genu varum, trident hands, large head with frontal bossing and hypoplasia of the mid-face. Both ACH and HCH are caused by missense mutation in the FGFR3 gene located on chromosome 4p16.

Objective: To emphasize the importance of genetic tests in establishing the correct diagnosis of clinically suspected ACH and HCH.

Methods: The clinical data and genetic test results of 17 suspected children with ACH or HCH were analyzed between 2019 to 2021. DNA was isolated from the peripheral blood of the patient using the CentoXome® Trio including CNV analysis (Double stranded DNA capture baits against approximately 36.5 Mb of the human coding exome are used to enrich target regions from fragmented genomic DNA with the Twist Human Core Exome Plus kit), performed by CENTOGENE AG, Rostock, Germany. The genetic results are interpreted in the context of the provided clinical findings, family history, and other laboratory data. Anthropometric data were elaborated by Anthro and Anthroplus software [z-scores are based on WHO standards (birth to 60 months) and WHO reference 2007 (61 months to 19 years] and statistical processing was done by SPSS.

Results: 17 patients (male /female ratio: 9/8) were clinically evaluated. 11 out 17 (64.7%) were clinically diagnosed with ACH and 6 out 17 (35,3%) with HCH. The first presented age was 3.96±3.60 years old (min. 0.09 yrs.; max. 12.99 yrs.). Heigh for age z-score (HAZ) of all patients at the time of clinical diagnosis was -3.51±1.44 z-score (min. -6,0 z-score; max. -0,75 z-score). The mean age of the patients at the time of genetic test was 6.27±4.21 yrs. (min. 0.32 yrs.; max. 14.77 yrs.) and HAZ was -4.56±1.76 z-score (min. -9.45 z-score; max. -0,75 z-score). After genetic test, the frequencies of diagnoses were as follow: FGFR3- mutation related Achondroplasia 13 (76.4%) patients; FGFR3- mutation related Hypochondroplasia 1 (5.9%) patient; ALPL mutation related AD hypophosphatasia 1 (5.9%) patient; IHH gene mutation related AD bradydactily type A1, 1 (5.9%) patient; COL2A1 gene mutation related to spondyloepiphyseal dysplasia congenital (SEDC),1 (5.9%) patient.

Conclusions: Genetic tests estimated +11.7% the frequency of ACH, -29.4% the frequency of HCH and identified a diagnosis discrepancy of 17.6% by detecting different pathologies than those suspected.

P1-23

Accelerated linear growth in children with selective tyrosine kinase inhibitior treatment: Hints to a growth factor and sex steroid independent growth promotion mechanism

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Background: Postnatal linear growth is characterized by a steady decline of growth velocity in healthy individuals, with the exception of sex-steroid induced pubertal growth. Pharmacologic interventions in growth disorders are limited to systemic application of growth factors such as growth hormone, and CNP analogues in conditions with FGFR3 overactivation.

Tyrosine kinase receptor inhibitors (TKI) represent a heterogenous group of drugs, mostly used for oncologic indications. Erdafitinib, a novel selective FGFR inhibitor has not been assessed in paediatric patients so far. To our knowledge, this is the first description of linear growth acceleration associated with pharmacologic FGFR3 inhibition.

Patients/Methods: We report on two patients with neurooncological conditions featuring an unanticipated growth spurt after initiation of FGFR-inhibition with Erdafitinib. Clinical, radiographic and biochemical data have been assessed to exclude sex-steroid or GH-driven effects.

Results: Both patients received Erdafitinib (2,8-5,2mg/kg/d) due to progressive, non-responsive FGFR-expressing CNS tumour disease at the age of 13.8 / 10.9 years, respectively. Both patients did not reveal clinical or biochemical signs of sex-steroid action at initiation or during treatment with Erdafitinib.

Besides known effects of TKI-inhibition, both patients revealed an unanticipated increase in growth velocity (body height +0.7SDS/9months; +0.5SDS/4.5months respectively) associated with onset of Erdafitinib. Clinical examination and biochemical assessment excluded sex-steroid induced effects and alteration in the GH-state. In line with a distinct mechanism of growth promotion, wrist radiographs revealed profound metaphyseal sclerosis without progression of bone age.

Discussion: The observed increase of growth velocity associated with Erdafitinib treatment in our patients points to a potent growth promoting effect of FGFR3 inhibition. While similar strategies are under investigation in patients with FGFR3-activating mutations, we observed this effect even in children with regular skeletal FGFR3 expression. The context of heavily pre-treated paediatric neurooncological patients with severe growth impairment before initiation of Erdafitinib underlines the hypothetical potential of a growth factor and sex steroid independent growth acceleration by selective FGFR3-inhibition. Future studies will reveal if pharmacologic interventions on FGFR3 can complement current treatment strategies for short stature.

P1-24

Cortical hyperostosis in an infant on prolonged prostaglandin infusion: a case report

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Introduction: Prostaglandin E1 (PGE1) is a drug used for ductal patency in cyanotic congenital heart disease, We are reporting an infant with cortical hyperostosis secondary to prolonged use of PGE1, with typical and extensive radiological findings.

Case Report: A 2-month-old girl, born at 37 weeks with APGAR scores of 9 & 10 at 1 & 5 min, and birth weight = 2.9 kg. She failed Critical Congenital Heart Defects Screening Methods at 12 hrs. of age with pre- and post-ductal oxygen saturation in the 80% with no respiratory distress. Echocardiogram revealed a complex congenital heart disease (Tetralogy of Fallot, complete atrioventricular canal defect, and pulmonary atresia). The patient was started on PGE1 infusion at 0.03 mcg/kg/min. Her oxygen saturation remained between 85: and 93 % in room air. She was feeding well and gaining weight appropriately for her age.

A palliative PDA stenting was planned but delayed because of social factors and the baby remained on PGE1 infusion. By the age of two months, the baby was noted to have diffuse upper and lower limb tenderness with swelling, irritability, and intense crying with minimal handling. The radiography of the large bones revealed an intense periosteal reaction with bilateral corticoperiosteal thickening of the diaphysis in clavicles, femur, tibia, humerus, radius, and ulna. The lesions were distributed along the middle portion of the long bones, except for the humerus, where the affection was distributed more distally. Laboratory findings showed raised alkaline phosphatase (ALP) (713 U/L) with normal serum calcium and phosphorus. The dose of the PGE1 was reduced to 0.02 and then 0.01 mcg/kg/min gradually while monitoring for PDA patency and oxygen saturation over 10 days. The infant did not tolerate the reduction of the drug, experiencing a rapid decrease in arterial saturation, and was eventually taken for PDA stenting on DOL 72. After 10 days, the swelling of all limbs and pain and tenderness disappeared and ALP decreased.

Discussion: Prostaglandin-induced cortical hyperostosis appears to be linked to the duration or dosage of the PGE1. It can occur as early as 9-11 days after PGE1 infusion. The percentage of patients developing it increases from 42% at <30 days to 100% at >60 days. Elevated serum ALP level helps in the diagnosis and follow-up of cortical hyperostosis.

Conclusion: Early and frequent radiological investigations should be made in patients undergoing intravenous PGE1 treatment for more than 7 days.

P1-25

A case of hypophosphatasia accompanying neurofibromatosis type 1

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Introduction: Neurofibromatosis type 1 (NF-1) is an autosomal dominant disease. The NF-1 gene is located on chromosome 17 and encodes a gene product called neurofibromin. Mutation or deletion of the NF-1 gene results in phenotypic features involving many systems. Hypophosphatasia is a group of inherited disorders characterized by impaired mineralization of bones and/or teeth and low serum alkaline phosphatase (ALP) activity. It occurs as a result of a loss-of-function mutation in the ALPL gene on chromosome 1, which encodes the tissue non-specific isoenzyme of ALP (TNSALP). No case with NF-1 and hypophosphatasia both together has been reported in the literature. We aimed to present our case diagnosed with hypophosphatasia and neurofibromatosis type 1 both together.

Case Report: The patient was admitted to our endocrine outpatient clinic at the age of 11 years and 10 months due to short stature. The patient, who was diagnosed with NF-1 genetics when he was 6 years old, and was followed up in the neurology and oncology departments, was born at term and weighed 3700 g. There was no consanguinity between his parents. It was learned from his history that he had unilateral hearing loss, specific learning disability and epilepsy. In addition, Arnold Chiari malformation was detected in MRI examinations for NF-1 and he was operated because he had symptoms. In the physical examination of the patient; her weight was 38 kg (-0.95 SDS), her height was 138.8 cm (-2.22 SDS). Her puberty was compatible with tanner stage 2. He had widespread cafe au lait spots on his body. Complete blood count, liver, kidney and thyroid function tests were normal in laboratory tests. Celiac markers were negative. Calcium 10.7 mg/dL, phosphorus 6.2 mg/dL, ALP 63 U/L, PTH 38 ng/L, 25(OH)D vitamin 10 ng/mL. Genetic analysis was performed with the preliminary diagnosis of hypophosphatasia, since the patient had similar low ALP levels in the previous examination results. A c.1354G>A/p.Glu452Lys heterozygous mutation was detected in the ALPL gene. As the patient with no history of fracture described only muscle pain, asphotase alfa treatment for hypophosphatasia was not planned at this time.

Conclusion: We diagnosed hypophosphatasia as a result of genetic testing performed on the patient who was followed up for a long time with the diagnosis of neurofibromatosis type-1. We shared this rare case of NF-1 and hypophosphatasia because there was no reported case in the literature.

P1-26

Bone mineral density of children with cow milk allergy

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Objectives and Study: To compare the bone mineral density (BMD) between children with cow milk protein allergy (CMPA) and those who are healthy as control subjects

Methods: This study was carried out on forty children with cow milk protein allergy attending the Alexandria University Children's Hospital nutrition clinic and compared to forty apparently healthy children of matched age and sex as a control group. Anthropometric measurements were recorded. Laboratory investigations including calcium profile and serum 25 (OH) vitamin D were done. All patients underwent a Dual-energy X-ray absorptiometry (DEXA) scan of the lumbar spine

Results: Ten patients (25%) were found to have normal BMD (Z score>-1 SD) while 23 patients (57.5%) were found to have osteopenia (Z score from -1 to 2.5 SD) and 7 patients (7.5%) had osteoporosis (Z score <-2.5 SD). There was a significant positive correlation between BMD Z score with dietary calcium intake in children with CMPA.

Conclusions: Children with CMPA had lower lumbar spine BMD Z scores than healthy controls, which likely resulted from lower calcium

P1-27

Treatment with Letrozole was safe and effective in the case of congenital adrenal hyperplasia

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Introduction: Patients with congenital adrenal hyperplasia (CAH) develop advanced bone age (BA) frequently. Treatment with aromatase inhibitors can slow down bone maturation and improve final height in cases of CAH. However, safety is not clear at this point.

Case Presentation N 1: 15.5 yrs. old boy was diagnosed with congenital adrenal hyperplasia, salt-wasting type at 4.9 years of age. His genetic analysis revealed that he didn't have functional CYP21A2 gene: Allele1: 30 kb Deletion and Allele 2: 30 Kb deletion. He was treated with Cortef 10 mg/m^2 and Florinef 0.2 mg (2 tablets) daily. At 4.6 years his bone age was 6.6 yrs. However, at 6.9 yrs. BA became 13 yrs., which could severely jeopardize his final height. His Target Height was around 176 cm at the 48 percentile. Treatment with aromatase inhibitor Letrozole 2.5 mg daily was initiated to slow down bone maturation. On Letrozole bone maturation slowed down, so at 7.9 yrs. BA was 13 yrs. and at 13.6 yrs. BA was 13.6 yrs. On his recent visit at 15.5 yrs. BA was 14.6 yrs. At this point, he was treated with Letrozole 2.5 mg daily for 8.5 yrs. His testosterone was normal 639 ng/dl (Nl. 350-970). At 11.4 yrs. his Z-score for the Lumbar spine was normal 0.8, the subtotal body Z-score was 0. At 14.4 yrs. his Z-score for the Lumbar spine was normal -0.5. The subtotal bone Body Z-score was -1.3, which corresponded to the 90th percentile for his age.

Case Presentation N 2: Brother was diagnosed with congenital adrenal hyperplasia, salt-wasting type at birth. He carried the same deletions and didn't have a functional CYP21A2 gene. He was treated with Cortef 8 mg/m^2 and Florinef 0.1 mg daily. At 10.6 yrs. his BA was advanced to 14 yrs. Treatment with Letrozole 2.5 mg daily started at 10.6 yrs. The last bone age at 12.6 yrs. revealed the same bone age 14 yrs., 2 yrs. after initiating treatment with Letrozole. Bone mineral density was obtained 1 yr. after beginning of the therapy at 11.6 yrs. and was normal. The Z-score for the lumbar spine was -1.5. The subtotal body Z-score was -1.7, normal, at the 88 percentile. His testosterone was normal for his stage of puberty 30 ng/ml.

Conclusion: Letrozole treatment can slow down bone maturation, and improve predicted adult height. Bone density was normal after 8.5 years of treatment with letrozole.

P1-28

Effects of romosozumab on bone ultrastructure and density in a patient with primary osteoporosis caused by a novel heterozygous *WNT1* mutation

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Background: Genetic defects in the Wnt signaling pathway lead to early-onset osteoporosis (EOOP). Romosozumab is a monoclonal antibody against sclerostin, an inhibitor of the Wnt/ß-catenin pathway. Romosozumab has shown great efficacy in adult osteoporosis, however its effect in patients with Wnt-related EOOP is unknown. In monoallelic loss-of-function *WNT1* mutations, romosozumab could potentially stimulate the defective Wnt signaling pathway and improve BMD and architecture. Here we present evidence in support of this hypothesis, demonstrating effective romosozumab treatment in a patient with EOOP due to a heterozygous *WNT1* mutation.

Case: A 40-year-old Caucasian man presented with a history of long-bone fractures from moderate trauma since early childhood, and back pain from multiple vertebral fractures. He had no deformities and no extraskeletal symptoms. Whole Exome Sequencing identified a novel, heterozygous variant in *WNT1* (c.761C>A).

At age 40 years, DXA-measured bone mineral density (BMD) was very low, both in the lumbar spine (LS-BMD Z-score -6.8) and in the femoral neck (FN-BMD Z-score -4.1). Volumetric BMD assessed by HRpQCT (XCT-II) in the distal tibia (22.0 mm from tibial plafond) was very low (Tt.vBMD Z-score -3.8), especially in trabecular bone (Tb.vBMD Z-score -4.1), compared to healthy controls (unpublished reference data). Trabecular bone was more severely affected (Tb.N Z-score -5.4, BV/TV Z-score -4.0, Tb.Sp

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Z-score +9.2) than cortical bone (30% diaphyseal tibia; Ct.vBMD Z-score +1.0, Ct.Ar Z-score -4.9, Ct.Th Z-score -3.2).

After one year of romosozumab therapy (210 mg s.c., once monthly; together with colecalciferol (2000-4800 IU/d) and calcium carbonate (1000-2000 mg/d)), aBMD by DXA had substantially increased (LS-BMD +41%, FN-BMD +24%). Volumetric BMD by XCT-II increased both globally (Tt.vBMD +5.4%) and in trabecular and cortical compartments (Tb.BMD +7.5%, Ct.vBMD +0.7%). Trabecular (Tb.Th +1.6%, Tb.N +0.9%, Tb.Sp -0.8%) and cortical structural parameters (Ct.Ar +0.6%, Ct.Th +1.5%) improved to a lesser extent. No fractures were reported, but subjective improvements in muscle and bone pain. Serum calcium and parathyroid hormone levels were maintained within normal range. No cardiovascular events were reported.

Discussion: Romosozumab treatment for 12 months substantially improved bone mass, volumetric BMD and bone structure, with greatest changes in trabecular bone. These findings are consistent with prior romosozumab studies in ovariectomized animals. The observed improvements in aBMD were equal or superior to those reported with antiresorptive therapy in a *WNT1*-related EOOP patient of similar age. Based on this single-case experience, romosozumab may be an effective treatment option for primary osteoporosis caused by *WNT1* mutations.

P1-29

An adolescent boy with PLS3 mutation causing severe thoracic kypho-scoliosis

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Introduction: Mutations of the *PLS3* gene (MIM 300910), encoding plastin 3, are an extremely rare cause of osteogenesis imperfecta (OI). It has an X-linked inheritance and is characterized by early-onset osteoporosis and kyphosis, which can cause compression fractures, especially in the thoracic vertebrae. Although there are reports showing that bisphosphonates are effective in improving the bone mineral density of patients with *PLS3* variants, data on treatment is limited.

Case: A 14.5-year-old male was referred due to kyphosis, and back and low back pain. On examination, his height was 150.8 cm (-2.1 SD), weight was 59 kg (0 SD), and mid-parental height was 170.3 cm (-0.9 SD). His body proportions were normal and he had significant thoracic kypho-scoliosis. He had white sclera, no joint laxity, and normal tooth structure. Puberty examination was compatible with Tanner stage-3.

He had a history of forearm fracture due to a fall at the age of 11 years. His family reported that his uncles and cousins had kyphosis, and there were short individuals on his mother's side.

Serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone (PTH), 25-hydroxy-vitamin-D, insulin-like growth factor (IGF) 1 and IGF binding protein 3 values were within normal limits. Spinal MRI revealed platyspondyly and loss of vertebral height at the thoracic and lumbar vertebrae. Lumbar bone densitometry (BMD) showed low BMD (L1-L4 0.504 g/cm2, z-score -2.5).

He received two courses of pamidronate (0.5 mg/kg over three days) with an interval of nine months. He experienced severe hypocalcemia (Calcium:6.5 mg/dL) and secondary hyperparathyroidism (PTH:513 pg/mL) after the first treatment.

The patient reported a decrease in complaints decreased during follow-up and he exceeded mid-parental height (171.4 cm, -0.4 SD). His BMDs improved in the first and second years of treatment (L1-L4: 0.741 g/cm^2, z-score: -1.6 and L1-L4: 0.879 g/cm^2, z-score: -0.4, respectively). On next-generation sequencing, a c.1444G>A (p.G482R) (p.Gly482Arg) hemizygous variant was detected in *PLS3*, which has not been previously reported and was classified as highly pathogenic (American College of Medical Genetics criteria). The same variant was also detected in his mother.

Conclusion: *PLS3* mutation screening should be considered in individuals with kypho-scoliosis with an X-linked inheritance pattern, fracture history and prominent vertebral involvement. Although bisphosphonates may help reduce symptoms and improve BMD, large observational and interventional studies would be needed to identify effective treatments, but given the rarity of the condition, publication of individual case reports will add to the available evidence.

P1-30

A Novel Stop Codon Mutation in Exon 6 (c.508A>T) of *TRAPPC2* gene in a Patient with X-Linked Spondyloepiphyseal Dysplasia Tarda: A Case Report

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Spondyloepiphyseal dysplasia tarda (SEDT) is an inherited disorder that is diagnosed in childhood or adolescence presents with disproportionate short stature and premature osteoarthritis with frequently affecting men. Here, we described a novel nonsense mutation, c.508A>T; p.Lys170Ter, in TRAPPC2 in a Turkish patient with X-linked SEDT.

The patient is a 15-year-old boy from Turkish non-consanguineous parents, presented decreasing height velocity last three years and also the patient has complaint of back pain without any physical activity. He was born from 30 weeks, followed pregnancy, weighing 1900 grams with caesarean delivery. He was observed in neonatal intensive care unit during 20 days after birth and no history of entubation. His growth and development stages were compatible with age until the adolescent period. His maternal grandfather and aunt's son had short stature. The patient's weight was 35 kg (sds:-3.85), height was 134 cm (sds:-5.44), father's height was 169 cm and mother's height was 155 cm therefore target height is 168.5 cm (sds:-1.25), bone age was 15 years old and prediction of adult height is 137.6 cm. Upper arm/lower arm proportion was 31/31 cm, upper- to lower-body segment ratio was 0.94 (65/69 cm), Sitting height/height ratio was 0.48 and tanner puberty stage was 5. Arm span was 144 cm and exceeded height by 10 cm, therefore the patient had not short upper extremities. He was noted the dysmorphic facial features: microtia, synophrys, hypotelorism, and barrel chest was observed to patient. Bone structure of the patient was appeared osteopenik when evaluate skeletal survey and hypoplastic odontoid process, platyspondyly with superior and inferior "humping" of the vertebra, narrow intervertebral disc spaces, scoliosis, short femoral necks, coxa vara and subchondral sclerotic changes were detected to the patient. When radiological, clinical signs and history of family was evaluated X-Linked SEDT was thought to the patient and genetic analysis was done. *TRAPPC2* gene (NM_001128835.3, c.508A>T; p.Lys170Ter) in exon 6 with Sanger sequencing revealed a hemizygous novel stop codon mutation. It was detected the same mutation in the patient's mother as heterozygous in the segregation study.

In adolescent or childhood, disproportionate short stature, short trunk, osteoarthritis, exceed arm span from height and family history of appropriate for X-Linked should be though to us of X-Linked SEDT. Skeletal survey should be performed to suspect to SEDT and radiological findings may be supported to diagnosis.

P1-213

Age at diagnosis of XLH amongst children with and without a family history: Findings from the International XLH Registry

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Background: X-linked hypophosphatemia (XLH) is a rare, progressive, genetic phosphate wasting disorder leading to rickets, lower limb deformities as well as short and disproportionate stature. The condition is inherited in the majority, however spontaneous mutations are reported in ≈30% of cases. Its rarity, coupled with its diverse clinical manifestations, may lead to delayed diagnosis and subsequently delayed treatment initiation. The objective of this analysis is to investigate if there is a delay in diagnosis for children without a family history (FH) compared to those with a FH.

Methods: The International XLH Registry (NCT03193476) is a multicentre, prospective, non-interventional study initiated in 2017, aiming to recruit 1,200 people with XLH, collecting data prospectively for a period of 10 years. All participants of all ages with a confirmed diagnosis of XLH, regardless of their treatment and management, are included in the Registry.

Results: At the database lock for the first analysis (29 March 2021), 579 participants had entered the registry before 30 November 2020, of which 360 were children. Date of diagnosis and data for FH were available for 195 of the 360 children. Of 195 children, 121 (62%) reported FH of XLH, defined as having a biological parent(s) affected, whereas 74 (38%) had no FH of XLH. Of those with a FH, the biological mother was affected in 77%, biological father affected in 22%, and both affected in 1% of cases. Children aged <18 years with no FH were significantly older at time of diagnosis (3.96 years) compared to those with a FH (1.47 years), p<0.001. Males (n=74) and females (n=121) did not differ in terms of age at diagnosis.

Conclusions: All XLH patients without a FH of XLH were diagnosed significantly later than patients with a FH. Younger patients with a FH appear to be diagnosed more quickly than older patients, suggesting increased disease awareness.

Table 1. Age at XLH diagnosis comparing children with and without a family history of XLH *p value<0.0167.

	FAMILY HISTORY OF XLH		**NO FAMILY HISTORY OF XLH**		
Age Group Years	**n**	**Age at XLH Diagnosis (years), Mean (SE)**	**n**	**Age at XLH Diagnosis (years), Mean (SE)**	**P-value**
<5	28	0.43 (0.06)	4	0.97 (0.15)	p=0.07
5 < 12*	58	1.43 (0.25)	38	4.31 (0.34)	p<0.001
12 < 18*	35	2.36 (0.51)	32	3.92 (0.51)	p=0.002

P1-214

Vitamin-D Dependent Rickets: a case series with presentation, clinical features and long term follow up

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Introduction: Vitamin D-dependent rickets (VDDR) describes a group of genetic disorders characterized by early-onset rickets that develops due to insufficient concentration of active forms of vitamin-D or unresponsiveness to active vitamin D. The aim of this study was to share the clinical features and long-term outcome of cases followed up in our center with the diagnosis of either VDDR-Type-1 and VDDR-Type-2.

Method: Presenting complaints, demographic-anthropometric measurements, laboratory and radiological examinations, molecular genetic analysis results and treatment responses were obtained from patient records and reviewed retrospectively.

Results: Ten patients from eight families were included. Eight cases had a diagnosis of VDDR-Type-1 and two cases had a diagnosis of VDDR-Type-2. The median (range) age of diagnosis was 20 (14-52) months. The most common complaints were delayed walking (n=9), skeletal deformities (n=8) and short stature (n=6).

Molecular genetic analysis revealed 1319–1325dupCCCACCC(Phe443Profs*24) duplication mutation in five of eight cases with VDDR-Type-1. A case diagnosed with VDDR-Type-2 had alopecia and the novel pathogenic variant NM_00117536.2c.352_356delGACAG(p.I118Qfs*29)(p.Ile118GlnfsTer29)(Homozygous) was detected in the *VDR* gene.

All cases had received vitamin D prophylaxis and/or treatment before diagnosis. The mean±SD serum 25-hydroxy-vitamin-D (25OHD3) at diagnosis was 47.1±9.6 ng/mL. Calcitriol at a mean dose of 25.2±3.8 ng/kg and calcium treatments when necessary were given in all cases. After a mean follow-up period of 8.2±2 years, significant improvement was observed in biochemical and anthropometric measurements (Table 1). No nephrolithiasis/nephrocalcinosis was detected in any of the patients on urinary system ultrasonography.

Conclusion: Rare genetic types of rickets should be considered in the diagnostic approach, even if short stature is not present in cases unresponsive to vitamin D therapy or with normal 25OHD3 levels. These cases should be referred to Pediatric Endocrinology clinics. Improvements in biochemical and anthropometric measurements show that calcitriol treatment was effective and safe in these cases.

Table 1. Anthropometric and laboratory results at the time of diagnosis and at the last visit.

Parameter	At diagnosis	At last visit	p
Serum Calcium (mg/dL) Mean±SD	7.2±0.3	9.06±0.14	<0.05
Serum phosphorus (mg/dL) Mean±SD	2.8±0.2	4.2±0.3	<0.05
Serum ALP (U/L) Mean±SD	1352±154	249±63	<0.05
Serum PTH (pg/mL) Median (range)	553 (238-940)	49.9 (11-366)	<0.05
Height SDS Mean±SD	-2.0±0.57	-1.55±0.22	<0.05

Abbreviations: SD, standard deviation; ALP, alkaline phosphatase; PTH, parathyroid hormone; SDS, standard deviation score.

P1-215

Clinical and genetic characteristics of primary hypoparathyroidism in children ：two-center experience in China

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Object: To analyze the clinical and genetic characteristics of primary hypoparathyroidism in children from two children's hospitals in China.

Methods: This study includes 47 patients (26 males, 21 females), who were diagnosed with primary hypoparathyroidism in Children's Hospital of Zhengzhou University and Children's Hospital of Zhejiang University School of Medicine from January 2015 to November 2022. We analyzed the age of onset, initial presentations, endocrine and radiological findings, and genetic etiologies.

Results: The median onset age was 3 years (range 1 day-15 years) and the median time taken from onset to diagnosis was 1 month (range 1 day-10 years). 31 patients were performed genetic tests, among which 25 cases were found to have HP-related variants. There are 11 cases (11/25, 44%) that have 22q11.2 microdeletion, 6 patients have AIRE variations (6/25, 24%), 3 patients have

GATA3 variations (3/25, 12%), 2 patients have CaSR variations (2/25, 8%), and the rest 3 patients with mutations of TBCE, PTH, and mitochondrial gene deletion respectively. Convulsion was the most common initial presentation, found in 28 cases, hypocalcemia in 6 cases, tetany in 5 cases, numbness of extremities in 1 case, developmental delay in 3 cases, and misdiagnosed as epilepsy in 2 cases. Laboratory tests showed that the PTH levels of these patients were (8.49±8.25 pg/mL), with decreased serum calcium levels (1.58±0.31 mmol/L) and elevated serum phosphorus levels (2.59±0.63mmol/L). Among the 42 patients who underwent brain CT or MR, 17(17/42, 40.5%) had basal ganglia calcification.

Conclusion: We conducted the largest cohort of childhood HP with genetic diagnosis, and our results indicated that genetic variations account for the majority in pediatric primary hypoparathyroidism, the most common of which is 22q11.2 microdeletion, and clinical manifestations are heterogeneous in childhood and adolescence. Identification of the genetic etiologies of hypoparathyroidism makes it possible to predict patients' outcomes and provide appropriate genetic counseling.

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Genetic Evaluation in a cohort of children affect by idiopatic short stature

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Short stature is a common clinical presentation in children. New genetics approache such as "Next Generation Sequencing" have recently reported many monogenic defects in genes related to the growth plate cartilage and in GH-IGF-1 axis.

The purpose of this study was to analyze a cohort of 64 patients (31 females and 33 males) affected by ISS. The patiens have been subjected to genetic investigations by performing an NGS panel of genes involved in growth, the evaluation of the phenotypic charachteristics of patients and their possible response to therapy.

Results stratified by sex, height SDS was -2.05 for females and -2.03 for males. Twenty-seven patients (42%) were carrier of variants of uncertain clinical significance (VUS) and 7 patients (11%) were carrier of pathogenic (P) or likely pathogenic (LP) variants. The gene of which we most frequently detected a variant was FLNB (5 variants in 5 patients), encoding for filamin B, a protein involved in the cytoskeletal structure of cells. The second most frequent variant was the ACAN gene (3 variants in 3 patients), it encodes for aggrecan, a primary proteoglycan component specific for the structure of the cartilage growth plate, articular and intervertebral disk. Two patients underwent recombinant human growth hormone replacement therapy, associated with gonadotropin releasing hormone therapy, in order to block early growth cessation and therefore reach a better final height.

The third most frequente variant was the CUL7 gene (3 variants in 3 patients), coding for the protein cullin7. This protein is involved in the processes of ubiquitination of damaged or excess intracytoplasmic proteins and in the regulation of major cellular activities such as the timing of cell division and growth.

Conclusion: specific diagnoses allows the clinician to assess the best diagnostic pathway, to choose the most appropriate and targeted therapy, to provide prognostic information about the patient's growth, to understand any associated co-morbidities that may compromise the patient's health and to identify other affected family members.

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ABSTRACT WITHDRAWN

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Osteoporosis pseudoglioma syndrome: a case report of a child with osteoporosis and impaired vision

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Introduction: Osteoporosis pseudoglioma syndrome (OPPG) is a rare autosomal recessive disease which is caused by mutations in the low-density lipoprotein receptor-related protein 5 (LRP5) gene and is characterized by severe early – onset osteoporosis and vitreoretinal complications leading to blindness by young adulthood.

Case Presentation: We present a case of an 8 years old boy, who was initially referred to our department by the Orthopaedic team due to radiology findings of osteoporosis when investigated for a six-month history of thoracolumbar pain. His physical activity was significantly reduced due to pain. He was born at 36w+5d by normal delivery and required admission to the Neonatal Unit for 2 days due to perinatal stress. His parents were not consanguineous. At the age of 3 months he was diagnosed with severely impaired vision due to retinal hemorrhage. Hypotonia and gross motor delay were also noted from infancy. At the age of 4 years old he underwent orchidopexy for bilateral undescended testis. Despite growing just below the 3rd centile for height and weight as well, he started gaining weight during childhood reaching the 85th centile by 8 years.

Extensive hematological and biochemical tests showed normal ALP, Ca, P and PTH values, vitamin D deficiency and increased CTX levels. Bone mineral density (BMD) was assessed by DEXA scan and confirmed the findings of severe osteoporosis (lumbar spine 0.204gr/cm^2, Z-score: -5.6). Dental and ENT examination was normal. At that time, he sustained an atraumatic fracture of the left femur and left radius. The combination of osteoporosis and vitreoretinal pathology raised the suspicion of OPPG syndrome. Direct sequencing of the LRP5 gene revealed the homozygous deletion c.2409_2503+79del (G804_G835delfsX49) in exon/intron 11. He was commenced on Calcium and Vitamin D supplements and bisphosphonate treatment with periodic intravenous zoledronic acid. BMD measurements in other family members revealed that his brother had osteopenia, his sister had a reduced BMD (Z-score -2.9) and scoliosis while his mother had premenopausal osteoporosis. Genetic testing for the family members is pending.

Conclusion: Although OPPG is a rare genetic disease, clinicians should consider its diagnosis in cases of severe osteoporosis with early onset of impaired vision.

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An investigation of vitamin D deficiency in children with new onset type 1 diabetes mellitus from Henan Province, China

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Several observational studies have reported vitamin D deficiency (VDD) in children with type 1 diabetes mellitus (T1DM). The investigation of VDD in children with new onset T1DM in China is lacking. The current study aimed to assess vitamin D status and examine the factors that influence VDD in children with new onset T1DM in Henan Province, China. Children with new onset T1DM (n=280) and healthy controls (n=710) were enrolled in Henan Province. Demographic and clinical data were collected from medical records. Children in the T1DM group and controls were divided into two groups according to 25-hydroxyvitamin D [25(OH)D] levels: the VDD group [25(OH)D < 20 ng/mL] and the vitamin D sufficient (VDS) group [25(OH)D ≥ 20 ng/mL]. The serum 25(OH)D level of children with new onset T1DM [17.8(12.1, 27.3) ng/mL] was significantly lower than that of healthy children [23.7(17.4, 32.4) ng/mL] with comparable age, gender, body mass index, and season (p<0.001). More children with T1DM had VDD than controls (56.8% vs. 36.3%, p<0.001). In the control group, the age and rate of males were lower in the VDS group than in the VDD group (p<0.001, p<0.001). The body max index was higher in the VDS group than in the VDD group (p=0.006). Seasonal distribution of VDD was also found in healthy children(p<0.001). In the T1DM group, the age and hemoglobin A1c level were lower in the VDS group than in the VDD group (p<0.001, p=0.002). Calcium levels were higher in the VDS group than in the VDD group (p<0.001). Moreover, there were significant differences in the prevalence of VDD among different age groups (p<0.001) and seasons (p=0.028) in T1DM group. The prevalence of VDD for children with T1DM was 50.5% in the non-DKA group and 48.4%, 67.2%, and 63.3% in the mild, moderate, and severe diabetic ketoacidosis (DKA) groups, respectively. There were no significant differences between different degrees of DKA (p=0.065). According to logistic regression analysis, According to logistic regression analysis, healthy children were 3.03 (95%CI: 1.90-4.84) (p<0.001) times more likely to be VDD in winter. The healthy children with 6-10 years age (OR: 5.50; 95%CI: 3.66-8.27) (p<0.001) and 10-14 years age (OR: 17.83; 95%CI: 10.01-31.5)(p<0.001) had the highest odds for VDD. For children with new onset T1DM, besides moderate DKA (OR: 2.94; 95%CI: 1.31-6.60) (p=0.009) and severe DKA (OR: 2.57; 95%CI: 1.12-5.91) (p=0.026), children with 6-10 years age (OR: 6.85; 95%CI: 3.45-13.57) (p<0.001) and 10-14 years age (OR: 17.07; 95%CI: 6.32-46.08) (p<0.001) had the highest odds for VDD. In conclusion, the prevalence of VDD among children with new onset T1DM was high in Henan Province, China. Besides DKA, increased age (6-14 years old) was the main risk factor for children with new onset T1DM. We recommend testing for 25(OH)D and supplementation in children with new onset T1DM, especially in 6-14 years old children with DKA.

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Evaluation of Bone mineral density and Nutritional status in children with Spastic Cerebral Palsy. Implications for Fracture risk and Quality of Life

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Introduction: Up to 75% of Cerebral palsy(CP) children are of spastic diplegic & quadriplegic types with severe malnutrition found in 35% of them which is multifactorial. Motor impairment is strongly corelated with Gross Motor Function Classification (GMFCS) level 3 and above,malnutrition,and low bone mineral density(BMD)assessed via dual energy x-ray absorptiometry(DXA) scan. These children have low age adjusted BMD z scores <-2SD subsequently increasing their fracture risk.

Objective: To evaluate the effect of motor impairment and nutritional status on Bone mineral density(BMD) in children with spastic diplegic and quadriplegic Cerebral Palsy(CP).

Methods: It was a prospective cohort study, done at the pediatric neurology clinic of Aga Khan University Hospital Karachi, Pakistan, from June to December 2022 with a sample size of 52 children. This was a funded study. Spastic diplegic and quadriplegic CP children with GMFCS (3 and above) between 3-18 years of age were included in study. A detailed nutritional evaluation was done using anthropometric measurement with weight & height/length for age on CP specific growth charts. Bone mineral density z-score was measured at lumbar spine, left hip, femur &left distal forearm with DXA scan. Z score value of <-2.0 SD was taken as low BMD indicating high risk of fracture. Mean and standard deviations were calculated for age, weight, height/length, BMI and BMD z-score. Chi square test was applied, P<0.05 was considered statistically significant between severely malnourished and BMD.

Results: Out of 52 children, 18 were spastic quadriplegic and 34 spastic diplegic CP.29% of them classified as GMFCS class 4 & 5 and 71 % GMFCS class 3. All the children had weight, height/length and BMI <5th percentile. Mean Bone mineral content according to DXA scans was reported -5.2 ±2.1SD on femur neck & -4.2±1.8SD on spine in spastic quadriplegic children. Whereas it was -4.2±1.6SD & -3.5±1.5SD on femur neck and spine respectively in spastic diplegic children. There was no statistical significance between age and gender however, BMI, motor impairment, fracture history, and pattern of CP had a significant impact on BMD and Z-score values of these children. 2 of the spastic quadriplegic children had history of femur fractures.

Conclusion: Our study highlights that low BMD is prevalent in children with moderate to severe CP especially those who were nonambulatory which is inturn associated with significant fracture risk. Early identification can lead to damage prevention,appropriate management including bone health optimization and bisphosphonates to prevent occurrence of further fractures, thus contributing to improved quality of life.

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Celiac disease in a patient with Sclerosteosis: an association or just a co-incidence?

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Sclerosteosis is a rare autosomal recessive disorder characterized by progressive skeletal overgrowth and increased bone density. Loss of function mutations of *SOST* gene, coding for sclerostin, are linked to sclerosteosis. Sclerostin plays a critical role inhibiting osteoblastic activity and preventing excessive bone formation by antagonizing the Wnt signaling pathway.

Sclerosteosis patients are often tall and have excessive body weight due to high skeletal weight.

To our knowledge, around 96 patients have been reported worldwide, the majority from South Africa. No patients have been reported to have celiac disease (CD) as well. Due to the scarcity of cases, a knowledge gap exists as regards the molecular mechanisms of sclerosteosis, leading to unsatisfactory diagnostic and therapeutic strategies.

We hereby report a *SOST* gene mutation causing sclerosteosis in an Egyptian patient with unusually poor growth and low bone density due to celiac disease.

Case Summary: A 14-year-old girl diagnosed with intellectual disability (IQ test score 40) was referred to the Pediatric Endocrinology clinic for assessment of skeletal abnormalities, poor growth and delayed puberty. She was born to consanguineous parents and had 2 healthy siblings. There was no history of fractures.

Her weight was 30 kg (-2.1 SD), height 152 cm (-1.36 SD), and head circumference 56 cm. She had normal arm span, and normal U:L ratio. She had dysmorphic facial features (large forehead, squared mandible, proptosis, crowded teeth), squint, elongated fingers, and dysplastic left index finger nail. She had breast Tanner I, and no pubic hair.

Laboratory investigations showed iron deficiency anemia and vitamin D deficiency (25-OHD 7.56 ng/ml) with secondary hyperparathyroidism suggesting nutritional cause versus malabsorption. She had normal ESR, renal and liver functions. Celiac screen revealed highly positive anti-tissue transglutaminase IgA>100U/ml. Upper GI endoscopy and biopsy showing villous flattening and atrophy confirmed CD. Bone age was delayed and basal LH was pubertal.

Skeletal survey showed mild C-shaped scoliosis at dorsolumbar spine, elongated cylindrical-shaped metacarpal and phalangeal metaphases with diffuse osteopenia. CT petrous bone showed marked medullary sclerosis and obliteration of medullary cavities suggesting sclerosing bony dysplasia. WES identified a homozygous pathogenic variant in *SOST* gene, which is associated with Sclerosteosis 1.

Conclusion: Sclerosteosis is a rare form of sclerosing bony dysplasia. Patients are usually tall with increased bone density. Thinking systematically in patients with unusual presentations can reveal new associations and may address knowledge gaps. The relation between sclerosteosis and CD needs to be further investigated.

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Height evaluation in a group of patients with Prader Willi syndrome after 3 years of treatment with growth hormone

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Introduction: Prader–Willi syndrome (PWS) is a genetic disorder caused by the lack of expression of genes on the paternally inherited chromosome 15q11.2-q13 region. Clinical picture of PWS changes across life stages. PWS is characterized by endocrine abnormalities, such as growth hormone (GH) deficiency, obesity, central adrenal insufficiency, hypothyroidism, hypogonadism, and complex behavioural and intellectual difficulties. The recombinant human growth hormone (rhGH) therapy is recommended by the international scientific literature and must be started as soon as the diagnostic is made.

Material and Method: A total of 45 genetically confirmed children with PWS (24 males) followed between 2004 and 2022 were retrospectively analysed. Height, weight, and body mass index were expressed as standard deviation scores (SDSs) according to Spanish child growth standards. Bone age has been assessed according to the Greulich and Pyle atlas, and to assess the delay or advance of the bone ages with respect to the chronological ones, bone age/ chronological age ratio. Comparisons were made using nonparametric tests.

Results: The mean age at the start of the treatment was 4.4 years and at the third year it was 8. Median height SDS increased during 3 years of rhGH in infants from -1.24 (-3.99 to 1.75) SDS to 0.2 (-2.22 – 3.25) SDS. Mid parental height SDS was 0.23 SDS. The mean bone age at the beginning of the treatment is delayed with respect to the chronological age, producing a statistically significant acceleration with the administration of rhGH. With the treatment there is a statistically significant increase in the mean sizes with a gain of 1.44 S.D.S. The body mass index does not suffer significant variations with the treatment. No serious adverse events were reported.

Conclusions: Recombinant human growth hormone therapy in PWS improved growth in infants and child. Changes in body composition and behavior with rhGH have been demonstrated in other studies. Multidisciplinary studies are necessary to assess the positive effect of growth hormone treatment in these patients.

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A rare cause of hypoparathyroidism: Barakat syndrome

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Introduction: Barakat syndrome, also known as HDR syndrome (OMIM 146255), is a clinically heterogeneous, rare, autosomal dominant genetic disorder, characterized by the triad of hypoparathyroidism (H), deafness (D), and renal disease (R). The phenotypic features are attributed to mutations of the *GATA3* gene, which encodes a transcription factor essential for embryonic development of the parathyroid glands, auditory system, and kidneys. Here, we report the case of a boy who presented with symptomatic hypocalcemia and was subsequently diagnosed with Barakat Syndrome.

Case: A 4.75 year-old male patient, who had a pre-existing diagnosis of Fanconi aplastic anemia, presented with generalized tonic-clonic, afebrile convulsions. The parents were first-degree cousins.

Laboratory Investigations Showed: serum calcium 4.25 mg/dL (8.8-10.6); ionized calcium 0.55 mmol/L (1.15 - 1.29); phosphorus 12.2 mg/dL (3.8- 6.5); magnesium 2.5 mg/dL (1.6-2.6); alkaline phosphatase (ALP) 226 U/L (55-377); 25-hydroxy vitamin D (25OHD3) 20.0 ng/mL (20-100); and parathyroid hormone (PTH) <1.2 pg/mL (12-88) indicating hypoparathyroidism.

He had normal renal functions on biochemical testing, but urinary system ultrasonography revealed a decrease in the size of the left kidney. He had bilateral sensorineural hearing loss, detected by audiometry.

While his seizures were controlled with intravenous calcium gluconate and calcitriol treatment, serum calcium and phosphorus returned to normal. Fluorescence in situ hybridization studies excluded DiGeorge Syndrome as the etiology of his hypoparathyroidism.

Next-generation sequencing of the patient, who was clinically considered to have Barakat Syndrome, revealed a c.480C>G (p.Asp160Glu) heterozygous, missense, variant of uncertain significance (VUS) in *GATA3*. Since no abnormality was found in his parents when examined for the components of Barakat Syndrome, the detected variant was thought to be de novo.

The patient, who is in the first year of follow-up, is being treated with 30 ng/kg/day calcitriol and 50 mg/kg/day elemental calcium and has had a normocalcemic course.

Conclusion: Although Barakat syndrome is rare, it should be kept in mind in the differential diagnosis of hypoparathyroidism, and urinary system imaging, hearing evaluation and *GATA3* gene analysis should be performed in suspected cases.

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Metaphyseal Dysplasia, Spahr Type: 12-Year Follow-up

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Introduction: Metaphyseal dysplasia, Spahr type(MDST) is an autosomal recessive primary skeletal dysplasia characterized by postnatal short stature, progressive bowing deformity, waddling gait, with an incidence of <1/1 million. MDST is caused by mutations in Matrix metallopeptidase 13(MMP13) gene. The MMP13 plays a role in the degradation of extracellular matrix proteins. It is required for embryonic bone development and ossification. It may be involved in the cartilage life cycle and pathophysiology of osteoarthritis. MMP13 mutations are cause of Spondyloepimetaphyseal Dysplasia, Missouri type, Metaphyseal Anadysplasia1 and Metaphyseal Dysplasia, Spahr type. Here we present 12-year follow-up of a patient with MDST to reinforce our experience in approaching metaphyseal dysplasias and understanding of diseases in this spectrum.

Case: A two-year-old girl was referred for short stature. She was born with normal height, from consanguineous parents with normal height, at term after IVF pregnancy, weighing 3000grams, as a triplet. Her paternal cousins, a girl and a boy, had rhizomelic short stature. Her developmental milestones were on time. Her weight, height, BMI and head circumference were 13,1 kg(0,76 SD), 79,3 cm(-2,18 SD), 20.9 kg/m2(2,85 SD) and 48 cm(-0,16 SD) respectively. Upper to lower segment ratio was 1,54 and she had rhizomelic shortening of limbs. Skeletal survey revealed reduced interpedicular distances of the lumbar vertebrae; rib ends and long bone distal metaphyseal cupping. Rickets was excluded. Homozygous c.673G>A(p.Gly225Ser) variant was detected in the MMP13 gene. On the 3,5 years of age metaphyseal flaring, O-Bain deformity and lumbar lordosis was determined; the bone age was found as 3 years. The puberty has started at the age of 9,5 years and menarche occurred at the age of 11 years. In the follow-up, vertebral rotoscoliosis, knee joint pains were observed and osteoarthritis was not detected. Metaphyseal cupping and flaring became indistinct and the bone age exceeded the chronological age over time. At the last control, she was 14 years old, bone age was 16 years of age, her height was 138,7 cm(-3,66 SD), BMI was 29,9 kg/m^2(1,13 SD), head circumference 56 cm(0,6 SD), upper to lower segment ratio was 1,2.

Conclusion: Since the ACAN gene is associated with the pathophysiology of MDST, clinical features such as osteoarthritis and advanced bone age are common. We think that the long-term follow-up of this case contributes to our experience in the approach to metaphyseal dysplasias and the pathophysiological process.

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Acrodysostosis: a case report

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A 2.6-year-old girl of Egyptian origins comes to our attention due to a deflection of the growth rate. The girl was born small for gestational age (SGA), and is affected by congenital hypothyroidism, with normal sized thyroid, treated with Levothyroxine.

At the age of 1.8, due to right lameness, an x-ray of pelvis and lower limbs was performed, as indicated by the orthopaedic. The examination showed absence of the distal tibial ossification nucleus in the right leg and entanglement of the trabecular design of the distal metaphyseal region; therefore, she underwent magnetic resonance imaging of the ankles, showing distal meta-epiphyseal dysmorphism in the right tibia, with dysmorphic and irregularly ossified epiphyseal nucleus. Moreover, the articular cartilage of the tibial epiphyseal nucleus presented with central chondral centimetric defect. These findings were seen to a lesser extent contra-laterally.

Her clinical examination revealed brachydactyly with short phalanges, saddle nose, round face, asymmetry in the lower limbs (the left leg was longer than the right one), attitude in flexion of the right elbow.

Blood tests showed PTH 121 pg/ml (normal range: 15-65), calcium 9.16 mg/dl (normal range: 9-11), phosphorus 5.55 mg/dl (normal range: 3.8-6.3), alkaline phosphatase in normal range, 25-hydroxy-vitaminD 33.9 ng/ml (lower limit of normal >20), screening for celiac disease resulted negative. TSH 23.1 microUI/ml (normal range: 0.36-3.74) with Ft4 1.44 ng/dl (normal range: 0.76-1.46), and negative antibodies therefore we adjusted the L-thyroxine posology.

The x-ray of the left hand-wrist confirmed the presence of brachydactyly with short and dysmorphic phalanges.

The tests and the clinical presentation of the girl were found compatible with congenital dysostosis or pseudohypoparathyroidism. Thus, genetic analysis (NGS) for genes related to pseudohypoparathyroidism and bone dysplasia was performed; this examination revealed a heterozygous variant of the PRKAR1A gene, classified as pathogenic and associated with acrodysostosis, a rare disease, related to pseudohypoparathyroidism.

Acrodysostosis is characterized by adult short stature, brachydactyly and facial dysostosis, it is associated with multiple hormonal resistances, always to PTH and TSH. These patients are often born SGA and have different degree of cognitive impairment. Diagnosis is based on clinical presentation, blood tests and genetic analysis (mutations of the PRKAR1A and PDE4D genes). Since this is a rare and heterogenous condition, the management of these patients must be based on a multidisciplinary approach. However, more evidence is needed to better understand long term clinical outcomes and treatment options.

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Hereditary Vitamin D Resistant Rickets (HVDRR) Case Series: Phenotype, Genotype, Conventional Treatment and Cinacalcet Therapy

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Background: Hereditary vitamin D resistant rickets (HVDRR) or vitamin-D dependent rickets type II is an autosomal recessive disorder caused by mutations in the vitamin D receptor (VDR) gene, causing end-organ resistance to the action of 1,25-dihydroxyvitamin D (calcitriol), thus resulting in the distinct characteristics of early-onset rickets, hypocalcemia, and secondary hyperparathyroidism. The currently accepted treatment modality is bypassing the affected receptor with high dose intravenous calcium, however, the calcimimetic cinacalcet has been used as an adjunctive therapy in a few limited case reports.

Methods: This case series describes the clinical presentation (phenotype), biochemical profiles, genetic mutations, and management of eight Saudi patients with HVDRR. Retrospective chart reviews were conducted to collect clinical and biochemical data prior to and after treatment, and genetic analysis to identify the disease-causing mutation was carried out.

Results: Eight patients, including two sets of siblings (three patients were brothers and two were sisters), were reviewed. Universal among the group were the findings of alopecia, hypocalcemia, elevated alkaline phosphatase, and secondary hyperparathyroidism. There was heterogeneity in the presence of skeletal signs of rickets at diagnosis, a finding which varied with age at diagnosis. Genetic analysis revealed three distinct mutations: first, a mutation in the ligand binding domain at exon 8:c.886C>A:p.Y295X in two unrelated patients; this resulted in a slightly milder phenotype as one patient was able to maintain normocalcemia on oral calcium alone, second, a truncating ligand binding mutation at exon 6:c.1035T>Cp.Y>X in two sisters, and third, a homozygous missense mutation of the DNA binding domain at exon 1:c.88C>T in three brothers. This DNA binding domain mutation resulted in a more severe phenotype than the two ligand binding domain mutations. All patients responded well to the current standard therapy of intermittent high dose intravenous calcium, as shown by the normalization of hypocalcemia, improvement in PTH levels, and, clinically, the ability to achieve independent mobilization. Additionally, four patients received adjunctive cinacalcet, the use of which, in our series, was safe (no episodes of hypocalcemia) and showed some initial promise in improving secondary hyperparathyroidism.

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Parathyroid Adenoma in a 12-year- old Child: A Case with Unusual Presentation

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Introduction: Acute pancreatitis (AP) is rarely seen in children and is typically not associated with common aetiologies seen in adults. AP secondary to hypercalcaemia due to primary hyperparathyroidism (PHPT) is very rare. The annual incidence of PHPT in adults is 30/100,000 with female predominance and 2–5/100,000 in children regardless of sex. We present a rare presentation of PHPT presenting with AP in a 12-year-old boy.

Case Discussion: 12-year-old boy presented with acute abdominal pain with biochemical evidence of elevated serum amylase, calcium, ALP and parathyroid hormone (PTH) levels with elevated urinary calcium creatinine ratio. USS showed features of AP. Diagnosis of AP was made, which was settled with conservative management. Hypercalcaemia was managed with IV fluids, hyper hydration and frusemide in acute stage. Since he had persistent hypercalcaemia, he was started on cinacalcet 15mg twice daily. His vitamin D was low and treated with cholecalciferol.

He didn't have other symptoms of hypercalcaemia such as bone pain, polyuria, polydipsia, weight loss or symptoms suggestive of urolithiasis or nephrolithiasis. Clinically he was euthyroid with normal thyroid function. There was no family history of renal calculi, hypercalcemia, thyroid or other endocrine neoplasms. His prolactin and IGF1 was normal and he didn't have episodes of hypoglycaemia.

Further investigations, namely CT and technetium 99m (Tc-99m) sestamibi scans, revealed a solitary lesion at left superior pole suggestive of parathyroid adenoma measuring 13×4×5 mm and thyroid gland was normal with no focal lesions. He subsequently underwent minimally invasive parathyroidectomy. Intraoperatively PTH dropped from 178.5pg/ml to 24.9pg/ml. Ca and PTH levels normalized postoperatively. Histology revealed a parathyroid adenoma.

Discussion: PHPT in children presents with hypercalcaemic symptoms such as bone pain, urolithiasis, nephrolithiasis, or nonspecific symptoms like fatigue and muscle weakness. However, adults are mostly asymptomatic and detected during routine laboratory testing.

Solitary benign sporadic parathyroid adenoma is the most common cause of PHPT in the general population, including children and adolescents. PHPT is often associated with rare genetic disorders such as multiple endocrine neoplasia 1 and 2A.

In the absence of genetic testing long term surveillance and follow up is needed for these children. Intraoperative PTH monitoring is an important investigation to confirm the success of the surgery and to plan further surgical interventions.

P1-411

The European Registries for Rare Bone and Mineral Conditions (EuRR-Bone): Collecting Core Data Elements and Clinician and Patient-Reported Outcomes

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Introduction: The European Registries for Rare Bone and Mineral Conditions (EuRR-Bone) was created in collaboration with the European Reference Network on Rare Bone Diseases (ERN BOND) and the European Reference Network on Rare Endocrine Conditions (Endo-ERN) to support the needs of healthcare providers, patients and researchers by providing high-quality registries. The Core Registry collects a set of Core Data Elements as well as longitudinal patient and clinician-reported outcomes in condition-specific modules.

Aim: To describe the patient population and data entered in the EuRR-Bone Core Registry between April 2020 and December 2022.

Methods: Core Registry clinical contributors are invited to register new and existing cases of rare bone and mineral conditions mapped according to the Orphanet classification. A set of core data elements collects demographic and diagnosis data. Furthermore, condition-specific modules are available for clinicians and Patient-Reported Outcome Measures (PROMs) are available for patients to complete through the 'patient platform'.

Results: Thirteen centres from 10 countries, of which 9 are based in Europe, have registered cases. Of 13 centres, 7 are joint ERN BOND and Endo-ERN members and 1 is Endo-ERN member only. To date, a total of 401 cases have been added to the Core Registry, 225 (56%) and 176 (44%) in the bone dysplasia and the calcium and phosphate condition group, respectively. Of 401 cases, 72 (18%) were within the age range 0-9 years, 48 (12%) 10-17 years and 280 (70%) over 18 years. The median age was 33 years (range 0-86). Of 401 cases, 336 (91%) were under active follow-up. Sixty-two (15%) had expressed interest in having access to the patient platform and of these 19 (31%) had an active account. Ninety-five PROMs outcomes had been completed, of which 55 were EQ-5D, 25 were WHO ICF (International Classification of Function and Disability) and 15 were BPI-SF (Brief Pain Inventory Short Form. Of 95, 90 (95%) were completed by clinicians and 5 by patients.

Conclusion: The Core Registry has proved its ability to collect clinician and patient-reported outcomes in patients of all ages. This makes the platform a suitable option for studying the natural history and long-term clinical outcomes of rare bone and mineral conditions. In order to increase participation, we should address the challenges healthcare professionals and patients might face to participate.

P1-412

Juvenile Paget's Disease: Evaluation of Novel Mutation and Treatment Response

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Introduction: Juvenile Paget's Disease (JPD) is an extremely rare disease of bone characterized by progressive painful bone deformities, fractures and increased bone turnover. Findings also include deafness, loss of vision, vascular calcification and aneurysm. Here, we report two siblings presented with recurrent fractures and diagnosed as JPD by very high alkaline phosphatase levels and radiographic findings. A novel homozygous mutation in the TNFRSF11B gene was detected in both siblings.

Case: A $14^{8/12}$-year-old male (case 1) presented with recurrent fractures. He was a product of consanguineous marriage of healthy parents. On initial examination, height SDS was −7,09(117cm), weight SDS −4,27(29 kg) and head circumference SDS +6.9(69 cm). He was noted to have severely deformed extremities, pectus carinatum, pseudoxanthoma elasticum, and macrocephaly (Figure 1). Laboratory tests showed very high levels of alkaline phosphatase (ALP)(10000 IU/L). X-rays showed increased diploic distance, enlargement-osteopenia and trabeculation of long bones (Figure 2). JPD was considered because of the family history of consanguineous marriage, history of recurrent fractures, radiological findings, and high ALP levels. His 11-month-old sister (case 2), who had a history of recurrent fractures, had a height of 73 cm (-0.49 SDS), weight of 8 kg (-1.18 SDS) and head circumference of 45.5 cm (-0.07 SDS)(Figure 1). She noted to have deformed extremities. Laboratory tests showed high levels of ALP (3718 IU/L). A novel homozygous mutation in the *TNFRSF11B* gene was detected in both siblings. Clinical improvement and near normalization of ALP values was observed with intravenous pamidronate therapy (Figure3). During the treatment period, no fracture was observed in both patients, a significant reduction in existing pain was observed in case 1, and the gain of gross motor skills was observed in case 2.

Discussion: It is predicted that the homozygous mutation in the TNFRSF11B gene that causes JPD, which we described in our cases, affects 'splicing' in intron 1 and leads to a truncated protein in which the entire ligand-binding region is lost. In both cases, severe JPD, in which the symptoms started in the first year, was observed, and a significant decrease in ALP values and improvement in clinical symptoms were observed after treatment. Improvement in bone symptoms after bisphosphonate treatment has been reported in the literature, but data on the improvement of non-skeletal findings and long-term follow-up are limited. Two cases are presented to evaluate the diagnosis, follow-up and treatment of the disease.

P1-413

Obesity and Insulin Resistance in Patients with Achondroplasia

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Background: Achondroplasia (ACH) is the most common skeletal dysplasia with an incidence of 1/20,000. Acanthosis nigricans (AN) is commonly seen in conditions associated with reduced insulin sensitivity. AN has been reported in association with skeletal dysplasias due to activating mutations in FGFR3, including ACH.

Objective: Our aim was to evaluate insulin sensitivity and glucose metabolism in patients with ACH carrying c.1138G>A (p.Gly380Arg) variant in FGFR3 gene.

Patients and Methods: The study cohort included 28 patients (15 females) with ACH. Physical examination, anthropometric measurements and puberty examination were carried out. Fasting plasma glucose (FPG), insulin and HbA1c levels were measured and oral glucose tolerance test (OGTT) was performed at a dose of 1.75 g/kg. Homeostatic model assessment of insulin resistance (HOMA-IR) and body mass index (BMI) were calculated. Total insulin level ^{3} 300 U/mL was accepted as decreased insulin sensitivity.

Results: The mean age of the patients was 12.4±4.5 (ranges 7.9-18) years. The FPG level of all patients was in normal ranges. OGTT was normal in 75% of patients. Approximately 17.9% of patients (n=5) had insulin resistance (IR) and 7.1% of patients (n=2) had impaired glucose tolerance (IGT) at 120 min. All patients with IR or IGT were obese or overweight. HOMA-IR was higher than 2.5 in four of five patients with IR. All of these patients 57.1% was Tanner stage 5, 14.2% was Tanner stage 1 and 28.6% had no information about puberty. Fifty percent of all patients (n=14) had AN. OGTT results of 71.4% patients with AN were normal, 21.4% had IR and 7.1% had IGT. One patient with IGT and another patient with IR did not have AN. The frequency of overweight and obesity were 31.8% and 27.3%, respectively. IR or

IGT was detected in 38.5% of overweight and obese patients. There was no significant correlation between IR and age, height SDS or HbA1c level. A significant positive correlation was found between BMI and HOMA-IR (p=0.003).

Conclusion: In our study, the frequency of obesity tendency and IR has been found to be high in ACH. It is important to monitor children with ACH for IR. HOMA-IR is not sufficient to detect IR alone, OGTT is a safe and practical method and can be recommended in patients with ACH to check for glucose metabolism. Prevention of obesity in these cases may prevent the decrease in IR. The frequency of AN was high in ACH patients, however we couldn't demonstrate a significant relation with IR.

P1-414

Multidisciplinary approach in achondroplasia – real world experience after drug approval of vosoritide

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Background: Achondroplasia (Ach) is a rare growth disorder caused by a point mutation in the fibroblast growth factor receptor 3 gene that results in dysproportionate extreme short stature and can lead to a wide range of multisystemic complications throughout the individual's life with reduced quality of life. In the past, orthopaedic and neurosurgical therapies have been developed to partially improve mobility, reduce pain and prevent neurological disability. With the discovery of new causative drugs, a better knowledge of the natural history of achondroplasia is essential to plan the healthcare resources required by individuals with achondroplasia throughout their lives.

Methods: A multidisciplinary working group together with representatives from 3 European patient associations developed a diagnosis-specific data set for patients with achondroplasia. These elements were integrated into a patient registry platform, CrescNet®, which has been established at the University of Leipzig for more than 20 years to monitor auxological, laboratory and treatment data in real time. Paediatricians, endocrinologists and hospitals entered data from > 1,000,000 children with various conditions.

Results: Currently, 259 (132 female) individuals with achondroplasia have been entered by 16 centres. N=17 in the age group <2 years, N=169 in the age group 2-15 years and N=74 > 15 years. A cranial MRI was performed in N=94 to exclude or diagnose cranio-cervical compression. An AFMSS score of 1 was diagnosed in 29, AFMSS 2 in 24, AFMSS 3 in 23 and AFMSS 4 in 14 children. Decompression surgery was performed in 19 patients at a mean age of 1.73 years. Bone age (Greulich/Pyle) was documented in N=110, with bone age below chronological age in 105 (mean bone age of 8.8 years at chronological age of 9.9 years). In N=85, treatment with Vosoritide was started at a mean age of 6.92 years (SD: 3.54) and so far documented for 1.23 years (SD: 0.75). Using achondroplasia-specific reference data (Merker et al., 2018), an increase of 0.45 H-SDS was confirmed, which is consistent with data from clinical trials.

Conclusions: The established CrescNet® registry can be used to evaluate the long-term outcome of a rare disease. It allows to monitor the frequency of multisystemic complications, e.g. AFMSS, and the use of health care resources. In Ach, 37 out of 93 (=40%) showed significant cranio-cervical compression of AFMSS 3-4. Visual bone age determination (VAD) showed delayed BA in 105/110 Ach subjects. An increase of 0.45 H-SDS was observed after the first year of vosoritide treatment.

P1-415

EuRR-Bone: Collecting Condition-Specific Outcomes on Fibrous Dysplasia/ McCune-Albright Syndrome

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Introduction: The European Registries for Rare Bone and Mineral Conditions (EuRR-Bone) were created in collaboration with the European Reference Network on Rare Bone Conditions (ERN-BOND). EuRR-Bone collects data using 2 platforms: e-REC, a tool that captures the occurrence of bone and mineral conditions, and the Core Registry which collects a set of Core Data Elements as well as longitudinal patient and clinician reported outcomes in condition specific modules. Until December 2022, 188 cases of fibrous dysplasia/McCune Albright syndrome were registered in e-REC.

Methods: The study group on Fibrous Dysplasia McCune-Albright Syndrome(FD/MAS) developed a disease-specific dataset including demographic, diagnostic and clinical outcomes including Patient-Reported Outcome Measures (PROMs). Built within the Core Registry platform, this module is open for contributors (ERN and non-ERN members) to register new and existing cases of FD/MAS since April 2022.

Results: Until March 2023, 92 cases of FD/MAS had been registered in the Core Registry by 4 centres from 4 European countries. The median age of patients in the Core Registry was 39 years (range 1-76) with 8 patients (8.6%) in the range of 0-17 years and 84 (91.3%) ≥18 years. The median age at condition onset and diagnosis were 0 (range 0-56) and 27 (range 0-67) years respectively. The median time to diagnosis in months was 242 (range 0-707).

Of 92 cases, 24 (26%) had polyostotic FD, 40 (44%) had monostotic FD, 8 (9%) had an unespecified form of FD, 16 (17%) had MAS and 4 (4%) had Mazabraud syndrome. Disease specific outcomes have been completed for 11/92 (12%) patients. FD related musculoskeletal outcomes were reported as follows: pain at FD site in 7 (64%) patients, fractures in 6 (54%) patients, limb deformities in 3 (27%) and scoliosis in 6 (36%). Past and current bone related medication such as oral and intravenous bisphosphonates and denosumab were used in 6 (55%) and 4 (36%) patients respectively, with pain being the indication in all cases.

Conclusion: The use of a Core Data set in combination with a disease-specific dataset developed by healthcare providers and patient representatives, can provide insight on the natural history and clinical outcomes of rare diseases such as FD/MAS. To date, patients and data have been entered by a small number of centres. Healthcare professionals and patients should be encouraged to participate while addressing the challenges this might represent.

P1-416

Treatment dilemma in a prepubertal patient with ACAN mutation but without advanced bone age

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Introduction: Aggrecan is a major proteoglycan component of the articular and growth plate extracellular matrix, encoded by the ACAN gene (MIM: 155760). Although short stature and various dysmorphic findings are observed in individuals with ACAN mutations, the relationship between genotype and phenotype is not clear.

Case: A 6.75-year-old pre-pubertal girl presented with disproportionate short stature. She was full term from unrelated parents with birthweight 3800g (1.21SD) and length of 52cm (1.22SD). At admission, her height was 110.7cm (-2.09SD) with a large trunk and sitting height/height ratio >2SDS. Paternal and maternal heights were 172cm (–0.68SD) and 159.1cm (-0.70SD), respectively, with mild dysmorphism of hands and feet. There was a strong paternal family history of short stature but none of osteoarthritis. She was dysmorphic (midfacial hypoplasia and high-arched palate), short neck, barrel chest, broad thumbs, shortmetacarpal (fourth, fifth) and metatarsal (third, fourth, fifth) bones, and pes planus. Growth hormone (GH) stimulation test peak was 7.9 ng/mL. There was no sign of skeletal dysplasia, besides cone-shaped epiphysis of the thumb distal phalanx on X-ray. Her bone age (BA) was consistent with chronological age (CA). Patient records from previous visitis showed BA was never advanced; she grew along the third percentile. Karyotype was 46,XX and SHOX gene analysis was normal. At the last visit, she was 12 years old with a height of 115.7cm (-2.07SD) and a growth velocity of 5.8 cm/year; and BA was consistent with CA with normal IGF-1 levels; she was still prepubertal.

Her younger brother also had milder dysmorphic features. At admission, he was 3 years old, prepubertal and proportionate with a height of 91cm (-1.89SD). His laboratory and endocrine assessments were normal and BA also corresponded with CA.

Whole exome sequencing was performed and a heterozygous variant of uncertain significance (c.3465G>T p.Ala116Ser) in the ACAN gene was found in the index patient, her father, and her brother. The evaluation of the affected children is continuing, although no treatment has started yet.

Discussion and Conclusion: It is reported that clinical course and phenotype of patients with short stature and pathogenic ACAN gene mutations are variable, even within families. For treatment, especially in patients with advanced BA, pubertal pause has been induced with GnRH treatment, and GH replacement therapy (GHRT) was attempted, but outcome data have been variable. Given the heterogeneity of growth in patients with ACAN variants, treatments should be tailored to affected individuals.

P1-417

Executive function, intelligence and bone mineral density: Do associations exist in childhood?

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Background: In later life, osteoporosis and poor cognitive function often co-exist. This has commonly been attributed to post-menopausal estrogen loss, but there is increasing recognition of cross-talk between the brain and bone. For example, in animal models, bone derived osteocalcin has positive associations with brain volume and cognitive function whilst brain-derived neurotransmitters appear to influence bone mass. Despite this, a common early life origin for osteoporosis and poor cognitive function has not been explored. We assessed the relationships between intelligence, working memory and bone mineralization in childhood.

Methods: The Southampton Women's Survey is a prospective mother-offspring birth cohort study (Southampton, UK). The children were assessed at age 6-7 years, including occipitofrontal circumference (OFC, proxy for brain volume), intelligence quotient (IQ) [Wechsler Abbreviated Scale of Intelligence] and visual-spatial working memory [CANTAB® Delayed Matching to Sample (DMS)]. Whole-body-less-head (WBLH) and lumbar spine dual-energy X-ray absorptiometry (DXA) were performed using a Hologic Discovery instrument yielding bone area (BA), bone mineral content (BMC) and bone mineral density (BMD). All variables were adjusted for age and sex and associations assessed using linear regression for standardized variables (β represents standard deviation (SD) difference per SD of cognitive function or OFC).

Results: 1331 children (mean age 6.8 years (SD 0.33 years), 51.5% male) attended for DXA. OFC, IQ and DMS was assessed in 1250, 551 and 490 of these children, respectively. OFC (β=0.25 SD/SD, 95%CI 0.20, 0.30), IQ (β=0.11 SD/SD, 95%CI 0.02, 0.19), and DMS (β=0.11, SD/SD, 95%CI 0.01, 0.20) were all positively associated with WBLH BA. Associations between OFC, IQ and DMS and lumbar spine BA were similar. Positive associations were observed between OFC, IQ and DMS and WBLH BMC, but only OFC was associated with BMD (WBLH: β=0.38 SD/SD, 95%CI 0.33, 0.43; LS: β=0.19 SD/SD, 95%CI 0.13, 0.24). Associations were similar when stratified by sex.

Conclusion: Childhood OFC was positively associated with bone size and mineralization, whereas IQ and visual-spatial working memory were associated only with skeletal size, although this relationship was assessed in a smaller cohort of children. These findings suggest that a common early life determinant for cognitive function and skeletal growth should be explored.

P1-418

Comparison of efficacy and safety of oral cholecalciferol administration at 4-week intervals and daily administration to correct vitamin D deficiency in adolescents

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Objectives: Vitamin D deficiency is prevalent in pediatric population. Since low compliance may inhibit appropriate vitamin D supplementation in daily dosing regimen, intermittent high dose administration may be considered. We aimed to evaluate the efficacy and safety of monthly administration of oral cholecalciferol compared with daily dosing regimen in adolescents with vitamin D deficiency.

Methods: This retrospective study included 299 children and adolescents who were vitamin D deficient (serum 25 hydroxy vitamin D (25(OH)D) concentration of <20 ng/mL) and diagnosed with precocious puberty on GnRH agonist between December 2019 and November 2022. 100 children received 1,000 IU of oral cholecalciferol every day [daily group], and 199 children received 25,000 IU of oral cholecalciferol every 4 weeks [monthly group]. After propensity score matching (PSM) using age, sex, season, and baseline 25(OH)D level, 100 patients of each daily supplement group and monthly supplement group were matched. Levels of blood chemistry, including 25(OH)D, total calcium, phosphorus, and alkaline phosphatase (ALP), were examined.

Results: Baseline 25(OH)D levels did not differ between two groups (mean ± SD, 14.0 ± 3.1 in daily group vs. 14.0 ± 3.2 ng/mL in monthly group, *p*=0.99). After median follow-up of 5.9 months (5.9 ± 2.5 months), increase in serum 25(OH)D concentrations were higher in monthly group than in daily group (10.7 ± 4.7 vs. 8.4 ± 7.1 ng/mL, *p*=0.025). The corrected dose-response was also higher in monthly group than in daily group (12.0 ± 5.3 vs. 8.4 ±

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7.1 ng/mL increase per 1,000 IU/day, respectively, *p*=0.001). The proportion of patients attaining non-deficient vitamin D status (25(OH)D > 20 ng/mL) after treatment was 79.0% and 59.0% in monthly and daily groups, respectively (*p*=0.004). Hypercalcemia was not observed in both groups.

Conclusions: Monthly administration of oral cholecalciferol 25,000 IU every 4 weeks showed higher efficacy and equivalent safety profiles compared with conventional daily administration in adolescents with vitamin D deficiency. It needs to be further investigated whether monthly administration of cholecalciferol have more benefits in pediatric population.

P1-419

Evaluation of the pediatric patients diagnosed with secondary osteoporosis

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Objective: Secondary osteoporosis has a high rate of accompanying chronic diseases. We aimed to review the clinical and laboratory features, underlying causes, Dual Energy X-ray Absorptiometry (DEXA) results before and after treatment of patients diagnosed with secondary osteoporosis and to determine the relationship between this condition and fracture rates.

Methods: This study was designed as a single-center, descriptive, cross-sectional retrospective study. A total of 70 patients diagnosed with secondary osteoporosis between 2019-2023 were included in the study.

Results: Of the 70 cases included in the study, 36 (51.4%) were male and 34 (48.6%) were female. The mean age was 10.37 ± 3.81 years. The mean height standard deviation score (SDS) was -3.0 ± 2.56 and BMI SDS was -0.15 ± 1.95. Oncological disease in 21 (30%) cases, nephrological in 11 (15.7%), hematological in 11 (15.7%), rheumatological in 15 (21.4%), neurological in 4 (5.7%) were detected and 8 (11.4%) had other diseases. The mean time to develop osteoporosis after the chronic disease was 5.76 ± 4.31 years. There was a history of steroid use in 35 (50%) cases, steroid and methotrexate in 16 (22.9%), methotrexate in 8 (11.4%), and antiepileptic drugs in 2 (2.9%) cases. While there were fractures in 7 (10%) cases at admission, it was absent in 62 (88.6%) cases. The fracture was observed in 1 patient (1.4%) during follow-up. It was not observed in 69 (98.6%). At admission, 24 (34.3%) had complaints, and 46 (65.7%) did not. In treatment, 62 (88.6%) received oral calcium and vitamin D, and 6 (8.6%) received intravenous bisphosphonates and vitamin D. The mean vertebral DEXA z score before treatment was -3.73 ± 0.94. Significant improvement was found when pre-treatment and 1st year of treatment, pre-treatment and 2nd year of treatment, 1st year and 2nd year of treatment were compared ($p<0.05$). When the pre-treatment and the second year of the treatment were compared, a significant increase was found in the serum calcium value ($p<0.05$). When the pre-treatment and the 2nd year of the treatment and the 1st and 2nd years of the treatment were compared, a significant decrease was found in the parathormone value ($p<0.05$).

Conclusion: In patients with chronic disease, the rate of detection of secondary osteoporosis without compliants is high due to medication side effects. For this reason, it is important to perform the necessary screening of patients in the risk group.

P1-420

Exploring Childhood Hypoparathyroidism: Stepwise Genetic Evaluation Approach

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Background: Primary hypoparathyroidism (HP) is a rare disease characterized by hypocalcemia, hyperphosphatemia and low/inappropriately normal parathyroid hormone (PTH) levels. We aim to characterize the clinical findings and molecular aetiology of childhood HP in our cohort.

Method: DiGeorge-VCFS FISH analysis was performed on all patients (n=28) as the initial step after the diagnosis. In whom, FISH analysis was negative, a stepwise approach with next-generation sequencing (19 genes related to HP), cGH array and the mitochondrial panel were applied in their respective order when the prior test concluded negative.

Results: DiGeorge-VCFS FISH analysis demonstrated deletion in 8 patients, two of whom had isolated hypoparathyroidism without syndromic features. Molecular aetiology was detected in three (15%) of 20 patients (*AIRE, FAM111A, GATA3*) by next-generation sequencing. A homoplasmic variant was detected in the mitochondrial disease panel in one patient who presented with congenital cataracts and hypocalcemic convulsions. The patient with *FAM111A* mutation (Kenny-Caffey syndrome), presented with short stature, wide fontanel, increased cortical thickness in long bones, and hypercalciuria. The patient with *AIRE* mutation had no other autoimmunity but hypercalciuria and mild hypomagnesemia suggesting activating *CaSR* pathway. The patient with *GATA3* mutation had no additional abnormality other than basal ganglia calcification. Presenting complaints of the patients were muscular cramps (n=8,28.5%), epileptic seizures (n=8,28.5%), and syncope (n=3,11%). Nine (32%) patients were referred due to incidentally discovered hypocalcemia. Hearing loss was detected in 21% of the patients, congenital heart anomaly in 25%, nephrolithiasis/nephrocalcinosis in 21%, cataracts in 11% and basal ganglia calcification in 18%.

Conclusion: Molecular aetiology was detected in 43% of all HP patients. 22q11.2 FISH analysis should be performed in the first step, whether the patient has syndromic features or not. The aetiology of hypoparathyroidism is obscure in more than half of the patients despite stepwise genetic approach.

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Clinical and Laboratory Characteristics of Patients with or without 22q11.2del

	22q11.2del (+) (*n*=8)	**22q11.2del (-) (*n*=20)**	***p***
Age at onset (years)	6.6±5.5	8.7±5.7	0.5*
Ca (mg/dL)	7.3±1.3	6.5±1.2	0.19*
Phosphorus (mg/dL)	6.6±1.2	7.7±1.5	0.07*
ALP (U/L)	274±173	277±164	0.86*
PTH (ng/L)	18±7.5	20±19	0.53*
Spot urine Ca/creatinine (mg/mg)	0.02±0.01	0.1±0.2	0.46*
Hearing loss (*n*)	1	5	0.46**
Congenital heart anomaly (*n*)	3 (ToF-2, VSD-1)	4 (Aortic Stenosis-1, Tricuspid Insufficiency-1, Aortic Insufficiency-1, VSD-1)	0.37**
Nephrolithiasis/nephrocalcinosis (*n*)	-	6	
Cataracts (*n*)	-	3	
Basal ganglia calcification (*n*)	1	4	0.63**

*Mann-Whitney U **Fisher's Exact Test

P1-421

Bisphosphonate, sirolimus, atenolol treatment in a 4-year old child diagnosed with Gorham-Stout disease

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Gorham-Stout disease (GSD), also known as vanishing bone disease is an extremely rare skeletal disorder characterized by idiopathic intraosseous proliferation of lymphatic vascular structures resulting in progressive resorption of bone. Herein, we report a case of a 4-year-old girl with GSD treated with the combination treatment with bisphosphonate, sirolimus, and atenolol.

A 4-year-old girl presented with prolonged back pain for 2 weeks. The thoracolumbar spine radiography revealed mild to severe compression fractures and diffuse verterbral body flattening in T9-L3. Spine magnetic resonance imaging (MRI) showed diffuse T1 and T2 low signal intensity in C1-T8 spines, suggesting bone marrow dysplastic or infiltrative disease. A soft tissue and bone biopsy from the supraspinous region of T12 vertebrae was done. The soft tissue lesion was composed of hyperplastic blood vessels and fibrous tissues, similar to hemangioma. Bone biopsy showed nonspecific findings. Based on the above clinical, radiological and histopathological findings, the diagnosis of Gorham-Stout disease was established. The treatment with sirolimus (0.5mg twice a day) was started. The patient persistently had back pain, and intravenous bisphosphonate (pamidronate, 1mg/kg for 3days, total 3mg/kg every 4 months) was added after 1month of sirolimus treatment. Following the combination with bisphosphonate and sirolimus, she showed immediate improvement of back pain. Trough level of sirolimus was monitored and the dose was escalated from 1mg to 2.75mg a day, and she maintained the dose for 9 months. At this point, initial dual-energy X-ray absorptiometry(DXA) was done, since the patient's age reached 5 years old, and her age-matched total body less head (TBLH) Z-score was -0.3. Spine radiography revealed ongoing scoliosis of the involved spines. Whole body MRI done after 9 months of bisphosphonate and sirolimus showed mildly increased extent of paraspinal lymphangiomatosis, and mild aggravation of compression fractures in T9-L5. Atenolol, a selective beta-blocker, which have been used in the treatment of infantile hemangioma, was added. Follow-up MRI after 4 months of the combination treatment with bisphosphonate, sirolimus, and atenolol showed decreased extent of paraspinal lesions at L1-L5. The patient underwent total 11 months of combination treatment of bisphosphonate, sirolimus, and atenolol, and MRI showed further regression of paraspinal lesions. Follow-up DXA showed increased TBLH Z-score of 0.1, compared to the previous data.

In conclusion, bisphosphonates seems to be useful in relieving pain and a therapeutic combination of bisphosphonate, sirolimus, and atenolol may be helpful in controlling disease progression and improving the prognosis of GSD.

P1-422

Stüve-Wiedemann syndrome: an extremely rare disorder causing recurrent fractures

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Background: Stüve-Wiedemann syndrome (SWS) is a rare autosomal recessive disorder, due to mutations in the leukemia inhibitory factor receptor (*LIFR*) gene. It is characterized by bowed-long bones, joint restrictions, dysautonomia, respiratory and feeding difficulties leading to death during infancy.

In SWS survivors beyond 2 years of age, orthopedic problems are the main concern e.g. spinal deformations, osteoporosis and recurrent spontaneous fractures which affects quality of life (QoL). This occurs mainly due to excessive osteoclastic resorption. Delayed motor development has been reported in all SWS patients, however, cognitive development is normal in all but one of the reported cases.

There is no specific treatment for SWS, and management is symptomatic. Limited number of cases have been reported so far, making it more difficult to understand the disease pathology.

We herein report a 5-year-old boy diagnosed with SWS and cognitive impairment at Alexandria University Children's hospital.

Case summary: A 5-year-old-boy presented with history of recurrent fractures in different long bones. He is the only child born to consanguineous parents. After birth, limb deformity was noticed and he was hypoactive. Skeletal survey showed bowing of lower limbs with no signs of active rickets and hip ultrasonography revealed delayed and defective ossification of both acetabular fossae with bowing of the metadiaphysis bilaterally, associated with lateral subluxation of both femoral head cartilaginous epiphysis suspecting osteogenesis imperfecta. CT brain showed subependymal hemorrhage involving lateral ventricles with mildly dilated ventricular system. Audiometry showed bilateral normal hearing. He had delayed developmental milestones and was diagnosed with intellectual disability and autistic features. EMG, NCV were normal.

Bowing of lower limbs progressed and he developed joint mobility restriction in knees and fingers.

He presented with faltering growth, facial dysmorphism (squared face, low-set ears), and limb deformities. He had no history of hyperthermic episodes or limited sensation. There was no blue sclera.

Calcium, phosphorus, magnesium, 25-OHD, 1,25-dihydroxyvitamin D, and PTH levels were normal. Dual x-ray absorptiometry height-for-age Z-score did not show low bone mineral density. WES identified a novel homozygous pathogenic variant in *LIFR* (c.703_704del, p.Trp235GlufsTer2) causing SWS.

Conclusion: SWS is a rare and lethal condition due to mutation in *LIFR* gene. Diagnostic criteria include the association of short, bowed-long bones, and dysautonomia with normal cognitive development. However, not all patients present similarly. More collaborations and research are required for better description and understanding of the disease, paving the road towards finding novel therapies to improve QoL of SWS survivors.

P1-423

Craniosynostosis in hypophosphatasia

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Hypophosphatasia (HPP) is a rare genetic disease caused by mutations with loss of function in the ALPL gene, which encodes for non-specific tissue alkaline phosphatase (TNSALP).

We report a case of infantile hypophosphatasia.

Due to positive family history for hypophosphatasia, a chorionic villus sampling was made, with evidence in composed heterozygous of variants c.407G>A and c.1489T>C in the ALPL gene.

At birth the patient did not have clinical complications, however the blood concentrations of alkaline phosphatase and vitamin B6 confirmed the diagnosis.

On the third day of life, treatment with asfotase alfa has been started at a dose of 2 mg/kg three times a week subcutaneously. Treatment has always been well tolerated.

Subsequent blood tests showed a progressive increase in alkaline phosphatase activity and a normalization of vitamin B6 concentrations, as expected. Plasmatic concentrations of calcium, phosphorus and parathyroid hormone have always remained within the normal limits.

Starting from the third month of age, a progressive worsening of the cranial conformation has been noted with the appearance of marked asymmetry of forehead (left > right) and apparent hypoplasia of the left eyebrow arch. The anterior fontanel was, however, of normal size and conformation and the neuromotor development progressed regularly.

At 6 months of life, Head CT with 3D reconstruction was carried out, with evidence of craniosynostosis of the right coronal suture. The patient was then referred for neurosurgical evaluation and is currently awaiting corrective surgery.

As reported in literature, about 2/3 of patients with childhood-onset hypophosphatasia present craniosynostosis as a complication; therefore, it is important to monitor the possible occurrence of this condition and eventually direct patients to a correct multidisciplinary diagnostic and therapeutic process. It is also important that the follow up continues for a long time after the surgical correction because due to the underlying metabolic defect, recurrences are more frequent than in patients not affected.

To date, further studies are needed to determine whether the introduction of enzyme replacement therapy can change the incidence and presentation of this complication. However, it is possible to hypothesize that treatment with asfotase alfa, will improve the quality of bones, contributing to the success of surgical correction, while reducing the risks associated with the pathology.

P1-424

Spondyloepiphyseal dysplasia tarda in a 10 years old boy treated for growth hormone deficiency

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We present a 10 years old boy, born from normal pregnancy, weght 3300 gr, lenght 51 cm. Normal motor and intellectual development. Family history for short stature - mother's height 150.3 cm (P2), target height 174.3 cm (P37). At 7 years of age the patient's height was 108.9 cm (- 2.4 SD) - below the target range. Bone age was delayed with more than -2 SD. Two stimulation tests for growth hormone (GH) assessment have been performed (with insulin and glucagon) – both positive with maximal GH of 3.57 ng/ml. There were no other hormonal deficites. MRI of hypothalamus-pituitary region was normal. Celiac disease and other chronic conditions were excluded. The diagnosis of isolated growth hormone deficiency was established and treatment with Genotropin (0.030-0,035 mg/kg/day) has been commenced. There was a good initial response to the treatment, but subsequently the growth rate did not show any additional catch-up. At 10 years of age the boy presented a slight body disproportion with height 120,3 cm, sitting height 59 cm, sitting height/height 0,49 (- 2 SD), arm span 123 cm. An additional skeletal radiographs showed an abnormal curvature of the spine (a mild scoliosis) with flattened (platyspondyly) and specifically hump-shaped vertebrae. The skeletal changes were indicative of Spondyloepiphyseal dysplasia tarda, which was confirmed after genetic analysis was performed – a hemizygous mutation c.3delinsTA, p.(Met1?) in TRAPPC2 gene has been found. The mutation is classified as likely pathogenic, based on the established association between the gene and the patient's phenotype, the variant's absence in control populations, well-characterized variant at the same start codon, and variant type (start codon). The boy is still on GH treatment which is planned to be discontinued.

P1-425

Recombinant human growth hormone treatment for *osteogenesis imperfecta*: report of two cases

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Background: Osteogenesis imperfecta (OI) is a genetic connective tissue disorder with variable phenotype, mainly characterized by bone fragility, short stature and non-skeleton findings. Since growth failure is a predominant feature of OI, recombinant human growth hormone (rhGH) has been suggested as a potential intervention. We describe two boys with OI type I treated with rhGH.

Case Reports: Patient 1 had the first fracture at 1.2 years, and 3 other fractures before starting bisphosphonate at 2.8 years. He has gray sclera, slightly valgus knees, mild spinal deformity and excavated thorax. Height Z-score (H-SDS) before bisphosphonate was -0.49 and target H-SDS was -0.76 (mother with OI). At 8-years-old the bone age (BA) was compatible with chronological age (CA) and endocrine workup showed: growth hormone (GH) peak of 9.03ng/mL after clonidine stimulation and normal IGF-1 concentration. Therapy with rhGH started (0.043mg/kg/day) when his H-SDS was -1.66. Puberty started at age 12, when H-SDS was -0.20. At the last visit he was 14,2-years-old, H-SDS was +0.04, at Tanner stage 4 and BA was compatible with CA. Bone mineral density (BMD) Z-score was +2.3 (total body less head, TBLH) and +0.3 (lumbar spine, LS), evaluated by DXA. Patient 2 had his first fracture at 8 months, and 4 other fractures before bisphosphonate at 6.1 years. He has blue sclera, excavated thorax, scoliosis, and mild limb deformities. H-SDS before bisphosphonate was -3.74, and target H-SDS was -1.72 (father with OI). At 10.1-years-old H-SDS was -2.83, BA was 7-years-old, and endocrine workup showed: GH peak of 10,1ng/mL after clonidine stimulation and low-normal IGF-1. rhGH treatment started (0.051mg/kg/day) at 10.1-years-old. Puberty started at 11-years-old, and at the last visit he was 13.7-years-old, H-SDS was -1.78, at Tanner stage 3, BA was 13-years-old, and the BMD Z-score was -0.8 (TBLH) and +0.2 (LS).

Conclusion: rhGH has been proposed as an intervention for mild forms of OI to improve growth rate, with conflicting results on fracture rate and BMD. Some studies have suggested positive effects of rHGH on height, however its use is not universally accepted. We present two cases of boys treated with rhGH, with positive results on growth and no negative influence on fracture rate.

P1-426

COMP Gene Variant causing short stature and skeletal dysplasia

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Introduction: Short stature is one of the main reasons leading a patient to the attention of the Pediatric Endocrinologist. It is important to know the possible causes of short stature, even the rarest genetic mutations associated with short stature. Although the diagnosis of short stature is primarily the result of physical examination with anthropometric measurements, biochemical and radiological data, genetical tests currently play an important role.

Case Presentation: We present the case of a 2.5-year-old boy who came to our attention for growth failure with a slowing growth rate in the last year. He was delivered at full term by an uneventful spontaneous vaginal delivery and his birth weight was 2820 g (AGA). Physical examination revealed a healthy infant with waddling gait and apparent disproportionately short limbs; his stature and weight were under 3rd percentile for his age (-2.87sds and -3.91sds, respectively) and under mid-parental height (delta target -1,87sds). Bilateral severe genu varum, sabre tibia and symmetrical limitation of hip abduction were reported. Basal blood tests including bone metabolism and IGF-1 levels were performed and resulted normal. Moreover, total body RX showed severe bone age delay (bone age of about 6 months) with flared appearance of the radio-ulnar and tibio-femoral metaphyses, suggesting a diagnosis of rickets. Biochemical tests about bone metabolism revealed increased values of phosphoremia and phosphorus tubular reabsorption and normal values of total calcemia and urinary calcium/creatinine ratio. Moreover, genetic panel of rickets was negative.

Results: The NGS analysis of short stature showed the probably pathogenic variant c.1336G>A in heterozygosity in exon 13 of the COMP gene, described in the literature in patients with pseudoachondroplasia and multiple epiphyseal dysplasia with autosomal dominant inheritance. In addition, a variant of uncertain significance in heterozygosity was reported in exon 2 of the IGFALS gene. Biallelic variants of this gene have been associated in the literature with short stature due to primary acid-labile subunit deficiency. Genetic tests on the patient's parents are still pending.

Conclusion: The patient is currently on clinical follow-up. Few cases of paediatric patients with COMP gene mutation have been described in the literature, so further studies are needed to better define the clinical alterations associated with this variant and the correct management.

Diabetes and insulin

P1-31

Metabolic trajectories during treatment of diabetic ketoacidosis described by breath analysis

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Objective: This feasibility study aimed to investigate the anabolic effect of insulin on metabolites captured in exhaled breath during acute diabetic ketoacidosis (DKA) for a better pathophysiological understanding.

Research Design and Methods: Children and adolescents with type 1 diabetes (T1D) with DKA (n=5) and without DKA (n=7) and children with epilepsy without ketogenic diet (n=18) were recruited into an observational breath analysis study. Study participants repeatedly inflated Nalophan bags, and its metabolic content was subsequently interrogated by secondary electrospray ionization high-resolution mass spectrometer (SESI-HRMS). Routine laboratory parameters, such as glucose, pH, base excess, bicarbonate, and ketone bodies, were measured for participants with DKA admitted to the intensive care unit (ICU) and were used to identify associated metabolic markers in breath.

Results: In 30 participants, the total amount of longitudinal individual breath measurements was 107 (88 in 12 diabetic participants and 19 in 18 non-diabetic participants). In 12 diabetic participants, 24/88 measurements were conducted during DKA in 5 participants and 56/88 in 5 participants after and in 7 participants without DKA. SESI-HRMS analysis showed that acetone, pyruvate and acetoacetate that are well known to be altered in DKA, were readily detectable in breath in participants with DKA (base excess (BE) < -2) compared to non-diabetic participants (acetone $p = 3x10^{-7}$, pyruvate $p = 5x10^{-3}$ and acetoacetate $p = 4x10^{-7}$ respectively). Further, they followed the expected dynamics during the switch from catabolic to anabolic state in DKA participants. In addition, a total of 665 mass spectral features were found to significantly correlate ($p < 0.05$; $q < 0.18$) with BE (219/446 features showed significant positive/negative correlation). These correlating features with BE prompt metabolic trajectories towards in-control state as they progress towards homeostasis.

Conclusion: This study provides proof-of-principle for using exhaled breath analysis in an ICU setting for DKA research. We found that, apart from the well-known association between acetone and DKA state, a completely new panel of exhaled metabolites (e.g. acetoacetate), describe the transition between catabolic to anabolic state in DKA patients. This non-invasive new technology provides new insights and a more comprehensive overview on the effect of insulin during DKA treatment.

P1-32

Continuous Glucose Monitoring: A possible aid to detect hypoglycemia event during insulin challenge tests

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Combined pituitary function test is a dynamic function test used to evaluate the anterior pituitary gland in patients suspected with hypopituitarism. The test comprises insulin challenge test where intravenous insulin injection in order to induce symptomatic hypoglycemia (serum blood glucose <40mg/dL). Insufficient increase in growth hormone and cortisol after the stimulation confirms the diagnosis of growth hormone deficiency and/or adrenal function insufficiency. However, the test is often very tedious as close medical supervision is required throughout the study and the possibility of life-threatening hypoglycemia event is unpredictable. Also, capillary blood sugar test (BST) and serum glucose level may differ greatly although glucose monitoring is essential. The continuous glucose monitoring system (CGM) is a medical device that allows real-time blood glucose readings. CGM has proven to be beneficial in improving glycemic control of diabetic adolescents and adults. Herein, we provide three cases in which CGM was successfully used in conjunction to BST and serum glucose level during combined pituitary function test to better detect and induce hypoglycemia. Three patients previously diagnosed with multiple pituitary hormone deficiency during childhood were recruited to be re-evaluated at adult age. Dexcom G6 CGM was applied to each patients 5 to 7 days prior to admission. Baseline serum pituitary hormone and glucose samples were obtained before injection of intravenous insulin, gonadotrophin hormone-releasing hormone (GnRH), and thyrotropin-releasing hormone (TRH). CGM sensor glucose level and BST were simultaneously recorded every 5 minutes to assess the glycemic status and monitor when adequate hypoglycemia is reached. In all three patients, CGM sensor glucose level, BST, and serum glucose showed similar glucose trend and suitable hypoglycemia was observed. CGM can not only free patients from frequent painful skin prick tests but also observe glucose decline on real time basis. Thus, continuous glucose monitoring may be a safe aid for clinicians to use during the insulin challenge tests where critical hypoglycemia is induced.

P1-33

Health-Related Quality of Life in Children and Adolescents with Type1 Diabetes Mellitus

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Background: HRQoL has been acknowledged as an essential health outcome measure. Studies have shown that enhancing the HRQoL and well-being of children with diabetes is as important as metabolic control in preventing secondary morbidity.

Objectives: to evaluate HRQoL of children and adolescents with T1D managed at our institute and investigate factors (patient and disease-related) associated with HQoL scores.

Methods: a cross-sectional study on patients (2-18 years) with T1D managed at a Tertiary Pediatric Diabetes Center in Sep-Nov 2022. Subjects were selected by their availability during routine visits and interviewed using Arabic translated version of PedsQL; Inventory 3.0 Diabetes Module which consists of a 28-item multidimensional instrument evaluating diabetes symptoms, treatment barriers and adherence, worry, and communication. Children aged 5–18 years provided self-reports, and parents of children aged 2–18 years provided parent proxy reports. Higher scores indicated better QoL.

Results: A total of 105 children with T1D and their parents participated. The median age of patients was 11.5 years (8.1- 17.7); 47.6% were males with an average duration of diabetes of 3.7 years and a median HbA1C of 8.4% (7.5 - 9.7). Of all, 73.3% were using MDI Insulin while 26.7% were on insulin pump therapy. Parents gave lower HRQoL scores than their children; highest differences were in treatment barriers, worry, and communication domains ($p < 0.0001$ and $p=0.001$ and $p=0.03$; respectively). Overall, there was excellent agreement in responses (Pearson coefficient= 0.92; $P=0.0001$) between children and parents; highest in Treatment Adherence (81%), Diabetes Symptoms, and communication (80% in both). There was a strong linear relationship between HRQoL and HbA1C, with better scores reported in those with HbA1C of 7% or lower ($p=0.004$). Univariate analysis revealed a significant association between better HRQoL and duration of diabetes ($p=0.002$), method of glucose monitoring ($p=0.02$), insulin regimen ($p=0.002$) while both gender and age didn't impact the HRQoL score. Stepwise multiple regression analyses confirmed that HQoL was better in those with lower HbA1C and diabetes durations beyond 5 years (p 0.01& p 0.002; respectively).

Conclusions: In our cohort, optimal glycemic control and diabetes duration beyond 5 years were significantly associated with higher HRQoL. The findings have implications for designing effective therapeutic interventions aimed at improving HRQoL of children with T1D. We recommend that assessment of QoL in children with a chronic disease should be a routine practice to facilitate communication, identify potential problems and implement an early intervention.

P1-34

Evaluation of Mitochondrial Bioenergetic Function in Mitochondrial and Type 1 Diabetes

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Background and hypothesis: Mitochondrial disorders are multisystemic conditions associated with sensorineural hearing loss, encephalomyopathy, lactic acidosis, and non-autoimmune diabetes. The majority of molecular etiologies involve mutations in the genes encoding the oxidative phosphorylation system's components. Superoxide generation is significantly increased and causes oxidative damage in the affected tissues in these disorders. The establishment of a definitive diagnosis is challenging due to diverse phenotypical expressions. Assessment of mitochondrial bioenergetic function can be an important functional tool to confirm the molecular diagnosis.

Objective: Assessment of mitochondrial bioenergetic function in patients with mitochondrial diabetes in comparison with type 1 diabetic patients with good and bad metabolic control and healthy control group.

Participants and Method: An 11-year-old girl with mitochondrial diabetes and her non-diabetic mother with a mutation in the *MT-CO1* gene (homoplasmic c.795delA, p.(E266Nfs*)) and the control group of healthy individuals (n=5), autoimmune type 1 diabetes (n=8) with good and bad metabolic control was used as a comparison. The mitochondrial bioenergetic function was evaluated by employing peripheral blood mononuclear cells (PBMC). PBMC were isolated from whole blood samples.

Results: Both the patient and her mother presented low basal OCR (oxygen consumption rate) (19 and 32% of healthy control), and low OCR during respiratory complex I-linked oxidative phosphorylation (OXPHOS), using pyruvate and malate (28 and 22% of healthy control) and when glutamate was added as substrates for mitochondrial complex I. The patient with mitochondrial diabetes also showed lower(<2SD) OCR suppression when the complex I inhibitor rotenone was added. Conditions such as the succinate-driven OXPHOS and maximal complex IV-linked OCR sustained were not affected, showing complex II and IV functions are preserved. Autoimmune type 1 diabetic patients did not exhibit any impairment of mitochondrial function, regardless of metabolic control. Western blot analyses suggested an upregulation of complex I expression in the patient. This pattern was not observed in the mother's sample. Mitochondrial dysfunction was not observed in children with autoimmune type 1 diabetes.

Conclusion: Increased complex I expression due to oxidative stress associated with the presence of diabetes was shown in the case. The further biochemical and functional evaluation may provide insights into the mechanisms of diagnosis and clinical manifestations.

P1-35

Effects of insulin therapy on respiratory functions, pulmonary exacerbation and nutritional status in cystic fibrosis-related diabetes

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Background and Aim: Cystic fibrosis-related diabetes (CFRD) is a common extrapulmonary comorbidity in patients with cystic fibrosis (CF). Since CFRD is clinically silent in the early period, it is recommended to evaluate glucose metabolism with an oral glucose tolerance test (OGTT) annually in CF patients aged 10 years and older. Insulin therapy is thought to improve lung function and nutritional status in patients with CFRD. In this study, we aimed to evaluate the glucose metabolism of patients with CF and clinical outcome in those who received insulin therapy.

Methods: 269 patients (132 girls, 137 boys) followed with the diagnosis of CF who had OGTT in the last 5 years were included in the study. Although 19 (7.1%) of the cases were under 10 years of age, OGTT was performed because they had symptoms or HbA1c levels suggestive of hyperglycemia. The clinical features of the patients, anthropometric measurements, pulmonary function tests (PFTs), OGTT, HbA1c, and the number of acute pulmonary exacerbations requiring oral/intravenous antibiotic treatment were examined retrospectively. The number of pulmonary exacerbations, anthropometric measurements and PFTs one year before and one year after the insulin therapy were compared in those receiving insulin.

Results: The mean age was 12.9±2.9 years (range: 6-18). 89.6% (241/269) had exocrine pancreatic insufficiency. OGTT revealed that 37 (13.8%) patients had CFRD, 18 (6.7%) had impaired fasting glucose (IFG), 47 (17.5 %) had impaired glucose tolerance (IGT) and 9 (3.3%) had IFG+IGT. Insulin therapy was started in 89.2% (33/37) of patients with CFRD and 32.1% (18/56) of total number of patients with IGT. Forty-one percent of the patients (21/51) were started only long-acting insulin analogue (insulin glargine), while 8% (4/51) were given rapid acting insulin analogue (lispro) during meals, and the remaining were received both basal and bolus insulin (51%, 26/51 glargine and lispro). Carbohydrates were not restricted. Insulin therapy led to a decrease in the number of pulmonary exacerbations requiring intravenous antibiotic treatment, an increase in FEV1, FVC, FEV1/FVC, MEF 25-75, a decrease in HbA1c levels, and an increase in BMI-SDS one year after the onset of therapy ($p<0.05$).

Conclusion: Insulin improves respiratory functions, decreases the number of pulmonary exacerbations requiring treatment, and increases BMI-SDS in CF with glucose metabolism disorders. Close monitoring of glucose metabolism, and early initiation of insulin therapy are important in patients with CF.

P1-36

Incidence of Newly Diagnosed Childhood Diabetes and Severity at Onset Between Pre-Pandemic and Pandemic COVID-19 Eras in Northern Thailand

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Background: The incidence rate (IR) of childhood diabetes is increasing globally. These upward trends were also found in Thailand. However, newly diagnosed childhood diabetes incidences are not updated, especially in Northern Thailand. There are possibilities that COVID-19 pandemic affects the development of acute diabetes after infection and the severity of the first clinical presentation of childhood diabetes. However, data are also conflicting regarding the incidence and severity at onset of childhood diabetes during a COVID-19 pandemic. Current information regarding childhood diabetes IR and the effect of COVID-19 on IR and severity at diabetes onset in Thailand is still lacking.

Objectives: To illustrate the incidence and type of newly diagnosed childhood diabetes in Northern Thailand and to compare IR and severity at diabetes onset e.g. DKA, death rate, etc. between the pre-pandemic and pandemic COVID-19 eras.

Methods: We retrospectively collected data on childhood diabetes between 2005-2016 and prospectively registered all incident cases since 2016-2022 in the Thai Type 1 Diabetes diagnosed Age before 30 years Registry, Care and Network(T1DDAR CN). Capture-recapture method was applied to estimate the completeness of ascertainment. The three-tertiary care centers served as primary source followed by hospitals in referral system and schools was secondary and tertiary source, respectively. The data were compiled from four provinces in northern Thailand. The IR, prevalence, and severity of DKA at diabetes onset were compared between the pre-pandemic (2017-2019) and pandemic (2020-2022) eras.

Results: A total of 210 patients were included. Type 1 diabetes (T1D) was identified in 56.2%, type 2 diabetes (T2D) in 39%, and other types in 4.8%. The IR of T1D significantly increased from 0.30 to 2.52/100,000 person/year in 2005 and 2022, respectively (P-value=0.014 [95% CI 0.24-2.68]), similar to the IR of T2D, which increased from 0.30 to 2.68/100,000 person/year (P-value=0.014 [95% CI 0.26-2.88]). The predicted IR of T1D and

T2D in 2023 were forecasted to be 2.0 and 2.29/100,000 person/year, respectively. The pre-pandemic IR of newly diagnosed diabetes, prevalence, and severity of DKA at first presentation including death rate were not significantly different from those of the pandemic period in both types of diabetes.

Conclusions: We demonstrate an increased IR of T1D and T2D in Northern Thailand over 18 years. However, the IR, prevalence, and severity of DKA at onset including death rate were not different between the pre-pandemic and pandemic COVID-19 periods.

P1-37

Dietary Intake in Children and youth with Type 1 Diabetes from Different Ethnic Backgrounds and its Relation to Different Metabolic Parameters

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Background: Medical nutrition therapy is one of the cornerstones of the treatment of type 1 diabetes. Nutrition is affected by many factors including ethnicity, socioeconomic background, and culture.

Objectives: To evaluate the nutritional status in a cohort of children with type 1 diabetes from different ethnic backgrounds and to seek differences among the groups. In addition determine the effect of nutrition on metabolic parameters in these children.

Methods: A cross sectional study from the diabetes clinic in Shaare Zedek Medical Center, Jerusalem, Israel. Dietary intake was assessed using food frequency questionnaire adapted to Israeli dietary habits.

Results: The study included 147 children with type 1 diabetes (52.4% males). The mean age of the children was 13.1 years with mean diabetes duration of 4.2 years. The cohort consumed an average daily 1384.2 Kcal, 182.2-gram carbohydrates, 55.1-gram protein and 54.8-gram fat. There was a statistically significant difference in the intake of different nutrients between the Jewish and the Arab Muslim population but not between different Jewish sub populations. We did not find a correlation between the nutrient intake and body mass index, HBA1c, lipid profile and blood pressure.

Conclusions: Nutritional patterns of Israeli children from different ethnic populations are diverse. This variability must be considered when providing medical nutritional therapy to these populations.

P1-38

Efficacy of faster aspart in insulin pumps in children and adolescents with Type 1 Diabetes Mellitus: A single-center study with real-world data

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Aim: To assess the efficacy of faster aspart (FIAsp) in paediatric population with type 1 diabetes mellitus (T1DM) and insulin pumps in real-world settings.

Methods: We conducted a prospective analysis of 16 children and adolescents with T1DM on insulin pump that switched from Aspart to FIAsp from September 2019 to June 2020. We performed within groups and between groups analyses in three time points: 3 months before FIAsp, 3 months after FIAsp and recent data of FIAsp. Data that were collected included: % of 24-h time in range of 70-180 mg/dl (TIR), time in hypoglycaemia (<70 mg/dl and <54 mg/dl) and hyperglycaemia (>180 mg/dl and >250 mg/dl), bolus and basal insulins doses (units/kg/day and %), total daily dose (units/kg/day), glycaemic variability, frequency of set changes and meals per day.

Results: Although data from the first trimester of FIAsp use did not show any statistical improvements, recent data showed significantly increased TIR (58.68 % vs 68.75%, P = 0.002) and decreased time in hyperglycaemia (>180 mg/dl, 27.31% vs 22%, P = 0.003 and >250 mg/d, 12.25% vs 6.75%, P = 0.004). The use of FIAsp, both 3 months after the switch and recent use, increased total daily dose (0.65 vs 0.72 units/kg/day, P = 0.008 and 0.65 vs 0.82 units/kg/day, P = 0.004, respectively). Surprisingly enough, frequency of set changes was significantly reduced in FIAsp in the first 3 months of use (1 every 2.36 days vs 1 every 2.66 day, P = 0.042).

Conclusion: Real-world data confirm that the use of FIAsp in children wearing pumps is associated with improvements in glycemic control. These results are more prominent in recent real-world data as during the 1st trimester of use patients/caregivers were limited by a strict protocol.

Parameter	Aspart	1st trimester FIAsp		Recent data FIAsp		
			p1		p1	p2
>250mg/dl	12.25 (7.38)	11.62 (7.63)	0.401	6,75 (5.07)	0.004	0.006
180-250mg/dl	27.31 (5.65)	26.00 (6.72)	0.308	22,00 (5.62)	0.003	0.046
TIR (70-180mg/dl)	58.68 (11.25)	60.75 (13.02)	0.234	68,75 (9.49)	0.002	0.021
55-70mg/dl	1.68 (1.35)	1.62 (1.31)	0.705	2,18 (1.37)	0.178	0.095
<55mg/dl	0.06 (0.25)	0.00 (0)	0.317	0.31 (0.60)	0.157	0.055
TDD (units/kg)	0.65 (0.14)	0.73 (0.19)	0.010	0.83 (0.15)	0.001	0.019
Set changes (1 per n days)	2.36 (0.68)	2.66 (0.65)	0.042	2,63 (1,03)	0.210	0.910

p1: compared to Aspart, p2: compared to 1st trimester of FIAsp

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P1-39

Prevalence of Insulin-induced Lipohypertrophy (LD) in children and Adolescents with Type 1 Diabetes Mellitus in relation to important risk factors: Review of literature in the past 15 years in 11 countries

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Abstract: Epidemiological and clinical data on LD in children and adolescents with T1DM are growing since 2010 because of the introduction of new insulin analogs and the use of insulin pumps (CSII). Many risk factors predispose to the occurrence of LD.

Objectives and Methods: We performed an electronic search in PubMed, Google scholar and Web of Sciences to evaluate the global prevalence and possible risk factors of LD in children and adolescents (2 -18 years) in the past 15 years.

Results: For children, 15 studies were included from 11 countries (Italy, India, Turkey, UAE, Saudi Arabia, Egypt, Canada, The Netherland, Iran, Austria and Ethiopia) after 2010. The pooled prevalence of the studies using MDII and CSII (15 studies, n= 3208 children, and adolescents, 1449 had LD) was 45.16 %. In these studies. the prevalence of LD varied greatly between 17% and 62% and was significantly affected by different risk factors. These variabilities can partially be explained by the different risk factors. Important risk factors found in these studies included: the longer duration of diabetes, the reuse of insulin syringe > 5 times, lack of rotating insulin injection sites, using a small area for injection, higher insulin dose/kg, BMI, the location of injection (more LD in the abdomen), low level of patient education, higher insulin antibodies and poor control of diabetes. In addition, the method of detecting LD markedly affect the prevalence of LD, ultrasound detection increased markedly the diagnosis of LD in these patients compared to palpation and inspection.

Conclusions: The pooled prevalence of LD in children and adolescents with T1DM was still considerably high (45.16%). Education about proper injection technique and regular examination of injection sites remain a crucial part of diabetes management.

P1-40

Neopterin and tryptophan pathways in children with type 1 diabetes: isoxanthopteridine as a marker of endothelial dysfunction

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Introduction: Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by damage to β cells in the pancreas. Neopterins and indolamine 2,3-dioxygenase (IDO) activity, which is shown by the ratio of kynurenine to tryptophan, can be used as an indicator in the regulation of cellular immunity. Oxidative stress produced by xanthine oxidoreductase has been shown to be associated with vascular endothelial dysfunction. It uses the conversion of pterin to isoxanthopterin to measure xanthine oxidase activity. In our study, we aimed to analyze pteridine derivatives in serum and urine, and tryptophan and kynurenine in serum in children with T1D and compare them with healthy subjects.

Methods: Within the scope of the study, the levels of 6-biopterin, neopterin, monapterin, pterin, isoxanthopterin and pterin-6-carboxylic acid in serum and urine, and tryptophan and kynurenine levels in serum were compared with healthy controls. High performance liquid chromatography methods were used for the analysis of pteridine and tryptophan derivatives.

Results: A median age of 14.0 (12.7-17) years, 93 (43 girls, 77 pubertal) with T1D, and a median age of 14.0 (10-15) years and 71 (38 girls, 51 pubertal)) healthy children were included in the study. There was no difference between the groups in terms of age, gender and puberty. The median age at diagnosis was 9.0 (6.2-12.2) years, and the median follow-up period was 4.0 (1-7.15) years. Serum neopterin, monapterin, 6-biopterin and pterin levels and urinary neopterin, monapterin, isoxantopterin, pterin-6-carboxylic acid, 6-biopterin and pterin levels were found to be higher in children with T1D compared to the control group, but the statistical difference was not significant. High isoxantopterin (p=0.01) and pterin-6-carboxylic acid low (p< 0.001) were statistically significant in children with type 1 diabetes. While serum tryptophan levels were statistically significantly higher in children with type 1 diabetes compared to the control group (p=0.021), the elevation in elevated serum kynurenine levels was not significant. There was a correlation between serum neoptrein level and duration of diabetes (p=0.045, r=0.209). There was a correlation between the neoptrein/creatinine and isoxanthopteridine/creatinine levels in the urine and the HbA1c level (p=0.005, r=0.305; p=0.021, r=0.249, respectively).

Conclusion: Type 1 diabetes may cause changes in the pteridine and kynurenine pathways. Because it is an indicator of vascular endothelial dysfunction, isoxantopterin can be used as biomarkers to predict complications of T1D.

P1-41

ADIPOQ gene (adiponectin) causing neonatal diabetes mellitus in a Palestinian newborn

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Background: Monogenic diabetes is a type of diabetes resulting from mutations of a single gene that may be spontaneous de novo or autosomal dominant or recessive. Reported incidence is 1-4% and confirmed by molecular genetic testing. Transient neonatal diabetes is usually diagnosed within the first week of life and resolves around 12 weeks. Permanent neonatal diabetes should be considered in all children presenting with diabetes in first month of age, and do not resolve. Genetic diagnosis may have major effects on treatment.

Here we describe a ADIPOQ gene as a cause neonatal insulin dependent diabetes mellitus in a Palestinian newborn.

ADIPOQ (adiponectin) affects fatty acid oxidation, glucose uptake, and glycogenesis, all of which are involved in the development of diabetes. As a result, ADIPOQ has being studied as a potential gene for type 2 diabetes mellitus (T2DM), which is a polygenic disease with genetic inheritance.

Clinical Data: A newborn Palestinian patient presented with clinical picture of insulin dependent diabetes mellitus during first days of life, managed with insulin analogues.

Molecular Data: next generation sequencing revealed a likely pathogenic homozygous mutation in the ADIPOQ gene. The Homozygote frameshift GTGTGGGATTGGAGACT->G indel at chr3:186572105 is predicted to result in abnormal protein translation of the ADIPOQ protein at amino acid position 116.

Conclusion: Monogenic diabetes is not very uncommon, higher rate of consanguinity predicts higher risk and is often misdiagnosed as type 1 or type 2 diabetes.

Diabetes diagnosed before 6 months of age will be monogenic diabetes and the underlying gene mutations can be identified in most of the cases, guiding the most appropriate management for patients.

A likely ADIPOQ gene causing neonatal diabetes has been identified, expression studies are being going.

This will enable genetic counselling, correcting the diagnosis of other family member & explain other associated features; predict the clinical course of the disease.

P1-42

Type 1 diabetes in the covid pandemic: what changed?

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Introduction: The COVID-19 pandemic adversely impacted general access to healthcare. An association between SARS-CoV-2 infection and new-onset type 1 Diabetes (T1D), a more severe disease at diagnosis and a worsening diabetes control have been described.

Aim: To evaluate COVID-19 pandemic's impact in incidence and presentation of T1D on paediatric patients.

Material and Methods: Retrospective analysis of newly-diagnosed T1D under 18years at our level-III hospital, between Jan 2017-Dec 2022. A demographic and clinical characterization was performed. Pre-pandemic (until Mar 2020) and post-pandemic patients were compared. Statistical analysis was performed with IBM SPSS Statistics 26.0.

Results: There were 127 new diagnoses of T1D, 63% male, median age 9,84 years (0,84-17,82). Predominant symptoms were polydipsia (87%), polyuria (77%), weight loss (63%) and polyphagia (27%). 13% had a 1st or 2nd degree relative with T1D.

At diagnosis, mean HbA1c was 11.73% (± 2.22), mean glycemia 484mg/dL (± 164), mean C-peptide 0,62ng/mL (± 0.58, low in 77%), mean insulin 3,5uUI/mL (± 4,26), mean eGFR 78,02mL/min/1,73m^2 (<60 in 69%) and mean BUN 21,49mg/dL (±11,26, elevated in 48%). 32% patients had high total cholesterol, 21% elevated LDL and 63% hypertriglyceridemia.

99% had at least one type of auto-antibodies [90,5% GAD2 (N=106/117), 44% IAA (N=52/118), 63,5% ICA (N=75/118), 96% IA2 (N=48/50).

80% were COVID-vaccinated. 65% had COVID infection: 17% before T1D diagnosis, mean interval 138 days; and 7 patients tested positive at admission.

There was a significant difference between pre- and post-pandemic groups: mean pH 7,31 vs 7,21 (p=0,018), mean HCO3- 20,7 vs 15,6mmol/L (p=0,002), mean ketonemia 3,1 vs 4,7mmol/L (p=0,004) and mean eGFR 84,9 vs 70mL/min/m2 (p=0,028), respectively. There was no significant difference between age at onset (p=0,617), symptom duration (p=0,277), mean HbA1c at diagnosis (p=0,804) and mean HbA1c one year after diagnosis (p=0,937). Incidence was 21 cases/year in both groups and cases were distributed throughout the year, with a non-consistent predominance in winter months (Jan-Mar).

In the post-pandemic group, patients with/without COVID at T1D onset had no difference in presentation severity (p=0,787), duration of hospitalization (p=0,281) and disease control after one year (p=0,947).

Conclusion: There was no difference in incidence of T1D in pre- and post-pandemic groups. The post-pandemic group had a worse severity at admission, but without a longer admission or a worse metabolic control at 1 year. In this study, we highlight the importance of the initial admission and the need of an experienced team for optimal control.

P1-43

Our experience in neonatal diabetes mellitus: clinical and molecular characterisation

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Introduction: Neonatal Diabetes Mellitus (NDM) is characterised by severe hyperglycaemia, usually diagnosed in the first 6 months of life. Genetic diagnosis helps distinguishing between its different causes and between transient (TNDM) and permanent (PNDM) forms, with repercussions on the therapeutic approach and follow-up.

Aim: Clinical and molecular characterisation of a series of NMD cases under endocrinological follow-up between 2014-2022.

Material and Methods: Descriptive, cross-sectional, multicentre study of 9 NDM cases genetically confirmed by targeted NGS panel. Detected variants were classified according to ACMG criteria and prioritised using confidence and quality criteria, coverage (20x bp >95%), allele frequency <1% (gnomAD controls, V2.1.1), impact ("missense", "nonsense", "frameshift", "splicing effect") and in silico prediction of pathogenicity (CADD V1.6, score > 20).

Results: 3/9 presented with Martinez-Frias Syndrome (MFS) caused by the homozygous RFX6 p.(Arg181Trp) founder pathogenic variant, product of consanguineous parents. All presented PNDM, IUGR, polyhydramnios, intestinal atresia and malrotation, vesicular agenesis, pancreatic hypoplasia, bile duct dilatation and cholestasis. The single survivor received a multivisceral transplant at age 20 months. 2/9 presented pathogenic variants in ABCC8: p.(Arg1379Ser) in an infant born at 33 weeks with BW 1490g, with persistent hyperglycaemias at two weeks of life, and p.(Ile1268Phe)(Ala1264Val) in compound heterozygosity in the second one. 2/9 presented likely pathogenic heterozygous variants in KCNJ11: p.(Trp68Cys), in a 57-day-old infant with hyperglycaemia, 849mg/dL, and ketonemia (up to 4.6 mmol/L), history of prematurity and IUGR, who was treated with continuous insulin perfusion (currently on sulphonylureas). The second case, a girl born to a mother with pregestational DM, presented the p.(Arg50Gln) with glycaemia of 153mg/dL at 3 days of life. 1/9 had NDM due to paternal uniparental disomy of chromosome 6 (preterm newborn, 31+6 weeks + IUGR), and finally, 1/9 presented NDM associated with a complete heterozygous HNF1B deletion with prenatal diagnosis of bilateral cystic renal dysplasia and persistent hypomagnesaemia.

Conclusions: Channelopathies, associated with mutations in ABCC8, coding for the SUR1 subunit of the K+ channel, and KCNJ11, coding for the Kir6.2 subunit, represent the most frequent molecular bases of NDM in our cohort. In consanguineous families with an association of PNDM and bilio-hepato-pancreatic malformations, MFS must be considered. Multivisceral transplantation is the only treatment capable of changing the fatal course of MFS. We report the fourth case of PNDM associated with a HNF1B variant, so its analysis should be included in NGS panels and assessment of the genitourinary tract and magnesaemia performed.

P1-44

New-onset DKA in a child complicated by hypertriglyceridemia and acute pancreatitis

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Introduction: DKA is one of the most common pediatric emergencies. Hypertriglyceridemia and acute pancreatitis are infrequent complications of DKA. We present a 9-year-old female with new-onset DKA who presented with acute pancreatitis and hypertriglyceridemia and resolved on follow-up.

Case Presentation: A 9-year-old female, previously healthy, non-obese, presented to the hospital with breathing difficulty, abdominal pain, and reduced oral intake. She had a history of polyuria, polydipsia, and weight loss for two months. She was found to have DKA (serum glucose 499 mg/dL, urine glucose > 1000 mg/dL, urine ketone 3+, capillary blood pH of 6.85, serum bicarbonate undetectable). She was in compensated shock and severe dehydration, so she received two IV boluses (10 ml/kg) of crystalloid fluid. She was admitted to PICU and started on DKA management protocol with IV insulin and IV fluids.

Her examination revealed Kussmaul's breathing, altered mental status, and signs of poor perfusion (tachycardia 140/min, capillary refill time 3-4 seconds, bilateral weak peripheral pulses).

Her blood samples were "too thick and milky." Her initial serum triglyceride (TG) level was 988 mg/dL (11.16mmol/l) and total cholesterol 115 mg/dL.

Abdominal ultrasound was consistent with acute pancreatitis and ruled out other pathologies. Her mental status gradually improved after 6-8 hours, along with the stabilization of serum glucose. Initial serum amylase was 239U/L (28 – 100), and lipase was 1982 U/L (13 – 60). After 12-36 hours, her appetite improved with a downward trend of serum TG 604 mg/dL (6.8mmol/l), serum lipase (273 U/L), and serum amylase 173 U/L. After 48 hours, she started on oral feeds and subcutaneous insulin. Two weeks after discharge, her TG level normalized to 127mg/dL (1.44mmol/l).

Discussion: Hyperlipidemia and acute pancreatitis are rare complications of DKA. Insulin deficiency in DKA causes hypertriglyceridemia by decreasing lipoprotein lipase activity, which converts triglycerides to fatty acids. The triad of DKA, hypertriglyceridemia, and acute pancreatitis have been well described in adult literature but rarely in the pediatric population.

Conclusions: In DKA, clinically significant acute pancreatitis can be attributed to severe hypertriglyceridemia if the serum TG level is > 1000 mg/dL (11.3mmol/l). Lipemic blood can be the clue to hypertriglyceridemia as a cause of acute pancreatitis and the resultant worsening of DKA despite standard insulin therapy. Early recognition has important implications in the management as insulin requirements and the tempo of recovery can be altered.

P1-45

Common challenges of one uncommon syndrome - single center experience with Congenital Generalized Lipodystrophy

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Aim: To present some therapeutic difficulties in patients with congenital generalized lipodystrophy (CGL) - a rare autosome recessive disorder characterized by complete absence of adipose tissue. For many years therapy was aimed only at metabolic consequences. In the past few years new pathophysiologic treatment has become available.

Methods and Materials: We present four girls – currently 25, 22, 16 and 15 years old, who belong to a small religious minority with high consanguinity risk. All of them share the same mutation of AGPAT2 gene.

Results:

Case 1: A 10-years old girl at presentation with typical phenotype, normal glucose tolerance but severe insulin resistance. Lost for follow up in the next 5 years. At 15 she developed symptomatic diabetes, poorly controlled with multiple drug therapy – metformin 2000mg, basal insulin 0.17U/kg/day, thiazolidinedione 45mg, fibrate 200mg, statin 80mg, ACE inhibitor 10mg, SGLT2 inhibitor 5mg and sulfonyulurea 6mg. The last two medications started after 18 years of age. She had bad adherence to therapy, poor metabolic control and many severe complications – liver steatosis, nephropathy, arterial hypertension, necrotizing pancreatitis and peritonitis, menstrual irregularities.

Case 2: The younger sister of case 1, actively tracked down and hospitalized at age of 13, the same phenotype, no symptoms. She had impaired glucose tolerance and mild hypertriglyceridemia with fewer complications - liver steatosis, severe kyphoscoliosis, secondary amenorrhea. On fewer medications – metformin 3000mg, basal insulin 0.16U/kg/day, thiazolidinedione 45mg and oral contraceptive pill. She had better adherence to therapy and satisfactory HbA1c.

Currently both sisters are beyond pediatric care.

Case 3: Presented at the age of 13 years with newly diagnosed diabetes and the most severe phenotype features of all four cases so far. Persistent poor metabolic control with early onset of complications (nephropathy, neuropathy, hepatic steatosis, cardiomyopathy, bone cysts, secondary amenorrhea). On multiple drug therapy – metformin 2550mg, basal bolus insulin 0.88U/kg/day, ACE inhibitor 10mg and Metreleptin 5,8mg. In July 2022 Metreleptin therapy was initiated showing metabolic and clinical improvement.

Case 4: Presented at 15 years of age with diabetes symptoms and already developed several complications (nephropathy, cardiomyopathy, arterial hypertension). On multiple drug therapy – metformin 2000mg, basal bolus insulin 0.7U/kg/day, statin 1mg, ACE inhibitor 5mg. Pending for initiation of metreleptin therapy.

Conclusions: Management of patients with CGL is difficult in terms of development of severe complications very early in the course of the disease and poor adherence to multi drug therapy. With the emerging new therapies there are chances for better disease control.

P1-46

Associated autoinmmunity in children and adolescents with type 1 diabetes mellitus

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Introduction: Autoimmune thyroid diseases (ATD) are the most common autoimmune disorders associated with type 1 diabetes (T1D). Most patients present hypothyroidism. Although hyperthyroidism is less frequent, severe forms of thyrotoxicosis coexisting with diabetic ketoacidosis (DK) have been described in children with either preexisting diabetes, thyroid disease, or both. Celiac disease (CD) incidence is higher and ranges from 0.6-16.4%.

Objetive: To evaluate the prevalence of autoimmune diseases in children and adolescents with T1D and its increase in recent years.

Methods: We studied 365 children (F:181,M:184) with T1D followed-up at our center between June 2007 and June 2022, with a median age at diabetic debut of 9.39 (6.46;11.29) years.

Statistical analysis: R version 4.2.2. Fisher's test exact was used to compare qualitative data.

Results: ATD was found in 119 patients (F:81,M:38). The prevalence was 32.6 %. Thirty two (F:23,M:9) children presented hypothyroidism (26.8%), 84 (F:57,M:27) had euthyroidism (69.7%). Four patients (F:2,M:2) presented hyperthyroidism (3.36%), one of them before, one simultaneously with diabetes onset, and the others at follow-up. Both children with hyperthyroidism at diabetic debut developed severe thyrotoxicosis coexisting with DK and requiring prolonged intensive care. All cases of hyperthyroidism were diagnosed in the last five years. Time between T1D onset and ATD was 0.95 (0; 2.37) years. There were 31 patients who had euthyroidism and in the follow up developed hypothyroidism in a median period of 0,94 (0.54;2.32) years. Thirty Three (F:18, M:15) patients had CD. Prevalence was 9 %. Median age at CD diagnosis was 10 years (6.8;11.6), and time between T1D onset and CD was 0.24 (0;0.87) years. ATD prevalence was compared between the last five years period and the previous 10 years. In the last 5 years (n:83) was 40,7% and in previous period was 22% (n:36) ($p<0,001$). Significant statistics differences were not found in CD prevalence between the two periods.

Conclusion: These patients with T1D showed a high prevalence of ATD and CD, similar to that previously reported. ATD prevalence seems to be increasing in recet years. These results emphasize the need of monitoring thyroid function and celiac disease in children and adolescents with T1D.

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P1-47

The retrospective/blind glucose monitoring (bCGM) system is valuable tool for hyperglycemic and hypoglycemic states

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Introduction: The retrospective/blind glucose monitoring (bCGM) system or glucose sensors commonly used for type 1 diabetes management. The approach to hyperglycemic and hypoglycemic states is an urgent and essential issue in terms of diagnosis/treatment. Many tests are performed for the diagnostic process. We aimed to evaluate the effectiveness of bCGM (iPro™2 system) in the follow-up and treatment of patients to our clinics with hypoglycemia/hyperglycemia.

Methods: The data from 69 cases with the iPro™2 system were analyzed retrospectively. The cases were divided into two groups according to the indications for sensor application (hypoglycemic and hyperglycemic group). Group characteristics and sensor data were analyzed in detail.

Results: 59.4% (n=41) of the cases were followed up due to hyperglycemia. Of the cases in this group, 21 had type 1 diabetes mellitus (T1DM), and 1 had neonatal diabetes. Five cases who did not meet the diagnostic criteria for diabetes at admission and planned to follow up were diagnosed with diabetes after sensor measurements. Three patients with Cystic fibrosis (CF) and one with thalassemia major were followed up with the sensor. Ten cases referred with the suspected hyperglycemia were normal. Treatment modification in the patient with diabetes was guided by the glucose variability and pattern in the sensor report. The sensor was a valuable tool in cases admitted in the prediabetes stage. Impaired glucose metabolism was detected in patients with CF and thalassemia major. So, an appropriate nutrition plan was made, and medical treatment was modulated. The cases with normal sensor data were excluded from follow-up, and there was no unnecessary further investigation.

Conclusion: This study shows that bCGM systems can be a valuable tool for diagnosing and management of hyperglycemic and hypoglycemic states.

P1-48

Changing Diabetes in Children Indonesia: Public-private partnership to improve healthcare access for children and adolescents with type 1 diabetes mellitus

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Background: In 2022, 1.52 million children and adolescents worldwide were diagnosed with type 1 diabetes mellitus (T1DM). During COVID-19, diabetic ketoacidosis (DKA) episodes in newly-onset and established cases increased in 44.2% and 30.1% of paediatric diabetes centres, respectively. In 2017-2019, 1,249 children were diagnosed with T1DM in Indonesia, and 70% were diagnosed with DKA at diagnosis in 2017. Changing Diabetes in Children (CDiC) is a public-private partnership (PPP) to enhance healthcare access for young people with T1DM in low-resource settings. Indonesia is a member of CDiC among 26 countries. Under the government-to-government partnership between Ministry of Health of Republic of Indonesia, Indonesia Pediatric Society, and Denmark, CDiC Indonesia is a non-profit organisation undertaking initiatives to improve patient registry, patient knowledge and skills, healthcare professionals (HCPs), and diabetes centres' capacity.

Methods: CDiC Indonesia's activities from 2021 to 2025 include: (1) Strengthening T1DM patient registry and diagnosis, using an application-based patient registry and distributing free glucometer and blood glucose (BG) strip tests for patients; (2) Patients and caregivers education; (3) Training HCPs for delivering high-quality paediatric T1DM care; and (4) Supporting the strengthening and establishment of paediatric diabetes centres.

Results: Per 19 June 2023, CDiC Indonesia has registered 981 T1DM children with a median(IQR) age of 12(6) years. They have received free glucometers or BG strips four times daily from CDiC. Seminars and workshops were attended by 1,528 children and adolescents with T1DM and their caregivers through 25 and two face-to-face and online sessions organised by CDiC Indonesia since November 2021. Online T1DM education for patients, caregivers and HCPs has generated over 7,200 engagements across Zoom and Instagram by March 2023. 3,482 HCPs consisting of paediatric endocrinologists, paediatricians, general practitioners, nurses, and dietitians have been trained through ten and six online and face-to-face seminars and workshops about T1DM care. Five paediatric diabetes clinics in Lampung, Medan, Jember, Banten, and Aceh were established between August 2022 and March 2023. Alongside with clinics' establishment, 848 HCPs were trained for T1DM care, and 113 new patients were recorded.

Conclusions: Established in 2021, the PPP of CDiC Indonesia has addressed barriers to healthcare access among children and adolescents with T1DM in Indonesia. Young patients with T1DM and their caregivers have received specialised education sessions and free BG monitoring kits, which the national health insurance scheme or programs have not provided. This partnership is also central to improving supply-side healthcare capacity for children and adolescents with T1DM.

P1-49

Quantiferon test versus Tuberculin test to screen for Latent Tuberculosis in Type 1 diabetic children: a single center experience

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Background: Type 1 DM (T1DM) is a chronic condition characterized by persistent hyperglycemia; which can impair immunity and increase susceptibility to infections. Latent TB infection (LTBI) is a subclinical infection caused by Myobactaeria tuberculosis antigens without clinical, bacteriological or radiological evidence of manifest TB disease. Tuberculin test (TST) is an inexpensive test used to identify LTBI status, but has limitations. False positive TST can occur due to BCG vaccination. Interferon gamma release assays (IGRA) can also be used to detect LTBI.

Previous studies suggested an association between DM and LTBI. Furthermore, diabetic patients with untreated LTBI were shown to be more likely to progress to active TB disease. However, there is no consensus on the standard screening test for LTBI in T1DM.

Aim of the Work: To determine the most preferred screening method for LTBI in T1DM children, in addition to confirming the association between LTBI and T1DM in children and its effect on glycemic control.

Methods: This cross-sectional study included 81 T1DM children aged 1-18 years, following up at Zagazig University Pediatric Hospital. They were compared to 81 healthy children as a control group. All patients were subjected to detailed history taking, and clinical examination with emphasis on BCG scar and chest examination. Investigations were done to all patients including HbA1C, TST using Mantoux technique, and chest X-ray. An induration of ≥10 mm was used as a cut-off to determine TST positivity. Quantiferon test was done to patients with positive TST.

Results: The mean age of patients at enrollment was 10.90±4.47 years. The mean duration of DM was 3.3±3.02 years. The percentage of positive TST was higher among T1DM patients than control group (32.1% vs 7.4%) ($p<0.001$). There was no statistically significant difference between positive and negative TST regarding age, sex, and duration of DM. However, there was a statistically significant increase in HbA1C among T1DM patients with positive TST than those with negative results (7.88 vs 7.42%) ($p<0.001$). Moreover, 40% of T1DM patients with positive TST had positive Quantiferon test confirming LTBI in 12.8% of patients.

Conclusion: T1DM patients are more likely to have positive TST than the control group. Patients with T1DM and LTBI had higher HbA1C. Quantiferon test-in addition to TST- is a preferred method to screen for LTBI than TST alone. More studies are required to detect the ideal method of LTBI screening in T1DM especially in countries with high incidence of TB.

P1-228

Secondary PREvention of Diabetes Type 1 with oral CALcitriol and analogs, the PRECAL study

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Type 1 diabetes (T1D) hits about 1:300 with rising incidence affecting increasingly younger children. Population screening at ages 2-6yrs with T1D associated autoantibodies (T1Ab) has been recently proven sensitive. While potential treatments to prevent or delay T1D are currently in development, a population based cost-effective preventive strategy is still lacking. Hence, 2000IU cholecalciferol daily in a large birth cohort study published in 2001 reduced by 80% the risk of T1D in 1yr. A pilot clinical trial in 2013, demonstrated negativation of T1Ab within 0.6(0.4-2.1) yrs under oral calcitriol.

In a prospective interventional non-randomized clinical trial, the PRECAL study (ISRCTN17354692). Between 2010-2022, 50 children (26 boys, 24 girls) aged 0.65-16.37 yrs identified as at high risk for T1D were included: 44 with +T1Abs (Insulin auto-antibodies, IAA; anti-tyrosinase abs, IA2, anti-glutamic decarboxylase abs, GAD; islet auto-abs, ICA; anti-Zn8 if available) and 6 with negative T1Abs but predisposing HLA A DQ DR haplotypes/genotypes. Nine had varied impaired glucose tolerance (IGT) (T1Ab+), 4 pre-T1D (3 T1Ab+ and 1 HLA+), and 9 new-onset T1D (T1Ab+). Serum T1Ab levels and fasting plasma glucose, HbA1c, c-peptide, Ca (tolerated ≤11.5 mg/dl), P, ALP, Ca/Cr 2-hr urine morning sample, 25(OH)D, 1-25(OH)2D with renal ultrasound in cases with hypercalcemia/hypercalciuria (tolerated ≤50%, or at the upper normal for age) were determined before and q3-6 months after initiation of calcitriol (0.05 mcg/Kg/day) 0.25-0.5 x 1-3/day or its synthetic analogue, paricalcitol (thrice the calcitriol dose) 1-4 mcg x 1-3/day p.o. under cholecalciferol repletion. Measurements are given as median and range.

Available data on 42 (7 dropouts, 1 follow-up <3m). All 26 without pre-T1D/T1D followed 3.06(0.5-10)yrs negativized T1Abs (15IAA, 3IA2, 4ICA, 2GAD, 1IAA/GAD, 1ICA/GAD) within 0.57(0.32-1.3)yrs or did not progress to T1D [5 +HLA, follow-up 3(1-4)yrs]. From 4 pre-T1D, 1 negativized T1Abs (follow-up 1yr), 1 with +HLA did not progress to T1D (follow-up 3.3yrs) and 2 with +T1Ab developed T1D in 6m/3yrs. Three out of 8 children with T1D progressed immediately to overt disease, 5 showed complete remission for 1yr (1m-2yrs). Five with +T1Ab relapsed and negativized again after resuming therapy. Four (<3yrs) negativized anti-TPO/TG, and two anti-transglutaminase-IgA. Eight presented mild hypercalciuria/hypercalcemia, resolving with dose titration/discontinuation.

Calcitriol, and paricalcitol were 100% effective and reasonably safe in negativizing T1Abs in healthy children, possibly preventing T1D, at least if started soon enough after seroconversion.

P1-229

Trajectories of glycemic control in transition-aged patients with type 1 diabetes

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Objectives: We investigated the trajectories in hemoglobin A1C (A1C) levels among transition-aged patients (age from 15 to 22 years) with type 1 diabetes (T1D).

Methods: Among the patients diagnosed with type 1 diabetes in pediatric age between 2001 and 2013 in Seoul National University Children's Hospital, 119 patients (54 males and 65 females) with a diagnostic age for under 14 and measurement of A1C at least once at every age were included. Patients were grouped according to potential factors; diagnostic age (61 patients of <10 years vs. 58 patients of ≥10 years), age of onset of intensive insulin therapy (84 patients of <15 years vs. 32 patients of ≥15 years), whether continuous glucose monitoring (CGM) was used for at least one year during transitional age (107 patient of non-CGM user vs. 12 patients of CGM user), and parental educational level (46 patients with highly educated parents vs. 41 patient with low educated parents). We defined parents with high level of education as cases where both parents were college graduates or higher. A1C changes from ages of 15 to 22 and factors associated with glycemic control were evaluated using repeated measured ANOVA.

Results: Median age at T1D diagnosis was 9.9 (IQR 7.3-11.5) years. Mean A1C was on the gradual decline across transitional ages ($p = 0.003$). Except for the age of 18, percentage of patients with A1C > 9% by the age of 15-19 were over 30%, starting to decline at the age of 20 and decreasing to 22.7% at the age of 22. There was no difference in A1C depending on sex, diagnostic age, age of onset of intensive insulin therapy, and whether CGM was used. The starting age of CGM in twelve CGM users was between 16 and 21 years, with one at 16 years, one at 17 years, one at 18 years, one at 19 years, three at 20 years, and five at 21 years. A1C was significantly lower in patients with higher parental educational level ($p < 0.05$ at all ages except at the age 18 years).

Conclusion: Patients with T1D at the transitional age tended to gradually decrease in A1C over time. Individuals with higher parental education level were more likely to show lower A1C.

P1-230

Motivational interviewing from the pediatricians' perspective: assessments after a 2-day training for physicians caring for adolescents with chronic medical conditions (CMCs)

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Background: Counselling adolescents with chronic diseases can be challenging when it comes to appropriate interview techniques and the doctor's attitude towards the patient. Successful communication can be a key element of treatment. Motivational interviewing (MI) is widely applicable in the management of behavioural problems and illnesses, as it increases patients' motivation for lifestyle changes. This plays a particularly important role in the treatment of adolescents with type I & II diabetes mellitus and chronic endocrine disorders. However, there is a lack of data on the applicability, feasibility and implementation of MI sessions in daily practice from the physicians' perspective.

Purpose: Our aim was to explore clinicians' experiences of MI training and subsequent use of MI in the routine care of adolescents with CMCs. Therefore, we wanted to find out if and how MI can be integrated into clinical practice and how training in MI should be designed.

Method: The present study has a descriptive and qualitative design. Twenty pediatricians were randomized to a 2-day MI course followed by MI consultations in a cluster-randomized controlled trial (COACH-MI). Data were collected one year after MI training using a questionnaire. Factors for effective training and possible barriers to successful use of MI were examined.

Results: Completed questionnaires were returned by 19 of 20 pediatricians. The pediatricians' experiences with MI demonstrate that MI is regarded as a valuable tool when working with adolescents with CMCs. 95 % of all respondents reported that they found MI education necessary for their clinical work and were using it also outside the COACH-MI study context. 73.7 % percent saw potential to strengthen the connection to their patients by using MI. The doctors were already using more MI conversation techniques after a 2-day MI course. Obstacles were seen in the short training, the lack of time, and missing undisturbed environment (interruptions by telephone, staff, etc.) during clinical flow.

Conclusions: MI techniques are not yet a regular part of medical training. However, a 2-day MI course was rated effective and providing a lasting impact by physicians caring for children and adolescents with chronic medical conditions (CMCs), although booster sessions should be offered regularly.

P1-231

Children with Type 1 Diabetes and Obesity show biochemical changes associated with insulin resistance

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Children with Type 1 diabetes are experiencing higher levels of overweight and obesity as a consequence of intensive insulin therapy as well as background socioeconomic and environmental factors that are contributing to excess adiposity in the general population. The consequences of obesity in people with type 1 diabetes are of particular concern, as obesity in adults increases the risk of both diabetes-related and obesity-related complications, including cardiovascular disease and various types of cancer. Obesity is understood to result in a state of low-grade inflammation. Recently IL 17 has been implicated in the pathophysiology of insulin resistance.

We performed a cross sectional study on children (5-16) with T1DM who had obesity and children who had T1DM but had a normal bodyweight. We also recruited otherwise healthy children and children with simple obesity to act as a control.

Eighty-eight children were recruited into the study. We measured pro inflammatory cytokines (IL17, TNF alpha, IL1) in the sera of these children by high sensitivity ELISA. We measured adipokines (leptin and adiponectin) by ELISA. We performed cell culture and measured inflammatory cytokine responses (TNFα, IL 17A, IL17F, IL17,sCD163, IL1beta, IFNgamma) of peripheral blood mononuclear cells to stimuli (LPS, TCR and PMA/ionomycin) in vitro. We measured residual c-peptide in children with T1DM.

Children with T1DM and obesity had higher serum TNFα levels and higher serum IL1 levels compared to children with T1DM with a normal BMI z-score. There was no difference in serum IL17 levels between both groups with T1DM whereas children who had simple obesity had significantly higher serum IL17. The PBMC of children with T1DM and obesity produced more IL17F in response to stimulation with TCR beads but had a similar TNFα, IFNγ, IL17A production and sCD163 response. Children with T1DM and obesity had higher leptin levels and lower adiponectin levels. Children with T1DM and obesity had the same HbA1c, and had no more microvascular complications than the T1DM lean controls. Children with comorbid obesity had a higher insulin units/kg/day despite no differences in residual c-peptide.

Our findings highlight some biochemical proinflammatory changes in the blood of children with Type 1 diabetes and obesity. This is reflected clinically in the higher insulin requirements of this cohor. These findings support the call to manage these children individually to optimise long term health. Balancing glycaemic control and weight management is an under met need in the care of paediatric diabetes.

P1-232

A Case with Alstrom Syndrome with a Novel Pathogenic Variant In ALMS1 gene as a Rare Cause of Diabetes Mellitus

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Introduction: Alstrom syndrome (ALMS) is an autosomal recessive disorder characterized by multiple organ involvement, including progressive cone-rod dystrophy, sensorineural hearing loss, childhood obesity, and type 2 diabetes mellitus. Pathogenic variants in the ALMS1 gene are the known cause for the occurrence of this devastating condition. Here, we reported a case of Alstrom syndrome with a novel homozygous variant in the ALMS gene, who presented to our clinic with diabetes mellitus.

Case Report: Twelve years old boy presented with diabetic ketosis. He had four months long history of polyuria/polydipsia along with 10 kg weight loss. He was the first child of third degree consanguineos parents. He had progressive vision loss due to cone-rod dystrophy. His initial signs were nystagmus and photosensitivity, beginning at six months of age. His height was 154 cm (SDS:0.2), his weight was 45 kg (SDS:-0.05), and his BMI was 18.9 kg/m2 (SDS: -0.48). Pubertal status was compatible with Tanner stage 2. Acanthosis nigricans was noted around the neck and axilla. He had also bilateral nystagmus, kyphoscoliosis and bilateral pes planus. Laboratory examination was compatible with type 2 DM. Serum glucose was 417 mg/dl, and concomitant insulin and c-peptide levels were 24.6 mU/L and 4.76 µg/L, respectively. HbA1c was 13.3% and diabetic autoantibodies were negative. Hypertransaminasemia was also present (ALT: 283 U/L, AST: 229 U/L). Serum lipid profile was normal, except HDL-C level (30 mg/dl). Echocardiographic evaluation was normal. Grade 2 hepatosteatosis was detected with abdominal ultrasonography. Hearing test revealed bilateral mild sensorineural hearing loss. Preliminary diagnosis was Alstrom syndrome with these clinical and laboratory findings. Genetic examination (WES) revealed novel homozygous pathogenic variant [c.6928dup (p. Thr2310Asnfs*5)] in ALMS1 gene.

Conclusion: Here, we reported a case with Alstrom syndrome with novel pathogenic variant in ALMS1 gene as a rare cause of DM. The clinical manifestations in Alstrom syndrome can be quite variable. Coexistence of type 2 DM, rod-cone dystrophy, sensorinal hearing loss should suggest Alstrom syndrome. Genetic diagnosis is worthwhile as it directs monitoring and treatment of the possible future comorbidities of the syndrome

P1-233

Diabetes Behind the Mask

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Keywords: diabetes, MODY,atypical

Introduction: Type 1 Diabetes (T1D) is the most common cause of diabetes in childhood, but Type 2 Diabetes (T2D) and monogenic diabetes has attracted increasing attention recently. Cases with atypical diabetes may be challenging for diagnosis, treatment and follow-up management. The purpose of this study was to present the characteristics of atypical diabetes cases from a tertiary referral center.

Method: Diabetes cases <18 years old and diagnosed between 2000-2022 were evaluated. Those with Type1, Type2, neonatal and secondary diabetes were excluded. Those with extra-pancreatic findings and/or with measurable c-peptide levels three years after diagnosis, and patients with at least one of the diabetes-specific auto-antibodies (anti-GAD, islet cell antibody, anti-insulin antibody) being negative were included. The age at diagnosis, family history, and clinical and laboratory findings at diagnosis and during follow-up, and treatments were analyzed retrospectively.

Results: Of the 1237 diabetic patients, 1059 (85.7%) were Type1 and 99 (8%) were Type2. The remaining 79 (6.3%) constituted the study cohort, of whom genetic variants were detected in 38 (3%). Median diagnosis age in the 79 was 7 (3-15.6) years and 61% were female. The rate of consanguineous marriage was 8.1% although 58% had a history of diabetes in three generations, and this rate was 17% for two generations. Eight had gestational diabetes and 19 (24%) had a sibling with diabetes. A total of 28 (35%) patients were diagnosed incidentally. The median c-peptide level was 1.1 (0.1-5.6)ng/mL and HbA1c 8.6 (5.8-17.6)%. Diabetes antibody positivity was GAD n=11, anti-insulin n=8, and anti-islet n=3. MODY (HNF4A, KCNJ11, INS) was diagnosed in 3/4 patients presenting with ketoacidosis. Among the 79,42 (53.2%) were treated with multiple insulins, 7 (8.9%) with basal-acting insulin only, 10 (12.7%) with oral antidiabetics, and 20 (25.3%) with diet. MODY-associated variants were present in 21 (26.6%). Seventeen had other diabetes-related variants (Table 1).

Conclusion: Clinician experience is important in the diagnosis of cases that do not suggest Type 1DM. To diagnose rare autosomal recessive monogenic diabetes and to offer appropriate treatment options, specific algorithms are needed for populations with a high rate of consanguineous marriage, such as in Turkey.

MODY genes (n=21)	Other genes associated with diabetes
GCK n=9	WFS n=6
HNF1B n=3	AKT2 n=3
ABCC8 n=2	PLIN n=1
KCNJ11 n=2	ENPP n=1
HNF4A n=1	SLC9A2 n=1
HNF1A n=1	RFX6 n=1
BLK n=1	MAFA n=1
PDX n=1	ZFP57 n=1
INS n=1	GPD2 n=1
	LRP6 n=1

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Health services for children with diabetes mellitus in Dnipro, Ukraine

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As of 2022, the Ukraine Pediatric Diabetes Register (UPDR) contained children aged <18 years with DM1- 11014 (1 in 677), with DM2 – 51 (1 in 146274), with neonatal diabetes (ND) – 69 (1 in 108115), and 59 cases (1 in 126440) with MODY. Most studies focus on such parameters as HbA1c, acute complications and quality of life, whereas investigations of the frequency of chronic DM1 complications and glycemic control for internally displaced persons (IDP) have not been widely described.

The UPDR was created in 2004. It contains all information about children with DM1 aged <18 years including HbA1c, the frequency of acute and chronic complications. We studied glycemic control, the frequency of acute and chronic complications and different treatment modalities including CSII (n=49) and MDII (n=337) for children aged 0-17 in the city of Dnipro. HbA1c and acute complications were also studied for IDP (n=30) who have been under our supervision for the last 9 months of war.

The number of children in Dnipro in 2022y with DM1 was 354. Among DM1, there are 238 children aged 0-14 years old (34 of whom receive CSII), and 116 adolescents (15 of whom receive CSII). The level of HbA1c in for the patients in the city of Dnipro was 7.8±0.76%. The proportion of children who had ideal or optimal glycemic control (HbA1c <7.5%) was 33.9%.

Our results showed the absence of a significant difference in the frequency of acute and chronic diabetes complications between CSII and MDII groups (p>0.05). However, a significant difference in the frequency of chronic complications and higher HbA1c was found in the 15-17 y.o. group vs 0-14 y.o. (p<0.05).

The children who were treated with CSII had significantly lower HbA1c compared to MDII group (7.3±0.59% vs 7.9±0.7%, p<0.05) despite the similar duration of DM1 in these groups (p>0.05). However, this can be due to the more frequent CGMS use in CSII group (p<0.05).

In IDP HbA1c and DKA1 were significantly higher compared to the Dnipro residents (8.2±1.1% vs 7.8±0.76% and 33,3% vs 5,9% respectively, p<0.05).

Further treatment modalities should be studied in a pediatric cohort with DM1, especially in adolescents (15-17 y.o). The treatment of IDP can be a challenge for the health care system due to the stress of children and guardians, the inability to carry out sufficient self-monitoring and insulin therapy, and the lack of affordable and timely medical care.

P1-235

Recurrence Risk Of T1DM In First Or Second Degree Relatives: First Indian Report

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Objective: Lifetime risk of having Type 1 Diabetes Mellitus [T1DM] increases when having a blood relative with T1DM. A Finish study reports 12.2% and 11.9% of T1DMs having a first degree relative [FDR] and second degree relative [SDR] with T1DM[1]. Data from India regarding proportion of children with T1DM FDR/SDR is non-existent. Objective is to find out the same.

Methods: We examined the electronic database of 902 T1DM patients visiting our pediatric endocrine clinic between March 2014 to October 2022 to find the history of affected FDR and SDR with T1DM. We also interviewed the cases and affected relatives for other autoimmune disorders.

Results: Out of 902 newly diagnosed index cases, 20 [2.2%] had one FDR and 2 [0.23%] had 2 relatives with T1DM [both parents]. Nine [1%] cases had SDR with T1DM. At diagnosis, the index cases were between 11 months and 12 years of age (median 4 years); and FDRs were between 2-35 years [median 20years]. Among the 22 FDRs, 14 [63%] were parents [7 mothers] and 8 were siblings. Among the sibling FDRs, 6 were brother-sister pairs and 2 were brother-brother pairs. Autoimmune thyroid was present in 2 index and 2 FDRs [unrelated to their index]. None of the 20 FDRs had other autoimmune diseases [celiac disease, vitiligo, alopecia or hypoparathyroid]. There were 2 pairs of T1DM married couples, and both have T1DM children [Onset at one year].

Conclusion: This is the first reported data on T1DM in the FDR/SDR of index T1DMs. Indian T1DMs have much less prevalence than the western literature. Index cases had earlier onset than the relatives. Parent-sibling were commoner, without any gender predilection.

Reference

[1] Parkkola A, Härkönen T, Ryhänen SJ, Ilonen J, Knip M; Finnish Pediatric Diabetes Register. Extended family history of type 1 diabetes and phenotype and genotype of newly diagnosed children. Diabetes Care. 2013;36(2):348–354.

P1-236

The impact of covid-19 pandemic on the incidence type 1 diabetes in children

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Viral infections may increase the risk of developing type 1 diabetes (T1D), and recent reports suggest that Coronavirus Disease 2019 (COVID-19) might have increased the incidence of pediatric T1D (M. Rahmati et al., 2022). In general, the course of viral infection in children is mild, the question of the long-term effects of COVID-19 on a child and adolescent, in particular, on pancreatic beta cells, remains unclear.

Purpose: To analyze the incidence of diabetes mellitus in children in the conditions of the COVID-19 pandemic.

Patients and Methods: We examined the trends in diabetes 1 type prior to and following the onset of the COVID-19 pandemic in Saratov region.

Results: Compared with pre-COVID-19 pandemic, the number of pediatric new-onset T1D during in the 2020 and 2021 years of the COVID-19 pandemic increased in 1.3 and 1.2 times respectively. The incidence rate of T1D in the 2019 was 24.74 per 100 000 children, in the 2020 – 31.92 per 100 000 and in the 2021 – 28.43 per 100 000.

Compared with pre-COVID-19 pandemic levels, the median glucose, and HbA1c values in newly diagnosed T1D children after the COVID-19 pandemic increased by 7.8% and 9.1%, respectively.

Conclusion: A significant increase in T1D cases occurred following the onset of the COVID-19 pandemic in Saratov region. Higher glucose and HbA1c values in newly diagnosed T1D children after the COVID-19 pandemic mandates targeted measures to raise physician awareness.

P1-237

Effects of the COVID-19 pandemic on anthropometric data, glycemic control, and lipid levels in children and young people with type 1 diabetes: two years of follow-up

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Introduction: The beginning of the COVID-19 pandemic encouraged a sedentary lifestyle and "covibesity" was reported. Concerns for consequences on anthropometric data, glycemic control, and lipid profile in subjects with type 1 diabetes (T1D) were raised.

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Objectives: Longitudinal and observational study aimed to investigate the 2-years effects of the COVID-19 pandemic on BMI, glycemic control, and lipid profile in children and young people (CYP) with T1D.

Methods: Anthropometric parameters, insulin total daily dose (I-TDD), glycemic control (A1c), lipid profile, and exercize were collected during the routine outpatient visits attended between December 2019 and February 2020 (T0, before the lockdown) and were compared with the ones recorded in the same months 1-year (T1) and 2-years after (T2).

Results: Eighty-three children and adolescents with T1D (65% male; at T2, median age 14.3 years and duration of diabetes 7.09 years) were recruited. BMI z-score significantly changed between periods (0.19 vs 0.08 vs 0.23 SDS; χ^2=15.9; p<0.001); values were increased in 68.7% of CYP at T2. Exercize was significantly different between periods (4 vs 0 vs 5 h/week; χ^2=128.4; p<0.0001). Rate of patients declaring low exercize (<6 h/week) decreased from 96.4% (T1) to 56.6% (T2). I-TDD was significantly changed (0.84 vs 0.92 vs 0.92 IU/kg/day; χ^2=8.19; p=0.017). Annual HbA1c (62.1 vs 60.5 vs 60.6 mmol/mol; χ^2=12.8; p=0.002) and TIR (48.1 vs 50.4 vs 55.4 %; χ^2=16.3; p<0.001) were improved. A worsening of TC (158 vs 162.5 vs 161 mg/dl; χ^2=8.45; p=0.015), LDL-C (77.6 vs 88.6 vs 92.4 mg/dl; χ^2=28.1; p<0.0001), and HDL-C (63 vs 60 vs 57 mg/dl; χ^2=21.3; p<0.0001) levels was found. Rate of subjects having TC >95th centile for gender and age increased from 9.76% (T0) to 12.3% (T2) (χ^2=11.4; p<0.001). LDL-C levels were positively related to BMI z-score (p<0.05) and HDL-C were negatively correlated (p<0.05).

Conclusions: Two-years after the COVID-19 pandemic, in our CYP with T1D we found an increase of the BMI z-score that was still within the normal range. Glycemic control remained improved, while a worsening of the lipid profile was found. Our data may be due to both the resuming of regular physical activity and the increased use of sensor that allowed us to continue with telemedicine visits in T2, adjusting patients' I-TDD. However, in some patients we must pay attention to the effects on cardiovascular health probably related to the increased consumption of canned food and industrialized foods during the pandemic.

P1-238

MiniMed 780G Advanced Hybrid Closed Loop System Outcomes According to Pubertal Status - Awesome Study Group Real-Life Experience

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Background and Aims: Achieving good glycemic control is a major challenge for adolescents with type 1 diabetes (TID). The introduction of the MiniMed 780G system, an advanced hybrid closed-loop (AHCL), that enables an automatic correction of insulin, gave hope for improved glycemic outcomes in adolescents. We assessed specific characteristics associated with glycemic measures in youth with T1D switching to Minimed 780G.

Methods: This retrospective observational real-life multi-center study from the AWeSoMe Group assessed continuous glucose monitoring (CGM) metrics of 22 patients (59% females, median age 13.9 [IQR 11,18] years), from a high socioeconomic background. CGM metrics were recorded for two-week periods prior to AHCL, after 1, 3, 6 months, and at the end of follow-up (median 10.9 [IQR 5.4, 17.4] months). Delta-variables (Δ) were calculated as the difference between the end of follow-up and baseline.

Results: TIR70-180mg/dL increased from 65% [52,72] to 75% [63,80], p=0.008, from baseline to end. TAR>180mg/dL, decreased from 28% [20,46] to 22% [14,35], p=0.047. Advanced pubertal stage was correlated with less improvement in ΔTAR>180mg/dL, r=0.47, p=0.05, and less CGM usage r=-0.57, p=0.05. A longer disease duration was associated with less improvement in ΔTAR180-250mg/dL, r=0.48, p=0.05. Lower pump site change frequency was associated with higher GMI, r=0.5, p=0.03, and lower TIR70-180mg/dL r=-0.52, p=0.08.

Conclusion: The use of AHCL enabled improvements in TIR70-180mg/dL in youth with T1D. More advanced pubertal stages, longer disease duration, and less compliance were associated with less improvement, stressing the need for continuous support and re-education in this age group.

P1-239

Epidemiology of Type 1 Diabetes among children under 15 years of age in Navarre (Northern Spain) between 2012–2022

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The incidence of TIDM varies greatly between different countries and regions.

In Navarre, located in the north of Spain, at the western end of the Pyrenees, there has been a clear increase in the incidence of TIDM, from 13,5 cases per 100000 in the decade 1990-2000 to 20,1 cases per 100000 between 2006-2011.

We wonder if this upward trend has continued in recent years

Our hospital is a reference center for Pediatric Endocrinology in Navarre.

Objetives: Update the incidence of TIDM in Navarre of children under 15 years of age between January 2012 and December 2022

Material and Methods:

- Capture-recapture methodology has been applied, using as primary source the tertiary and secondary hospitals in Navarre, and as secondary source the data from other hospitals (private, limiting communities), primary care centers and the diabetes association of Navarre
- Statistical analysis: SPSS

Results: During the 11 years analyzed, 248 patients were diagnosed (145M/103F), mean age 8,80±3,85 years and mean incidence rate 22,42 cases per 100.000 person-year (95% CI: 21,7-23,1), increasing to 31,7 cases in the last two years. The incidence by age group was: 10-14 years (30,3), 5-9 years (22,99) and 0-4 yr (13.2).

Of the cases, 25,5% of the cases were immigrants with a predominance of the North African population.

As for seasonality, there were no differences (winter 26%, spring 26%, summer 25% and autum 23%).

35.9% of the patients had diabetic ketoacidosis at onset: mild (19,4%), moderate (6,8%) and severe (9,7%). DKA is significantly higher in the 10-14 (42%) and 0-5 age groups (41% each) vs. the 5-10 age group (19%) ($p<0.05$).

Children of immigrant origin significantly debut at a younger age with higher percentage of DKA ($p<0.05$)

Conclusions: The incidence of in Navarre is high according to the WHO classification, with a progressive increase in recent years.

There is a high proportion of patients with mild DKA, especially at early ages and puberty

Finally, it is worth noting the high incidence of the Maghreb population, especially in children under 5 years of age.

P1-240

Age differences in the distribution of diabetes-specific antibodies in children and adolescents with type 1 diabetes mellitus

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Background: The assignment to type 1 diabetes mellitus (T1DM) can be confirmed by the determination of diabetes-specific autoantibodies. Five different antibodies can be determined. The determination of several antibodies is more expensive than the determination of a single antibody. In times of scarce resources, the sequential determination of antibodies could save costs. The aim of this study was to determine the frequency of antibodies and their age and gender distribution.

Methods: In 200 children and adolescents with T1DM (85 female, age 0.9 to 16.6 years), islet cell antibodies (ICA), glutamate decarboxylase AK (GADA), tyrosine phosphatase IA-2 Ak (IA-2A) and insulin autoantibodies (IAA) were determined at onset. The zinc transporter 8 antibody (A-ZT8-A) was only determined in a few patients and is therefore not included.

Results: ICA was positive most frequently in 176 (88%) patients. IA-2A was the second most frequent positive antibody (74.5 %). GADA were positive in 70 %, IAA in 49.5 %. Of the 24 ICA-negative patients, 14 were positive for IA-2A and 10 for GADA, of which 7 were only GADA positive. In one patient only, IAA were detected and 3 were negative of all 4 antibodies. Significant gender differences were only found in the 0-5 year age-group. In this group, ICA and IA-2A were equally common in males (both 81%) and ICA was most common in females (92%). In this age group, GADA was the second most common antibody in girls, while IAA was the third most common antibody in boys and girls.

Conclusion: In the overall group, the determination of ICA identifies 88% of patients with T1DM. The additional determination of IA-2A identifies 95% and the further determination of GADA identifies 98.5% of patients with T1DM. In the youngest age group, the first antibody in girls and boys should be ICA, the second antibody GADA in girls and IA-2A in boys. The third antibody should be IAA. Sequential determination can appropriately confirm the autoimmune genesis of existing diabetes while saving costs. The additional determination of A-ZT8-A could identify further children who were previously considered seronegative.

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P1-241

Association between osteocalcin and secretory function of islet beta cells in diabetic pediatric population: a pivotal study

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Background: Osteocalcin plays a role in glucose metabolism in mice, but its relevance in human energetic metabolism is controversial. Few data are available on osteocalcin in pediatric patients with T1DM. The aim of our monocenter observational study was to evaluate the role of the main remodelling bone biomarkers in the regulation of glucose metabolism at the time of type 1 diabetes diagnosis and to evaluate their potential relationship with insulin sensitivity and pancreatic β cells secretion.

Material and Methods: Our study population consisted of 29 patients with a mild prevalence of male subjects (51.7%). We evaluated the following biochemical parameters: basal blood glucose, HbA1C, C-PEP, total cholesterol, HDL cholesterol, LDL cholesterol,triglycerides, thyroid function (fT3 and fT4, TSH), renal and liver function, serum electrolytes, arterial hemogasanalysis and bone remodeling biomarkers (Osteocalcin, CTX, PTH, ALP, 1.25-OH Vit-D)

Results: The mean age of study participants was 8.4 ± 3.7 years. Most patients (62%) were on pre-pubertal stage, and only 3 subjects had completed the pubertal development. HbA1c mean value at the time of diagnosis was 108 ± 24.7 mmol/mol (12.0 ± 2.3%). Less than half of the patients (37.9%) presented DKA at diabetes onset. 6 patients (54.5%) had severe DKA and the remaining 5 patients had moderate or mild DKA. Basal and stimulated serum c-peptide levels were 0.65 ± 0.59 mg/dL and 1.02 ± 0.66 mg/dL, respectively. T1D-specific autoimmunity was present in 86.2% of patients. Other autoimmune diseases were found in only 3 patients (10.3%). In particular, two patients had celiac disease and one female patient was diagnosed with Hashimoto's thyroiditis concomitantly with diabetes onset. Regarding bone remodeling biomarkers, the following serum levels were detected: ALP 241.5 ± 85.6 IU/L, osteocalcin 56 ± 40.4 ng/mL, CTX 2.3 ± 0.7 mcg/L, PTH 17.5 ± 13.5 pg/mL, and 1,25-OH Vitamin D 23.8 ± 14.7 ng/mL. Low osteocalcin levels were observed in patients with DKA, with a positive correlation between osteocalcin and C-peptide levels (p value = 0,026). No correlation was observed between osteocalcin and other variables (pH, HCO3-, HbA1C, glycemia).

Conclusion: Low osteocalcin levels, observed in our population, could be an indirect expression of a poor pancreatic reserve in diabetic pediatric patients at onset of the disease.

P1-242

Prevalence of Insulin-induced Lipohypertrophy (LD) in Type 1 Diabetes Mellitus (T1DM): CSII versus MDIT and Children versus adults.: Review of literature in the past 15 years in 10 countries

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Abstract: Lipohypertrophy (LD) represents the most common cutaneous complication of insulin therapy worldwide. Epidemiological and clinical data on LD in children and adolescents with T1DM are growing since 2010 because of the introduction of new insulin analogs and the use of insulin pumps (CSII).

Objectives and Methods: We performed an electronic search in PubMed, Google scholar and Web of Sciences to evaluate the global prevalence and possible risk factors of LD in children and adolescents (2 -18 years) and adults (>18 years) on insulin therapy in all publications in the past 15 years.

Results: For children, 15 studies were included from 11 countries (Italy, India, Turkey, UAE, Saudi Arabia, Egypt, Canada, The Netherland, Iran, Austria and Ethiopia) after 2010. The pooled prevalence of the studies using MDII (15 studies, n= 2963 children, and adolescents, 1342 had LD) was 45.3 %. In these studies. the prevalence of LD varied greatly between 17% and 62% and was significantly affected by different risk factors. In three studies on children <18 years using CSII, (n = 423, from Italy, Canada, UAE, and Austria) the prevalence of LD was 47%, 42%, 36% and 46% respectively with pooled prevalence = 44.9%. This was not different compared to the pooled prevalence of patients using MDIT (45.3%).

For Adults on insulin therapy 10 studies including metanalysis and multi-country studies (n = 48992, using MDIT and pens, 20239 had LD) the prevalence of LD = 41.3%. The prevalence of LD is significantly higher in children versus adults (z is -4.27, p < .00001

In conclusion, it appears that in children with T1DM, the use of CSII did not change the prevalence of LD. However, the prevalence of LD is slightly higher in children versus adults on insulin therapy.

P1-243

A comparison of Quality of Life in Children with Diabetes Type 1 in Cyprus treated with Multiple daily injections of insulin to children utilizing CGM as adjutant to MDI and to children treated with Continuous Subcutaneous Insulin Infusion

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Background: Insulin remains the mainstay treatment for diabetes type 1(T1D), more recently several technological advances have been introduced to assist with the treatment. Continuous Subcutaneous insulin infusion (CSII) devices and continues glycose monitors (CGM) have gained a lot of popularity and are thought to help patients achieve better glycaemic control. HbA1c levels can be used to assess glycaemic control. There are conflicting reports on whether those devises improve quality of life (QoL). Cyprus seems to follow the worldwide increase in incidence of T1D but not many studies investigating QoL in children with T1D have been performed.

Methods: A cross-sectional study included 62 paediatric patients with T1D. Participants were divided in to three groups. Children treated with multiple daily injections (MDI N=27) of insulin, children utilizing CGM as adjutant to MDI (MDI/CGM N=25) and children treated with sensor augmented continues subcutaneous insulin infusion (CSII/CGM N=15). We used the Paediatric Quality of Life inventory 3.0 Diabetes module to assess health-related quality of life (HRQoL) in children with diabetes.

Results: Carbohydrate counting was correlated with better HbA1c (7.4 ± 0.95 vs 8.48 ±1.85), (F (1,50) = [7.644], p=0.008). Females had worse HBA1c levels (HbA1c 7,98±1.46) than males (HbA1c 7.33 ±1.00); t(65)=-2.111, p=0.039 and reported worse overall HRQoL.(F (58,1)=3.984,p=0.05. Children using CGM were experiencing less diabetes related symptoms (65.02 ±13.87 vs 56.14 ±14.50; t (46) = -2.164, p= 0.036). Participants using CSII/CGM had more difficulties sleeping statistically significant compared to MDI/CGM group (mean 56.25 ±33.92 vs mean 81.52±22.88, p= 0.054)

Conclusion: A proper use of carbohydrate counting can assist children without CGM or CSII to improve glycaemic control. MDI/CGM group reports less diabetes related symptoms which subsequently enhance QoL. Special attentions need to be given to female patients. Further studies with larger sample are necessary to accurately assess HRQoL in children on insulin pumps as number of participants was very small compared to participants in the other groups.

P1-244

Knowledge of healthcare practitioners before and after paediatric T1DM diagnosis and management training

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Background: An underestimated figure of 1,249 children with type 1 diabetes mellitus (T1DM) was diagnosed in Indonesia from 2017 to 2019. In 2021, there were around 0.05 paediatricians per 1,000 children in Indonesia. Only 1.2% (N=54) were pediatric endocrinologists practising in 17 out of 38 provinces populating urban areas in Indonesia. Therefore, Changing Diabetes in Children (CDiC) Indonesia, a public-private partnership, has delivered training for healthcare professionals (HCPs) to improve access to healthcare for young people with T1DM. This study assesses the knowledge of HCPs before and after paediatric T1DM diagnosis and management training in Indonesia.

Methods: A quasi-experimental study was conducted in three urban areas in Indonesia (Jember, Lampung, and Medan) from August 2022 to March 2023. Total sampling was done on HCPs who completed pre-test and post-test (consisting of 15 multiple-choice questions) before and after the paediatric T1DM diagnosis and management training. The training was organised by CDiC Indonesia, consisted of one-day in-person, two-days hybrid, and two-days in-person seminar and workshop sessions in Lampung, Medan, and Jember, respectively. The sessions were delivered and facilitated by pediatric endocrinologists. Categorical variables were presented in frequencies and percentages. Continuous data were assessed visually and statistically for the distribution and shown in mean(SD) or median(IQR). Wilcoxon signed-rank test was used to compare the pre-test and post-test. Analysis was done using IBM SPSS Statistics 25.0.

Results: Data from 210 participants who completed the pretest and post-test were analysed. 157 (74.8%) were women, practised in Jember (N=120; 57.1%), Lampung (N=56; 26.7%), and Medan (N=34; 16.2%). Participants were general practitioners (N=101; 48.1%), paediatricians (N=80; 38.1%), nurses (N=17; 8.1%), and dietitians (N=12; 5.7%). Before and after training, less than half of the participants could correctly answer four questions regarding insulin dose (40.5% and 50.0%), diabetic ketoacidosis management (31.0% and 41.9%), operation for T1DM (26.2% and 20.5%), and urine albumin-creatinine ratio (20% and 45.7%). There was strong evidence of median (IQR) increase of the pre-test and

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post-test results before and after the training, which was 53.3 (20) and 73.3 (20), respectively (p<0.001).

Conclusions: Paediatric T1DM diagnosis and management training for HCPs was associated with increasing HCPs' knowledge of T1DM before and after training. However, HCPs' knowledge of T1DM was low, mainly about the appropriate operation timing for T1DM patients. Pre-test and post-test results suggest the importance of training evaluation to improve the participants' understanding and material retention.

P1-245

Combination of mutations in the HNF1A and ABCC8 genes: clinical polymorphism in members of the same family

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Mutations in HNF1A gene underlie the development of maturity onset diabetes of the young type 3 (MODY3). Mutations in ABCC8 gene are the cause of neonatal DM and the rare MODY12, which is clinically similar to MODY3. In these forms of MODY, there is a high sensitivity to sulfonylurea.

Patient A, 17 y.o. He was born to woman with gestational DM. At the age of 12.5, fasting hyperglycemia of 13 mmol/l was detected. Insulin therapy was not prescribed due to the parent's refusal. At the 14.5 y.o, since his mother was diagnosed with MODY3, a pathogenic variant p.R54X in HNF1A was detected, a MODY3 was diagnosed. At the age of 15, he was hospitalized with hyperglycemia 13.8 mmol/l. HbA1c - 9.8%. Long-acting insulin was assigned. Subsequently, the patient used insulin irregularly and consumed large amounts of carbohydrates. His maximum HbAc1 was 20,5%. At 17 y.o, he was admitted to hospital: glycemia was 18.6 mmol/l, HbAc1 - 12.6%, islet antibodies were negative. Intensified insulin therapy (0.9 units/kg/day) led to the normalization of glycemia. Specific diabetic complications were not detected. In addition to the variant in the HNF1A, a p.R521X variant was found in the ABCC8. After 3 months, the boy was successfully transferred to glibenclamide 7.5 mg/day.

Patient L, 37 y.o, proband's mother. At the age of 20, gestational DM was diagnosed: fasting glycemia was 6-9 mmol/l, she refused insulin therapy. At the 32 y.o, an examination for cholelithiasis revealed hyperglycemia, the variant p.R54 X in the HNF1A was detected. To date, she has not received hypoglycemic therapy, followed a carbohydrate-restricted diet. At the last examination at the age of 37, HbAc1 was 6.7%, a variant of p.R521X was found in the ABCC8 as in the son.

Patient S, 8 y.o, proband's sister. HbAc1 – 5.4%, fasting glycemia – 4.7 mmol/l. There are variants of p.R54X in the HNF1A and p.R521X in the ABCC8.

Conclusion: MODY associated with variants in the HNF1A and ABCC8 is characterized by a different degree of carbohydrate metabolism disorders, depending on the location of mutation in gene and its severity. We have presented a description of clinical polymorphism in members of family with a combination of identical mutations in the two MODY genes. The more severe disease in proband, apparently, is due to the low compliance. Normoglycemia in sister may be due to age, which requires further dynamic observation.

P1-427

Quality Improvement Initiative to Improve Influenza Vaccination Uptake Rates in Paediatric Patients with Diabetes Mellitus

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Introduction: The annual incidence of severe influenza infections reaches 5 million cases globally. Patients with diabetes mellitus (DM) are known to suffer more severe influenza infections, with increased mortality. Despite vaccination being recommended as standard of care, vaccination uptake rates have remained low for our DM patients. We undertook a quality improvement (QI) initiative to improve influenza vaccination uptake rates in our paediatric DM clinic.

Methods: Standard QI tools were employed for this initiative, beginning with understanding the expectations of the different stakeholders, process mapping, and constructing the affinity diagram. With the patient, staff, system and process factors identified through team brainstorming, a "cause-and-effect" fishbone diagram was constructed. A pareto chart was developed based on the factors that received the highest priorities by team members through independent voting. We proposed 4 interventions to target the root causes, which were executed through 3 Plan-Do-Study-Act cycles: (1) Inclusion of influenza vaccination in the DM Patient Management Template used in DM clinics, (2) Education Campaigns for the DM team to create awareness of the initiatives, (3) Patient Education Campaign through poster and patient-information leaflets, and (4) Inclusion of influenza vaccination in the electronic DM clinic documentation template. Data on vaccination offer and uptake rates were collected over a 10-month period.

Results: Our DM clinic had a mean of 84 patients per month. The median pre-intervention vaccination rate was 7.7%. At the first month of intervention, vaccination offer rate (surrogate for non-patient factors) was 40.9%, while vaccination uptake rate was 23.9%. After interventions (1) and (2), the median vaccination offer and uptake rates increased to 88.6% and 54.4% respectively. Post-interventions, the median vaccination uptake rate was 59.3% (maximum at 66.1%), while the median offer rate was 90.1% (maximum at 94.2%). Vaccination uptake rates reached a plateau around 60-65% towards the end of the initiative, which has been sustained to date. There were no serious adverse effects from influenza vaccination and no hospitalizations from influenza infections among DM patients during the study period. Using existing data and predictive models, the savings from the increase in influenza vaccination rates among DM patients is around SGD 250,000 (Euros 170,000) per year.

Conclusion: This QI initiative has established sustainable methods to improve vaccination uptake rates among paediatric DM patients, which translates into decreased morbidity and significant cost savings. These may benefit other high-risk groups with chronic disease who are at risk of severe influenza infection.

P1-428

WITHDRAWN

P1-429

Increased Incidence of New-Onset Type 1 Diabetes and Diabetic Ketoacidosis in Children and Adolescents During Coronavirus Pandemic

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Introduction: Since the beginning of the coronavirus pandemic, an increase in cases of new-onset type 1 diabetes (T1D) in children and adolescents has been observed in many countries, including Brazil.

Objectives and Methods: In this descriptive study, we aimed to investigate the frequency of new-onset T1DM and the frequency and severity of diabetic ketoacidosis (DKA) in a referral Brazilian University Hospital, 38 months before (from January 2017 to February 2020) and 34 months during the coronavirus pandemic (from March 2020 to December 2022). Clinical and laboratory data from all new T1D cases attended to the paediatric emergency from January 2017 to December 2022 were obtained. The pre-pandemic and pandemic periods were compared using means, percentages, and hypothesis tests when appropriate.

Results: One hundred and thirty-four new-onset T1D cases were diagnosed between 2017 and 2022 (mean age 8.7 years old [1-16]). Compared to the pre-pandemic period, the number of new cases increased by 57% in the pandemic period (52 vs. 82, respectively). The proportion of new T1D cases in the pediatric emergency was 70% higher during the pandemic: from 3.9 to 6.7 T1D for each 1,000 general cases at the paediatric emergency (p=0.005). Considering only the year of 2020, this proportion was 110% higher than the mean of the three years before (8.7: 1,000 during 2020 vs. 4.1:1,000 mean in the pre-pandemic period). The frequency of DKA at diagnosis increased from 42.3% in the pre-pandemic period to 65.8% during the pandemic (p=0.007), and the severe DKA was slightly more common in the pandemic period: 31.8% vs. 40.7% (p=0.24). There was no difference in nutritional status (mean body mass index z-score: pre-pandemic = 0.15; pandemic = -0.27, p=0.14), age (mean age: pre-pandemic = 9 years; pandemic = 8.5, p=0.24), and sex proportion (males: pre-pandemic = 55%; pandemic = 53%). Only six patients were infected by SARS-CoV-2 during the new-onset.

Conclusion: There was an increase in the frequency of new-onset T1D during the pandemic, and the higher peak of cases matches with the first coronavirus wave in Brazil. Additionally, there was an increase in the severity of T1D presentation, with a higher frequency of DKA and severe DKA at the diagnosis.

P1-430

What do they eat? Calculation of carbohydrate, fat and protein intake in children with type 1 diabetes (T1D) by use of an image based analysis by smartphone

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Background: Carbohydrate counting is essential in diabetes management to match insulin doses to carbohydrate intake. Though recommendations concerning macronutritient composition exist (ISPAD Clinical Practice Consensus Guidelines 2022: Nutritional management in children and adolescents with diabetes), fat and protein intake is usually not calculated. Therefore, little is known if these recommendations are followed. Lower carbohydrate intake is reported to be associated with better metabolic control, but data in children are limited.

Aim: This study aimed to assess daily intake of carbohydrates, fat and protein of children and adolescents with type 1 diabetes (T1D) and to compare the results with current nutritional guidelines. Furthermore, an association of macronutrient intake with metabolic control was studied.

Patients and Methods: Children aged 7 to 18 years with T1D for > 6 months were recruited into a 14 day observational study. All study participants used continuous glucose monitoring (CGM) and documented meals by taking pictures with a smartphone application using image-based nutrition analysis to quantify meal macronutrient content while continuing their usual eating habits. HbA1c and demographics were collected during a routine visit preceding the study. Percentage time spent in range (TIR) was calculated from CGM data. Carbohydrate, fat and protein intake was calculated and correlated to HbA1c and TIR.

Results: 20 children (10 female, mean age 12.3 (range 7.6-18.5) years) with a mean HbA1c of 7.4% (range 6.1-9.1) and TIR of 58% (range 23-87) participated in the study.

Dietary analysis and recommendations are shown in the table below:

	Study Results: mean (range)		**Guidelines**	
Age group (n)	7-< 12 years (10)	>= 12 years (10)	Children	Adolescents
Carbohydrates g/d	118 (78-158)	131 (84-211)	170	213
Protein g/kg/d	1.3 (0.7-2.4)	0.7 (0.4-2.1)	1	0.9
Fat g/kg/d	1.2 (0.7-2.4)	0.7 (0.3-1.4)	1	0.9
Meals documented/d	3.5 (1.9-5.1)	4.4 (2.4-6.6)		

Carbohydrate intake showed a weak correlation to HbA1c (r=-0.5) and TIR (r=0.5), which was not found for the intake of fat (r=-0.2 and 0.3) or protein (r=-0.1 and 0.05).

Conclusion: In view of current guidelines, meal analysis revealed for children a lower carbohydrate intake, while fat and protein intake approximately correspond to recommendations. In adolescents, the amounts of carbohydrates, fat and protein were lower then recommended.

The use of macronutrient calculation via smart-phone application may offer the possibility of integration into more targeted insulin dosing in future.

In contrast to studies in adults, lower carbohydrate intake was not associated with better metabolic control.

P1-431

Telemedicine usefulness in the follow-up of young people with diabetes 1 diabetes 2-years after the spread of COVID-19

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Introduction: Telemedicine was adopted during the lockdown due to the COVID-19 pandemic in the follow-up of patients with type 1 diabetes (T1D). Because of its potential to reinforce self-management support outside health care settings it was used still after the lockdown.

Objectives: Longitudinal and observational study aimed to investigate effectiveness of telemedicine in the follow-up of young people with T1D over the 2nd year by the pandemic spread.

Methods: Data on type and number of annual visits, insulin dose and delivery methods, blood glucose monitoring methods, A1c, AGP, and time spent for physical activity were collected during the routine outpatient visit performed between December 2020 and February 2021 (T1) and were compared with the ones recorded during the same months 2-years after the COVID-19 spread (T2).

Results: Eighty-three children and adolescents with T1D (65% male; median age 14.3 years; T1D duration 7.09 years) were enrolled. Patients were divided into Group A (28 patients; Italian, 85.7% - at least one telemedicine at T2) and Group B (55 patients; Italian 58.2% - none telemedicine at T2). Groups were comparable for number of telemedicine visits at T1 and this data was longitudinally increased in Group A (p=0.013). Physical activity significantly improved in both groups and was comparable at T2. In Group A, rate of insulin pump users increased longitudinally (42.9 vs 53.6%; χ^2=18.2; p<0.001). CGM users was 96.4% in both studied periods. In Group B, rate of CGM users increased longitudinally (58.8 vs 61.8%; χ^2=64.9; p<0.001). Insulin pump users was 20% in both studied periods. Average of annual HbA1c levels were lower in Group A respect to Group B both at T1 (52.6 vs 65.4 mmol/mol; p<0.0001) and T2 (52.8 vs 63.1 mmol/mol; p<0.0001). HbA1c values were longitudinally unchanged in Group A, while improved in Group B (p=0.015). Rate of HbA1 ≤53 mmol/mol was 53.5% in Group A during both period time; in Group B it was 9.1% at T1 and 10.9% at T2. TIR was significantly higher in Group A respect to Group B both at T1 and T2 (p<0.001).

Conclusions: Our data suggest that telemedicine is effective to maintain a good glycemic control still 2-years after the beginning of the COVID-19 pandemic. We should consider an individual approach for telemedicine use, mainly for patients with a good glycemic control and diabetes technologies users. Next challenge for an easier use of telemedicine should consider to address disparities in access and use.

P1-432

Prevalence of sleep disorders in children and adolescents with type 1 diabetes and its relation to glycemic control: A single center study

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Background: Poor sleep quality has been linked to insulin resistance and impaired glucose metabolism, but little is known about sleep and type 1 diabetes (T1D). People with T1D experience higher rates of sleep disturbances than people without diabetes, and these disturbances have negative implications on glycemic control, as well as psychosocial and cognitive outcomes.

Objective: To study the prevalence of sleep disorders and sleep characteristics in children and adolescents with T1D and the possible association between sleep disturbances and HbA1c.

Subjects and Methods: A case control questionnaire study that was conducted on 189 cases and 106 age and sex matched controls. The sleep was evaluated by using Sleep Disturbance Scale for Children (SDSC) in children 6–12 years old and Adolescent Sleep-Wake Scale (ASWS), total nocturnal sleep duration, sleep disordered breathing, daytime sleepiness scores in adolescents 12–18 years old.

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Results: The study showed higher prevalence of sleep disorders in T1D group in comparison to controls (57.1% vs 11.3%; *p* <0.001). T1D group showed a statistically higher prevalence of daytime sleepiness versus control group (18.5 % vs. 8%, *p*=0.04). Multivariate analysis showed that younger age and higher HbA1c are significant independent predictors of sleep disorders in T1D cohort (OR= 3.5 (1.01-12.4); *p*=0.048, 1.7 (1.4-2.1); *p* <0.001, respectively). Median HbA1c % was higher in T1D with sleep disorders as compared to T1D subjects without sleep disorders (10.2% (8.9% – 11.5%) vs. 7.6% (6.9% – 9.2%), P= 0.001). There was a significant negative correlation between duration of sleep and HbA1c (r= -0.54; *p* <0.001). 3.7% of T1D cohort with good glycemic control (HbA1c ≤7%) had sleep disturbance, while 96.3% of T1D cohort with average glycemic control (HbA1c >7%) had sleep disturbance; (p value < 0.001).

Conclusion: Young people living with T1D have a higher prevalence of sleep disorders as compared with healthy controls. Glycemic control is significantly affected by the presence of sleep disorders and vice versa.

P1-433

Effects of triple cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy on glucose metabolism in cystic fibrosis patients

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Introduction: Triple CFTR modulator therapy has been shown to improve lung function and quality of life in patients with at least one F508del mutation in the CFTR gen. However, effects on glucose metabolism are not yet well defined.

This paper aims to describe the effects of this treatment on glucose metabolism in CF patients.

Methodology: Ambispective study.

Inclusion criteria: patients ≥8years old with CF genetic diagnosis, undergoing triple modulator therapy with ivacaftor-tezacaftor-elexacaftor, who have OGTT and/or continuous-glucose-monitoring (CGM) performed before (±4months) and after therapy onset (tests performed under baseline conditions, without exacerbation of background disease or corticotherapy at the time of testing or 4 weeks prior).

OGTT: normal (NGT), indeterminate (INDET), impaired (IGT) or diabetes (CFRD).

CGM: FreeStyleLibre2-Abbott performed for 14 days with exercise and regular diet; patients were classified according to previous published data, NGT: <4,5% of glucose monitoring time >140mg/dl, AGT ≥4,5% of monitoring time >140mg/dl or a glucose peak ≥200mg/dl and CFDR ≥2 glucose peak ≥200mg/dl on different days.

Results: Nine patients (3 females), mean age 14,75 years. All patients have pancreatic insufficiency and HbA1c ≤5,9% before and at the therapy, except for patient 9 who started with HbA1c of 7,9%.

Patient 9 required nasogastric tube feeding, insulin (CFRD) and was a lung transplant candidate before beginning triple therapy, nowadays he doesn't need nasogastric tube feeding, stopped insulin after 16 months on therapy and he is no longer a transplant candidate.

We observed CGM glucose peaks >200mg/dl while having at the same time a normal OGTT (patients 1, 8 and 9).

Conclusions:

- The effects of triple CFTR modulator therapy on glucose metabolism is still uncertain. Larger prospective studies are needed.
- CGM is more sensitive than OGTT in detecting changes of glucose metabolism in CF patients.

Nº.F/M	Age at start of therapy (years)	F508del mutation	Basal study		Study (months)	Follow-up study	
			OGTT	CGM		OGTT	CGM
1.F	9,08	2	NGT	IGT	11	NGT	CFRD
					24	IGT	IGT
					30		CFRD
2.F	12,83	1	IGT	CFRD	11	NGT	NGT
					34	NGT	NGT
					47	NGT	NGT
3.M	13,75	2	INDET	CFRD	8	INDET	IGT
4.M	14,58	1	NGT	NGT	5	NGT	CFRD
5.M	15,08	2	IGT	CFRD	7	IGT	IGT
6.M	15,42	2	CFRD		19	IGT	
7.M	17,17	1	NGT		13		CFRD
8.F	17,33	1	NTG	CFRD	7	IGT	CFRD
					12		CFRD
9.M	17,58	1	NGT	CFRD	9		IGT

F508del, 1:homozygous, 2:heterozygous

Red/blue lettering: impairment/improvement of the test

P1-434

Monogenic Diabetes gene variants in 323 Greek MODY patients: Targeted NGS increases diagnostic accuracy and allows identification of rare MODY subtypes

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Introduction: Maturity Onset Diabetes of the Young (MODY) is clinically and genetically heterogeneous type of Monogenic Diabetes (MD) and to date 14 genes have been associated with different MODY subtypes. It is a rare disease characterized by early onset hyperglycemia, autosomal dominant inheritance, and defect in β cell insulin secretion, often misclassified as T1DM or T2DM.

Materials and Methods: Genetic analysis was performed in 323 Greek unrelated patients, fulfilling MODY criteria over a period of 4 years. 279/323 patients underwent targeted Next Generation Sequencing (tNGS) with a custom panel for: *GCK, HNF1A, HNF4A, HNF1B, INS, ABCC8, KCNJ11, NEUROD1, CEL, PDX1, APPL1, WFS1, INSR*. Copy Number Variation Analysis (CNVs) was performed by MLPA. Confirmation of the detected variants and segregation analysis was performed employing Sanger Sequencing. 44/323 patients with mild fasting hyperglycemia phenotype, suggestive of GCK-MODY, underwent Sanger Sequencing of *GCK* gene.

Results: By tNGs genetic diagnosis was achieved in 30% (83/279) of the patients, while by Sanger sequencing the *GCK* gene genetic diagnosis reached 45.5% (20/44). MLPA analysis revealed 2 heterozygous deletions: *GCK* gene exon 1 and whole *HNF1B* gene. Furthermore, we identified 3 digenic cases (*GCK-ABCC8, HNF4A-KCNJ11, HNF1A-HNF1B*), in which each variant was of paternal and maternal origin. Overall, the frequency of the different MODY subtypes were: *GCK* (17.6%), *HNF1A* (8.2%) followed by *ABCC8* (4%), *HNF4A* (1.43%) and *HNF1B* (1.43%). Rare MODY subtypes such as *KCNJ11* (1.07%) and *INS* (1.07%) were also detected.

Five patients, who presented with diabetes without any syndromic clinical features were carrying heterozygous variants in syndromic monogenic diabetes genes: three patients carried a variant in *WFS1* (1 LP, 2 VUS), one patient two variants in cis in *WFS1* (1 LP, 1 VUS) and one patient a variant in *INSR* (VUS).

Conclusions: Genetic diagnosis was achieved in 32% of tested patients. The most frequent MODY subtypes in this study were found to be *GCK, HNF1A* and *ABCC8*, while rarer subtypes and patients with variants in syndromic genes were also detected. Genetic diagnosis is important since different MODY subtypes require different treatment. The application of NGS increases molecular diagnosis rates in MODY patients, reduces diagnostic time and cost and allows identification of rarer subtypes. Multiple gene screening in MD patients, through expanded panels of MODY and syndromic diabetes genes, provides early diagnosis of atypical presentations, disease progression prognosis and family genetic counseling.

P1-435

Management of severe diabetic ketoacidosis with extremely high doses of insulin in a girl with severe insulin resistance syndrome due to compound heterozygous mutations in the insulin receptor gene

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We report a girl born small for gestational age with a birth weight of 1970g. At the age of 2 years she developed marked dystrophy, height was -4.39 SDS and BMI was -3.1 SDS. Later she developed severe insulin restistance and hyperglycaemia due to compound heterozygous mutations in the insulin receptor gene: exon 16: c.2986A>G (paternal) and intron 9: c.2029+1G>T (maternal). Clinical findings included severe acanthosis nigricans, mild hypertrophic cardiomyopathy, abnormal enamel formation, polycystic ovarian hyperplasia and hyperandrogenemia. She was treated with rhIGF-1, resulting in catch-up growth. At the age of 11, the patient developed severe diabetic ketoacidosis following an influenza A infection. Only with an extremely high insulin dose of up to 2,000 U/kg BW/h = 50,000 U/d and an extremely high sodium bicarbonate dose of >1 mmol/kg/h did a slow improvement occur. In the course of time, the insulin intake could be reduced to about 3000 U/day at discharge. Discharge was by insulin pump therapy with U500 insulin.

P1-436

Should the diagnostic criteria of childhood obesity depend on the nutritional status of national pediatric population? A lesson form assessment of Ukrainian children with type 1 diabetes in Poland after Russian aggression against Ukraine

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Introduction: Childhood overnutrition is a global challenge of public health. Both WHO and different countries have prepared BMI charts for pediatric population. Proper assessment of nutritional status is particularly important in children with type 1 diabetes (DM1). Due to Russian aggression, some Ukrainians with DM1 have to continue treatment in Poland.

Aim: to compare HbA1 concentrations and the incidence of overnutrition (overweight and obesity) with respect to WHO and national BMI reference charts between Ukrainian (UA) and Polish (PL) children with DM1 with respect to methods of insulin administration and glucose monitoring.

Methods: Retrospective analysis included 96 patients, age 7-18 years, with DM1: 32 UA and 64 PL, matched by age, sex and DM1 duration, by *k*-nearest neighbors algorithm. Overweight and obesity were defined as BMI exceeding 1 SD and 2 SD above the median for age (85th and 97th centile, respectively) and their

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incidence in UA and PL groups was calculated with respect to both WHO (2007) and national (Nyankovskyy et al. 2018 for UA, Kułaga et al. 2010 for PL) reference charts.

Results: Both personal insulin pumps and sensors (CGM or FGM) were significantly ($p<0.05$) more frequently used in PL (82.8%) than in UA (68.6%) children. There was no difference in HbA1c and nutritional status between PL and UA patients, except for significantly higher HbA1c and lower BMI SDS in UA children on pens than in these on pumps (8.6±2.1% vs. 7.0±1.1% and -0.25±1.01 vs 0.68±1.14, respectively).

According to WHO charts 9.4% PL and 6.3% UA children were obese, while 17.2% PL and 21.9% UA overweight. With respect to the national charts, the incidence of overnutrition was significantly lower in PL (13.5%), while similar in UA (25.0%). Application of national charts for UA children, resulted in re-classifying 2 overweight girls as obese, while 2 overweight boys as normal. There was a difference between the children aged below and over 13 years in the incidence of overweight (13.0% vs. 24.0%) but not of obesity (8.7% vs. 8.0%) according to WHO charts.

Conclusions: There is a difference in the control of DM1 between UA but not PL children using pens and pumps. The incidence of overweight and obesity in children with DM1 exceeds values (centiles) defining the disorders. Discrepancies between the national charts cause difficulties in the correct assessment of nutritional status of children in case of cross-border migration.

P1-437

Efficacy of the Tubeless Insulin Management System on Glycemic Control in Children and Adolescents with Type 1 Diabetes Previously Treated with Multiple Daily Injections and Flash Glucose Monitor Over the First 12 Weeks of Use

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Introduction: Assessment of real-world use of diabetes technology recently introduced in the region can provide information on clinical outcomes to help with advancement of care in a developing country like Egypt.

Objectives: This prospective pilot study included patient-reported clinical outcomes on glycemic metrics in pediatric and adolescent patients with T1DM before (baseline) and 12 weeks after (follow up) the initiation of a tubeless insulin pump (Omnipod DASH® Insulin Management System) previously treated with multiple daily injections and monitored by FreeStyle Libre, flash glucose monitor (FGMS; Abbott, Alameda, California).

Methods: Data captured during study period were aggregated and analyzed. Percentage of time spent within (TIR= 70–180 mg/dl), below (TBR) and above (TAR) glycemic ranges, mean glucose management indicator (GMI), total daily dose (TDD) and frequency of adverse events in users with 14 or more days of sensor glucose data were determined. Baseline and follow-up visits were carried out for assessment of outcomes.

Results: Patients (n=28) aged 9.4±3.7yrs and 64.3% were males. When compared with pre-pump initiation (MDI therapy); time in range significantly increased from 61.6% at baseline to 73.2 %($p<0.001$). Time above range (for both >180 mg/dL and time >250 mg/dL) significantly decreased from 39.2% to 24.7% ($P < 0.001$), while time below range (for both <70 mg/dL and time <54mg/dL) significantly decreased from 7.4% to 2.6% ($P < 0.001$). Mean glucose levels were reduced from 169.5 mg/dL at baseline to 143.7 mg/dL ($P < 0.001$) at last visit. Coefficient of variation (%) decreased from 49.4% to 35.5%. Significantly improved glycemic control was observed as GMI was reduced by 0.9% ± 0.4% while there was a reduction in TDD of insulin of -5.2±7.8 U/d ($p<0.01$) and mean bolus frequency was 4.8 times per day. No episodes of severe hypoglycemia or DKA were reported.

Conclusions: Real-world data document that tubeless insulin pump therapy is associated with clinically meaningful improvement in glycemic control, reduction in daily insulin requirement and reduction in the hypoglycemic and DKA episodes in an age group prone to acute complications.

P1-438

A qualitative study of knowledge, attitudes and perceptions of new diabetes technologies in A&E department

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Background: In August 2022, the National Institute of Health and Care Excellence recommended that all adults and children with type 1 diabetes (T1DM) should have access to Continuous Glucose monitoring systems (CGM). This guidance will increase the number of T1DM patients who present in the A&E department and the use the new diabetes technologies in clinical practice. In addition, hybrid closed-loop (HCL) systems which integrate CGM and insulin pumps to automate insulin delivery are also being increasingly used.

Aim: We undertook a single-center qualitative study to explore the knowledge, attitudes, and perceptions of A&E doctors around the new diabetes technologies such as CGM, pumps and hybrid-closed loop systems in order to identify specific areas that could be improved.

Methods: We conducted semi-structured interviews with 16 doctors working in A&E department. The interviews were recorded and transcribed and thematic analysis methodology was used to analyse the data.

Results: The vast majority of doctors (87.5 %, 14/16) had encountered T1DM patients with either a CGM, pump or and HCL system. 87.5% described their knowledge around them as insufficient, and 94% (15/16) rated their confidence as extremely low. Other common emotions around the new technologies were

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Table 1. Doctor's emotions around the new diabetes technologies.

Unconfident	15/16 93.75%
Patient are more knowledgeable around the devices	11/16 68.75%
Can offer minimum input in management	7/16 43.75%
Anxious	7/16 43.75%
No stress	6/16 37.5%
Avoid interaction with the device	4/16 25%
Uncomfortable	4/16 25%
Fear of looking inadequate to the patient	3/16 18.75%
Worry of making mistake	3/16 18.75%

fear and anxiety (Table 1). All doctors (16/16) stated that further training around new diabetes technologies would be welcomed as it would improve their confidence (68.75%,11/16) and improve patient care (87.5%, 14/16). The most common areas of interest mentioned are the need for education surrounding the principles of function of the devices, troubleshooting and how to clinically manage common patient presentations.

Conclusions: We recommend that appropriate educational training programs and modules be implemented to support A&E doctors and staff in managing T1DM patients presenting with new diabetes technologies.

P1-439

Determinants And Characteristics Of Insulin Dose Requirements In Children And Adolescent With New-Onset Type 1 Diabetes: Insights From The INSENODIAB Study

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Aims: In children with new-onset type 1 diabetes mellitus (T1D), insulin dose regimens vary substantially. According to current ISPAD recommendations, the initial total daily dose (TDD) should range from 0.7 to 1.0 IU/kg BW/day. Adjusting TDD to achieve normal blood glucose concentration can take several days. The primary objectives of our INSENODIAB (INsulin SEnsitivity in New Onset type 1 DIABetes) study were to assess how patient characteristics influence insulin dose requirements in children and adolescents with new-onset T1D and to establish a predictive model of their recommended TDD. The second objective was to evaluate potential correlations between insulin dose requirements and patient outcomes at 3 and 12 months after diagnosis.

Methods: INSENODIAB study is composed of two distinct cohorts: rINSENODIAB (retrospective) and pINSENODIAB (prospective). Chart review was conducted for children (6 months-18 years) admitted for new-onset T1D between 2013 and 2020. Descriptive statistics were computed for demographics, clinical and paraclinical data. Multivariable linear regression was performed using all baseline variables from admission, with a 5% nominal Type I error. Goodness of fit was characterized by the adjusted R-square and the Pearson correlation between the observed and predicted TDD. The model was then applied on pINSENODIAB for robustness assessment.

Results: Complete clinical records were available for 103 patients in rINSENODIAB and 80 patients in pINSENODIAB with a median age of 9.2 years old (IQR 6.9) and 10.6 years old (IQR 5.6) respectively. Median TDD was 1.1 IU/kg BW/day (IQR 0.5). Using a multivariable analysis, we computed a predictive model of optimal TDD as such: (TDD (IU/d) = [0,09 x Age2] + [0,68 x %Weight Loss] + [28,60 x Veinous pH] – [1,03 x Veinous bicarbonates] + [0,81 x Weight] – 194,63). This model was then independently validated in the multicentric pINSENODIAB cohort (R= 0.74, $p<0.05$). In our cohort, no correlation existed between TDD and glucose homeostasis markers (IDAA1C, C-peptide) at 3 and 12 months after diabetes onset. These results suggest that TDD at diagnosis mainly reflects an acute metabolic state rather than a particular patient phenotype.

Conclusions: In newly diagnosed children with T1D, the square of age, percentage of weight loss, weight, veinous pH and bicarbonates influenced the optimal insulin TDD. These results helped us develop a dosing algorithm to potentially reduce the time currently needed to stabilize glycemic control in children and adolescents with new-onset T1D as well as help to transition diabetes care to more individual treatment regimens.

P1-440

Monogenic forms of neonatal diabetes: our casuistics and evolution

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Neonatal diabetes (ND) occurs in 1/100,000-150,000 newborns with hyperglycemia in the first six months of life, requiring insulin treatment for at least two weeks, with no autoimmune basis. Two forms are described, transitory (TND) and permanent (PND). In 50% cases of TND, remission presents within the first year of life, only to relapse later before puberty in 50% of cases.

- Case 1: Newborn with sustained hyperglycemia since the third day of life, requiring insulin perfusion. His mother had been diagnosed with T1DM in severe ketoacidosis in her third month of life. Not ketosis. Negative pancreatic autoimmunity. A heterozygous pathogenic variant of exon 1 of the KCNJ11 gene (p.Arg201His, c602G>A) was detected in mother and child. At 3.8 months of life, he was switched to sulfonylurea therapy according to the GIND protocol, with current Glibenclaminda requirements of 0.08 mg/kg/day.

- Case 2: Male newborn with sustained hyperglycemia from the 4th day of life requiring insulin infusion at 0.02U/kg/hour for control. Mother diagnosed with T1DM at 9 years of age, with ketoacidosis. Grandmother diagnosed at 38 years old, on insulin therapy. Negative pancreatic autoimmunity. A heterozygous mutation of exon 21 of the ABBC8 gene (p.C24982G>c, GLy.833G>Ala) was detected in the mother, grandmother and son. The three generations were switched to sulfonylurea therapy.

Glibenclamide was suspended at 7 years of life, being reintroduced at 9 years with a current dose of 0.010 mg/kg/day.

- **Case 3:** Male newborn with persistent hyperglycemia since the first day of life, his mother was diagnosed with gestational diabetes. Small for gestational age. Negative pancreatic autoimmunity. Uniparental Unidisomia 6q24 was detected. Insulin therapy was required at a dose of 0.5UI/kg/day. Treatment with glibenclamide was started, but the patient refused it after 2 years. At 7.5 years occasional hyperglycemia, at 8 years already maintained.
- **Case 4:** 6-month-old infant admitted for nocturia. healthy parents. Normal neonatal anthropometry. Glucose 250 mg/dl, HbA1c 11%. Insulin 0.6 mIU/ml, C-Peptide 0.58ng/dl. Negative pancreatic autoimmunity. A heterozygous pathogenic variant is detected in exon 2 of the INS gene (p.gly32Ser,c.94G>A). Insulin therapy is started, which is currently maintained at 0.8-1 IU/kg/day.

Conclusions: We must request a genetic study for patients diagnosed with diabetes in the first six months of life, whatever their current age, in order to identify its etiology and a possible switch to Sulfonylureas, improving their metabolic profile and quality of life.

P1-441

A Case Series of Two Adolescents with HNF1B MODY and Multisystem Disorders

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Introduction: *HNF1B* gene (OMIM*189907) encodes the transcription factor HNF1B, which is expressed early in embryogenesis, controls gene expression and is involved in multiple tissue and organ development. Mutations of *HNF1B* account for a complex disorder with multisystemic manifestations (Renal Cysts and Diabetes syndrome, OMIM #137920). Congenital urinary tract abnormalities and HNF1B MODY, a rare cause of diabetes mellitus (DM) (≤5% of MODY cases), are key phenotypic features. HNF1B MODY is a consequence of β-cell dysfunction in a setting of pancreatic hypoplasia and hepatic insulin resistance. Inheritance is autosomal dominant, with a high rate of *de novo* deletions (50%). This study aims to compare the cases of two adolescents diagnosed with HNF1B MODY with multisystem involvement.

Patients And Methods: The first patient was a 16-year-old adolescent from an immigrant shelter with family history of diabetes, who was hospitalized for diabetic ketoacidosis and was initially diagnosed with DM. Investigations revealed HbA1C:15.3%, normal c-peptide concentration, negative T1DM autoantibodies, impaired renal and hepatic function, hypomagnesemia, and dyslipidemia. Ultrasonography showed an atrophic pancreas and renal cysts. The second patient, a 14.3-year-old adolescent with a personal history of nephrectomy due to polycystic kidney, was investigated because of hyperglycemia. The OGTT was diagnostic of DM alongside with HbA1C:5.5%, borderline c-peptide concentration and negative T1DM autoantibodies and hypomagnesemia, hypertransaminasemia, hyperparathyroidism, and hyperuricemia. Imaging tests showed pancreatic hypoplasia and steatosis, hepatic fibrosis, and non-communicating hydrocele with cystic formation of the epididymis and normal bone density.

Results: The above phenotypical findings suggested HNF1B MODY. DNA was isolated from peripheral blood and genetic testing was undertaken. Sanger sequencing *HNF1B* gene did not reveal any single nucleotide variant and MLPA revealed heterozygous deletion of *HNF1B* gene in both patients. The first patient was treated with subcutaneous insulin but showed poor diabetic control and was lost to follow-up two years later. In the second case, an expectant management approach was adopted, including follow-up by a multidisciplinary team, lifestyle intervention and DM education, which led to glucose control at 12 months, postponed the need for insulin treatment and prevented the onset of diabetic ketoacidosis.

Conclusions: HNF1B MODY presents a heterogeneous and broad phenotype with multisystemic manifestations (extra-pancreatic and/or exocrine pancreas). The different diagnostic context of the two patients highlights the socioeconomic differences in access to preventive medicine and health services. These patients benefit from early diagnosis and require comprehensive follow-up to prevent and manage complications and comorbidities.

P1-442

Identification of GCK-MODY in case of neonatal hyperglycemia

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Neonatal Diabetes mellitus (NDM) is a rare genetic disease. In this report, we presented a case of NDM due to mutation in GCK gene. A male baby born to a non-consanguineous parent at 42 weeks of gestation with a birth weight of 3.2 kg. The mother was diagnosed with gestational diabetes; no special treatment was given. The first episode of hyperglycemia was registered at the age of 13 days at hospitalization due to bronchitis /blood glucose -6.2~7.9 mmol/l. Due to mild hyperglycemia no treatment was given. A regular monitoring of glycemia until 6 months of age, with values ranging from 5.0-6.2 mmol/l FBG and 5.2-9.7 mmol/l PBG, HbA1c 6.2 %. At 3 months of age, he became ill with COVID-19 and was hospitalized. Episodes of mild hyperglycemia were also recorded during that period.

At this time, the child was referred to a hospital for diagnosis and choice of treatment tactics. During hospitalization, clinical and laboratory tests were performed, as well as glycemic monitoring, in which the increase in FBG did not exceed the values of 6.2 mmol/l, and PBG 8.2 mmol/l, C peptide with normal range. There was no special treatment given to the child.

Sanger sequencing of GCK was performed, which revealed a heterozygous GCK nonsense mutation (c.1183G>T (p.E395*)), which was also present in her mother. Heterozygous inactivating mutations in the gene encoding the glucose sensing enzyme glucokinase are not rare and result in partial glucokinase deficiency. This causes mild hyperglycemia often diagnosed incidentally in adulthood as maturity-onset diabetes of the young (MODY). The degree of hyperglycemia is uniform irrespective of mutation type, and treatment of hyperglycemia is not required, as it does not result in the micro- or macrovascular complications seen with type 1 and type 2 diabetes. In this case GCK-MODY diagnosed in cases referred for genetic testing for suspected NDM, we have shown that neonatal hyperglycemia is an incidental finding, does not require treatment and follows a benign course in childhood and the same time this report contains the first description on GCK mutations in Armenian patients with non-consanguineous parents.

P1-443

To study the prognostic significance of the molecule intercell adhesion type 1 (ICAM1 – intercellularadhesion molecule type 1, CD54) and adhesion moleculesvascular endothelium type 1 (VCAM1 - vascularcell adhesion molecule type 1, CD106) in children with type 1 diabetes mellitus after COVID 19 infection

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Abstract: The study was aimed at assessing the relationship between increased titers of intercellular adhesion molecules ICAM VCAM in order to assess the risk of developing vascular lesions in children with type 1 diabetes

Introduction: COVID-19 induces a systemic inflammatory response, including dysregulation and misexpression of many inflammatory cytokines [1]. Inflammatory cell recruitment and activation depends on the expression of many classes of inflammatory mediators such as cytokines (interleukin [IL]-1, IL-6, and IL-18), chemokines (fractalkin [FKN]), and adhesion molecules. (intercellular adhesion molecule 1 [ICAM-1)] and vascular cell adhesion molecule-1 [VCAM-1]) [2].

The aim of the study: To study the level of ICAM and VCAM in the blood serum of children with type 1 Diabetes mellitus after a Covid infection.

Research Methods: The titers of ICAM and VCAM in blood serum were determined by enzyme immunoassay in 60 children with type 1 Diabetes mellitus who had Covid infection.

Reultats: 60 children with type 1 diabetes mellitus who had COVID infection were examined. In 75.9% of children, covid was asymptomatic. It was possible to identify such children by interviewing and collecting anamnesis. They had an outbreak in their family. The titers of antibodies to COVID in parents and patients are increased. The titers of antibodies to SARS CoV were 559.7 ±117.9 (norm >1.0). In the blood serum, the ICAM titer was 45.9 ± 3.9 at the norm (0.84 – 8.45 ng/ml), the VCAM titer was 665.1 ± 120.1 (5.08 – 47.72 ng/ml), which indicates a significant increase in these indicators.

Conclusion: Many studies have been conducted to assess the informativeness of the ICAM 1 VCAM-1 definition in various infectious pathologies. But there is little data for an increase in ICAM VCAM in children with diabetes mellitus after a covid infection. Which once again suggests the idea of further studying this phenomenon and predicting future complications.

P1-444

From human insulin to insulin analogues: what impact on the BMI of children with type 1 diabetes?

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Introduction: Despite the widely proven value of insulin analogs in the treatment of children with type 1 diabetes (T1D), pediatric studies of Increased weight gain in T1D are complicated by the age-dependency and gender-dependency of BMI, and also by a trend towards obesity in the general population.

Objective: to assess the impact of switching from Humain Insulin (HI) to insulin analogues on the BMI of children with T1D.

Patients and Methods: It was a retrospective descriptive study evaluating, in 80 children with type 1 diabetes, the impact of switching from human insulin (NPH + rapid insulin) in a twice-daily protocol to insulin analogs in the Basal-Bolus protocol on their nutritional status. Epidemiological, clinical and therapeutic parameters as well as glycemic homeostasis of each child were analyzed before and after the change of insulin therapy.

Results: At the time of switching from human insulin to insulin analogs, the mean age of the patients was 10.9 years and the mean history of diabetes was 3.7 years. The rate of compliance with the diet varied non-significantly before and after introduction of the analogs (19% vs. 21%, p=0.8). Before or after the introduction of analogs, the majority of patients did not practice sports regularly: 53% versus 51% (p=0.752). Glycated hemoglobin A1C decreased mainly in children who adhered to their diet (from 9.93% to 9.38% (p=0.06)) and/or practiced regular sports activity (from 10.40% to 8.61% (p=0.043)). The mean BMI was 18.04% for a mean duration of human insulin use of 3.7 years. It had significantly increased to 19.20% after a mean duration of 1.83 years of analogs use (p=0.026). When analyzing the change in BMI we found: a decrease in the rate of obesity (9% vs. 8%; p=0.51), a decrease in malnutrition (31% vs. 15%; p=0.012) and an increase in overweight (11% vs. 24%; p=0.038). The age distribution of BMI did not change after introduction of the analogs. The rate of malnutrition was more pronounced in children aged > 10 years (p=0.001). Overweight and obesity were more prevalent in children aged 5 and 10 years (p=0.001). After switching to analogues, there was no significant change in BMI according to gender.

Conclusions: The switch from human insulin to insulin analogues has significantly increased the BMI of children with diabetes. The therapeutic education of type 1 diabetic children should encourage physical activity and compliance with the diet in order to reduce excess weight and obesity.

Fat, metabolism and obesity

P1-50

The Gut Microbiota Profile of Children with Prader–Willi Syndrome in China

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Background: Prader–Willi syndrome (PWS) is a rare genetic disorder associated with hyperphagia, and excessive weight gain. Patients with PWS are at elevated risk of developing morbid obesity and associated life-threatening complications. Although gut microbiota has been suggested to play a role in disease phenotypes, little is known about its composition and how it relates to hyperphagia.

Objective: The aim of this study was to characterize the gut bacterial and fungal communities of children with PWS, and to understand the role of the microbiome in the course and outcome of hyperphagia, obesity, and metabolic deterioration in PWS.

Methods: We conducted a case-control study with 29 children with genetic diagnosis of Prader–Willi syndrome and 28 age-, sex-, and body mass index-matched controls. The subjects were metabolically characterized and we obtained fecal samples to assess microbiota composition by 16S rRNA sequencing.

Results: The composition of the fecal microbiota in children with PWS differed from controls. Principal coordinate analysis (PCoA) showed a significant difference in the microbial community structure between the two groups. At the phylum level, the PWS group was characterized by a significantly lower abundance of Firmicutes and higher abundance of Actinobacteriota and Proteobacteria than in the control group. At the genus level, dysbiosis in PWS was characterized by a decrease in many butyrate-producing genera within Firmicutes, including Faecalibacterium, Blautia, Agathobacter, Lachnospira, and Prevotella, and an expansion of genera such as Streptococcus, Escherichia-Shigella, Klebsiella. Random forest analysis showed PWS-related specific gut microbiota profile has high predictive accuracy for this disorder with area under the curve (AUC) values of 0.9. The PICRUST functional prediction results revealed overall down-regulation of metabolic pathways and reduced capacity for complex carbohydrate metabolism in PWS group of gut microbiota.

Conclusions: The gut microbiota of children with PWS differs from matched controls. Microbial taxa linked to butyrate production and intestinal mucus metabolism are identified as putative mediators of metabolic regulation. Future studies should explore the effect of metabolic regulation with probiotics intervention on the degree of hyperphagia, obesity, insulin sensitivity and lipid metabolism.

P1-51

GLP1 agonists improve glycaemic dysregulation, satiety levels and quality of life in adolescents with obesity

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Introduction: GLP-1 receptor agonists (GLP1A) have been shown to be effective in achieving weight loss in adolescents with obesity and improve glycaemic control in type 2 diabetes mellitus (T2DM). We aimed to investigate the glycaemic alterations and satiety levels in patients treated with the GLP1A, liraglutide. To the best of our knowledge, this is the first study of its kind.

Methods: In total, 22 patients managed in a tier-3 multidisciplinary weight management service completed 3-months of liraglutide treatment in addition to lifestyle modification (mean dose: 2.4mg; range 1.2-3). Continuous glucose monitoring (CGM) was undertaken at baseline and at 3-months for 15 patients. PedsQL 4.0 Generic Core Scales and three-factor eating (TFEQ-R18) questionnaires to assess quality of life (QoL) and hunger, respectively, were completed.

Results: The mean age was 14.46 years (range: 12-16.7) and 63.6% (14/22) were female. A significant reduction in weight (-2.94kg; 95%CI 1.4-4.74; p<0.05), BMI (-1.44kg/m^2; 95%CI 0.68-2.21; p<0.05), BMI SDS (-0.10; 95%CI 0.04-0.16; p<0.05) and body fat percentage was observed [Table 1].

CGM revealed improvements in the mean glucose levels and the percentage time in range increased from 77.96% to 87.16%. The percentage time above 10mmol/L reduced from 5.26% to 1.86%. Both child and parent reported QoL were shown to increase. The TFEQ-R18 showed an improvement in cognitive restraint, emotional eating and uncontrolled eating, with the latter being statistically significant (-9.79; 95% CI 2.37-17.20; p<0.05) [Table 1].

Conclusion: The results from our study show for the first time that GLP1A therapy improves glycaemic status and satiety levels, along with improvements in anthropometric measurements and QoL in CYP with obesity. The improvement in glycaemic dysregulation is promising and demonstrates the potential to prevent long-term glucose complications including the development of T2DM.

Table 1. Measurements obtained at baseline and 3-months post liraglutide treatment

Measurement	Baseline mean (SD)	3-months mean (SD)
Weight kg	123.18 (±14.44)	120.24 (±15.21)*
BMI kg/m^2	44.85 (±6.66)	43.41 (±6.85)*
BMI SDS	3.76 (±0.41)	3.67 (±0.47)*
Body Fat Percentage	52.90 (±10.20)	50.88 (±9.68)
Average Glucose mmol/L	6.74 (±1.18)	6.18 (±0.89)*
% Time in Range [3.9-7.8mmol/L]	77.96 (±27.55)	87.16 (±14.70)
% Time >7.8mmol/L	21.22 (±27.97)	11.36 (±15.42)
%Time >10mmol/L	5.26 (±10.82)	1.86 (±4.09)
Child-reported Total Score [PedsQL]	48.38/100 (±25.04)	53.26/100 (±25.96)
Parent-reported Total Score [PedsQL]	40.64/100 (±23.17)	41.16/100 (±18.64)
Uncontrolled Eating [TFEQ-r18]	48.53/100 (±26.08)	38.75/100 (±28.37)*
Cognitive Restraint [TFEQ-r18]	40.18/100 (±18.60)	41.88/100 (±18.23)
Emotional Eating [TFEQ-r18]	58.98/100 (±22.42)	48.72/100 (±30.62)

*statistically significant ($p<0.05$)

P1-52

Effects of Relaxation of COVID-19 restriction measurements on glucose and insulin metabolism in overweight and obesity youth

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Background: COVID-19 restriction measurements have determined profound alterations in glucose and insulin metabolism in children with overweight and obesity. However, to date few data have explored the effects of the relaxation of restrictions in the pediatric population. Thus, we compared anthropometric and OGTT data in children with overweight and obesity during the two years after (2021-2023) compared to the two years during (2020-2021) and before (2018-2019) COVID-19 pandemic.

Subjects and Methods: Data from 266 children with obesity and overweight were retrieved and clustered into three groups: pre-COVID-19 group (103 children), COVID-19 group (78 children), post-COVID-19 children (85 children). Differences in anthropometric measurements and fasting and post-load glucose/insulin metabolism were evaluated across the three groups.

Results: No difference in terms of age, puberty and gender was documented across the three groups. In contrast, Waist Circumference (WC) was different across the three groups showing significantly higher values in COVID-19 group compared the the other two groups, while no significant differences were documented between the lastest groups. Similarly, fasting glycaemia and insulin values, indexes of Insulin resistance as well as glucose and insulin excursions during OGTT were significantly different across the three groups having the COVID-19 group significantly higher values, while no differences were documented between the pre-COVID-19 and post-COVID-19 groups.

Conclusions: Relaxation of Covid-19 restriction measurements in children with overweight and obesity during the two years after pandemic have induced positive effects on anthropometric parameters and insulin sensitivity indices and glucose/insulin metabolimsm, reaching values documented in the pre-COVID-19 pandemic.

P1-53

First results from the ongoing Med4Youth European study: comparing Mediterranean diet with a Low-Fat Diet for adolescents with obesity

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Obesity is increasing, and the related complications are well known. Clinical Trials related with specific diets are currently lacking in paediatrics. There is an increasing interest in Mediterranean diet (MD). The Med4Youth European study* has enrolled 240, 13- to 16-year-old subjects with a BMI above the 90th percentile(WHO curves) in a multicenter randomized controlled trial (Italy, Spain and Portugal) to evaluate the effects of MD. We present the data relative to the 80 subjects enrolled in Parma, Italy, that were randomized to receive a MD or a low-fat diet (LFD) for 8 months.

Dietary adherence, food diaries, physical activity, sociodemographic and quality-of-life questionnaires were used. Anthropometric, biochemical parameters, fat mass, free-fat mass and body water percentage were evaluated using bioelectrical impedance at baseline, at 2, 4 and 8 months on diet. Moreover, the patients had the opportunity to download an app through which they could keep in touch with healthcare personnel. Patients in the MD group received specific free food (bread, hummus, pomegranate juice, olive oil).

Forty patients were included in each study group. During the initial 6 months of the trial, mostly after 1 and 4 months, 16 subjects dropped out in each group. Therefore, the data presented are relative to 48 subjects.

After two months on diet, we observed a significant lower systolic blood pressure (SBP;$p=0.006$) in the MD group, and a higher pulse rate ($p=0.041$) in the LFD group suggesting that fitness worsened in this latter group. After 4 months, the anthropometric and biochemical data were not significantly different between the 2 groups. The children on the MD decreased their weight by 2.5%, BMI by 5.4%, Hip circumference(HC) by 2.4% with respect to measurements at baseline, whereas the subjects on the LFD presented a small increase in weight, BMI and HC. We observed a 10% decrease in the TG/HDL-C ratio in both groups. A reduction in fat mass, and an increase in fat-free mass were observed in the subjects on the MD only, although not significant, whereas a reduction in body water percentage was very clear(p=0.000). Multiple regression analyses showed that MD had a positive and significant effect on HC, waist circumference/HC ratio, SBP, and on Diastolic Blood Pressure. The 8-month follow-ups are ongoing.

In conclusion, MD was more effective on BMI, body water percentage, fat distribution, and biomarkers of cardiometabolic risk compared with LFD during the first months on diet.

P1-54

Early corneal nerve fiber regeneration in children with obesity and impaired glucose tolerance treated with the GLP-1 agonist Liraglutide

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Background: Glucagon-like peptide-1 receptor (GLP-1R) agonists are approved for the treatment of T2DM and obesity and high dose liraglutide is FDA approved for chronic weight management in pediatric patients aged 12 and older who are obese. GLP-1R may also have a beneficial effect on the central and peripheral nervous system. Corneal Confocal Microscopy (CCM) has been used to show early nerve fiber regeneration in adults with obesity with and without diabetes.

Methods: Five obese children aged 14.2±1.9 years, weighing 101.86±7.83kg treated with Liraglutide 3.0mg daily underwent CCM to quantify corneal nerve fiber density (CNFD), branch density (CNBD) and length (CNFL) over 3 months.

Results: Despite no change in weight (101.86±7.83 vs. 103.28±7.26, P=0.14) or body fat percent (51.32±4.43 vs. 48.46±2.5, P=0.31), CNFD (24.37±2.72 vs. 30.29±4.1, P=0.017) and CNFL (15.75±2.88 vs. 17.91±1.35, P=0.046) improved significantly with no change in CNBD (29.17±13.23 vs. 28.72±7.02, P=0.944) over 3 months of Liraglutide treatment.

Conclusion: Corneal confocal microscopy identifies early corneal nerve regeneration after 3 months of Liraglutide treatment in obese children without diabetes. Liraglutide may induce nerve regeneration, independent of weight loss.

P1-55

Association between serum uric acid and blood pressure in children and adolescents: A systematic review-meta regression

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Background: Hyperuricaemia has been associated with increased risk of metabolic syndrome in adults and children. Elevation in serum uric acid (SUA) is hypothesized to be a critical initiator of the development of essential hypertension. The exact relationship between SUA and blood pressure (BP) has not been established in the pediatric population. We conducted a systematic review to evaluate the association between SUA and BP in well, obese/overweight and hypertensive children and adolescents.

Methodology: A PRISMA-compliant systematic review of major databases (Pubmed, MEDLINE, Embase and Cochrane) was conducted using the key concepts "uric acid", "blood pressure" and "paediatrics". Articles were selected based on predefined criteria. Quality appraisal of articles was done using JBI critical appraisal tools. Data extracted were categorized into well, obese/overweight or hypertensive cohorts. Meta-regression was conducted for studies where primary numerical data on SUA and BP were reported.

Results: This systematic review identified 1203 articles, where 68 articles comprising 67,620 patients fulfilled inclusion and exclusion criteria. In well children (n=58,180), 36 of 42 studies showed a significant association between SUA-BP. In obese/overweight children (n=7,566), 15 of 20 studies demonstrated significant associations between SUA-BP while 12 of 14 studies showed a positive association between SUA-BP in children with hypertension (n=1,874). The meta-regression analysis conducted included data from well (23 studies), obese/overweight (11 studies) and hypertensive (8 studies) cohorts. A significant association between SUA and diastolic BP (DBP) was found only in the hypertensive cohort, with beta coefficient of 15.6 (95% confidence interval 8.2 – 23.0, p-value<0.005), even after adjusting for age. There was no significant association between SUA and systolic BP in the same cohort. In addition, there was no association between SUA-SBP or SUA-DBP in well children, obese children or when all cohorts were combined in the meta-regression, though data for this analysis only accounted for 35 of the 68 studies included.

Conclusion: Positive associations between SUA and BP have been reported in many studies involving well, obese and hypertensive children. When available primary data from a subset of these studies were analyzed in a meta-regression, a clear association between SUA-DBP was found only in children with hypertension. Large multinational longitudinal studies may be required to clearly establish the SUA-BP relationship for well, obese and hypertensive paediatric cohorts. This would allow specific strategies targeting SUA control in the prevention and treatment of hypertension in groups in which SUA confers a higher risk of hypertension.

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P1-56

Lipoma slice cultures as a new model to examine the effects of PI3K inhibitors on lipid accumulation

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Introduction: PTEN hamartoma tumor syndrome (PHTS) is a rare genetic disorder caused by germline mutations in the tumor suppressor gene Phosphatase and tensin homologue (PTEN), a negative regulator of the phosphoinositide-3 kinase (PI3K)/AKT/mechanistic target of rapamycin (mTOR) pathway. Children with PHTS frequently develop adipose tissue overgrowth, so called lipomas that can lead to loss of organ function due to displacing lipoma growth. Currently, except for surgical resection, no systemic therapy exists. We aimed to establish an ex vivo, Pten deficient lipoma slice culture model as a platform to study and compare the efficiency of different PI3K inhibitors to counteract proliferation and lipid accumulation.

Methods: Lipoma tissue and control epigonadal white adipose tissue (WAT) from mice with conditional Pten and retinoblastoma (Rb) knockout was cultivated on air-liquid interface membranes. After 72 hours of treatment slices were fixed, H&E stained and analyzed using automatic image analysis or frozen for measurement of gene expression and determination of PI3K pathway activation via Western blotting.

Results: We found excellent tissue preservation and no impairment of cell viability after 72h of slice culture. After treatment with the pan-PI3K inhibitor wortmannin we detected a decrease of adipocyte size in both lipoma and control WAT slices. Interestingly, the PIK3CA-specific inhibitor alpelisib showed opposite effects in lipoma and control tissue, with bigger adipocytes in lipoma, and smaller ones in epigonadal WAT. The proliferation marker Pcna was significantly downregulated both in wortmannin- and alpelisib-treated lipoma tissue (wortmannin: by 0.23fold, p=0.02, n=8, alpelisib: by 0.51fold, p=0.0001, n=8). In contrast to wortmannin, alpelisib incubation lead to a significant downregulation of fibrosis marker Tgfβ (by 0.59fold, p=0.0004, n=6). The adipogenic transcription factor Pparγ was downregulated in lipoma, but not in control adipose tissue after alpelisib incubation, but not after incubation with wortmannin, indicating a differential effect on adipocyte differentiation. Interestingly, we observed a significant upregulation of glucose transporter Glut1 after treatment with alpelisib (5.39fold, p = 0.0043, n=7), and wortmannin (0.72fold, p=0.046, n=7). On the protein level, we detected a decrease of AKT phosphorylation after wortmannin and alpelisib treatment. We did not see consistent differences between lipoma and control slices regarding the effect of inhibitors on AKT pathway activation.

Conclusion: We established an ex vivo model for the investigation of inhibitor efficacy against lipoma development. Incubation with PI3K pathway inhibitors did affect adipocyte size, gene expression and PI3K pathway activation both in lipoma and control tissue.

P1-57

Trends in prevalence of overweight, obesity and severe obesity among Norwegian children from 2010 to 2022

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Aim: Data on weight status are essential to guide the development of preventive measures, which can reduce adverse consequences for health. The aim of this study was to estimate trends, from 2010 to 2022, in the prevalence of overweight, obesity and severe obesity, using the International Obesity Task Force cut-off values. Weight trends were explored in children between 2 and 14 years in the municipality of Bergen, Norway.

Methods: This study had a repeated cross-sectional design. Data on weight and length were obtained retrospectively for calculation of BMI from standardised electronic child health and school health records. Trends in the proportion of children above IOTF25, 30 and 35 were analysed using Chi-square test for trend and linear regression, separately for girls and boys at scheduled contacts at 2, 4, 6, 8 and 13 years.

Results: A total of 180 648 BMI measurements from 77970 children were included. The participation rate was approximately 90% in preschool children and 80% in schoolchildren. The overall prevalence of overweight and obesity (IOTF≥25) increased from 9.8% in 2-year-old children to 19.2% in 13-year olds, that of obesity and severe obesity from 1.1% to 3.7% and 0.2 to 0.6% respectively. There was a significant increase in the prevalence above IOTF25 in girls for age groups 2 and 8, and a decrease in the prevalence for 13-year-old girls through the study period. In boys, there was a significant increase in the prevalence above IOTF25 for 8-year-old boys, and a decrease in the prevalence for the 13-year-old boys.

Conclusion: The prevalence of overweight and obesity in preschool and school-aged girls increased between 2010 to 2022, and decreased for the adolescent girls. Whereas for boys, the prevalence was stable in the preschool children but increased for the 8-year-old boys. Similar to girls, the prevalence decreased in the adolescent boys.

P1-58

Neck circumference and metabolic score before and after long-term impact of a lifestyle intervention in patients with abdominal obesity

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AIM: To assess and follow-up neck circumference and its relationship with a metabolic score in patients with abdominal obesity after a lifestyle intervention.

Patients, Material and Methods: 122 children and adolescents with abdominal obesity, aged 7 to 16 years, were included in a control randomized intervention study (NCT031472). Abdominal obesity was diagnosed using the waist circumference. The intervention included an intensive phase during 2 months and follow-up at 12 and 24 months. Participants were divided in two groups: intervention and usual care. Intervention group was treated with hypocaloric Mediterranean diet and the usual care group with the standard recommendations from Community Nutrition Spanish Society, 2007. Both groups were advised to increase in 200 minutes per week their moderate-vigorous physical activity. Anthropometric parameters measured were: weight, height, body mass index (BMI), neck, waist, and hip circumferences, fat mass and fat-free mass, blood pressure was also determined. Biochemical parameters determined were: glucose, insulin, leptin, cholesterol and triglycerides. A metabolic syndrome score was calculated using the following formula: (2xwaist)/height + (glucose/5.6)+triglycerides/1.7 + (systolicBP/130)-HDL/1.02 (glucose, triglycerides and HDL in mmol/L).

Results: At onset, most of anthropometric and biochemical parameters were similar in both groups, except for glucose and leptin. Usual care group (n=30) had higher both glucose and leptin levels, than intervention group (n=84).

Neck circumference significantly decreased (p<0.001) at 2 and 24 months in control group and at 2 months in the intervention group. The metabolic score improved significantly at 2 and 12 months in both groups. There were not significant differences between both groups. There was a highly significant association between the metabolic score and neck, waist and hip circumference (p<0.001).

The decrease in both BMI-SDS and waist to hip ratio (WHR) was statistically significant at 2, 12 and 24 months in both groups. In the intervention group, fat mass percentage significantly decreased, at 2, 12 and 24 months; and at 2 and 12 months in the usual care group. Lean mass (Kg) significantly increased at 12 months.

Conclusions: In this intervention study, BMI-SDS, body composition improved significantly, likewise the metabolic score. All these favourable changes persisted at 12 and 24 months follow-up, in both groups, without finding relevant differences between them. The neck circumference was the parameter, which showed a higher statistically significant association with the metabolic score. Therefore, the neck circumference could be used as an indicator of metabolic risk in patients with obesity.

P1-59

Diagnostic value of soluble LEPR levels in the serum of patients with disease-causing biallelic *LEPR* variants

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Introduction: The soluble leptin receptor (sLR) is the main binding protein of leptin in the serum. It reflects the amount of membrane-bound leptin receptors (LEPR) as the sLR is produced by proteolytic cleavage of the extracellular domain of membrane-bound LEPR. Low sLR but high leptin levels were measured in patients with severe obesity. In patients with monogenic obesity caused by biallelic *LEPR* variants, sLR levels were found to be either undetectable or extremely high, leading to high circulating leptin levels. The aim of this analysis was to investigate whether a disease-causing *LEPR* variant results in low or high sLR levels in patients with biallelic *LEPR* variants.

Methods: 13 patients with disease-causing biallelic *LEPR* variants presented to our outpatient clinic were included. SLR levels were measured using the Enzyme-linked Immunosorbent Assay (kit R07, Mediagnost, Reutlingen, Germany), which is a Sandwich-Assay using two specific high-affinity antibodies against the sLR in the serum. Anthropometric and laboratory parameters such as lipids, liver enzymes, parameters of glucose metabolism, thyroid hormones, sex hormones, growth hormones, bioactive and total leptin levels were assessed at the first visit to our outpatient clinic.

Results: Patients with biallelic *LEPR* variants due to frameshift or nonsense variants (n = 7) had significant lower sLR levels than patients with biallelic *LEPR* variants due to missense variants (n = 6) (0.57 ± 0.33 ng/mL versus 7.05 ± 6.87 ng/mL, p <0.05). Patients with nonsense/frameshift variants had a significant higher BMI SDS (4.57 ± 0.59 versus 3.38 ± 0.75, p <0.05), and a trend toward lower leptin SDS (-7.02 ± 6.14 versus -0.83 ± 3.91, p = 0.057) than patients with missense variants. There were no significant differences in the laboratory parameters between patients with frameshift/nonsense and missense variants. After adjusting for sex, age and BMI, patients with frameshift/nonsense variants presented significantly higher adjusted means for cholesterol (5.79 ± 0.63 mmol/L versus 2.71 ± 0.32 mmol/L, p <0.05), LDL cholesterol (4.21 ± 0.67 mmol/L versus 2.11 ± 0.34 mmol/L, p = 0.05) and TSH (4.72 ± 0.59 mIU/L versus 2.47 ± 0.3 mIU/L, p <0.05) than patients with missense variants.

Conclusion: In contrast to patients with biallelic *LEPR* variants due to missense variants, patients with frameshift or nonsense variants have extremely low sLR levels and are thus discriminable. Patients with frameshift or nonsense variants are associated with a more severe obesity phenotype than patients with missense variants. Future studies are required to verify these results.

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P1-60

Clinical usefulness of bioimpedance analysis in children and adolescents with severe obesity. Preliminary results of the Polish-German study project on severe early-onset obesity

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Aim: Childhood obesity has become extremely important issue worldwide. The aim of this study was to determine associations between data from bioimpedance analysis with the antrophometric measurements and biochemical results obtained from children and adolescents with severe obesity.

Study Population and Methods: Study group consisted of 128 children recruited in four regional reference centers including 70 girls (54.7%) and 58 boys (45.3%) aged 9-18 years with severe obesity defined as BMI>35 kg/m^2 in children aged 6-14 years and BMI>40 kg/m^2 in adolescents> 14 years. Derived parameters were: BMI 41.7 (range 35-63.8, SD=4.7), BMI Z-score 3.7 (range 2.6-6.3), WHR 0.9 (range 0.7-1.2, SD=0.1), WHtR 0.7 (range 0.6-1, SD=0.07). Blood samples levels of ALT, AST, glucose and insulin concentrations were measured in fasting. Derived HOMA IR was calculated 6.9 (range 1.6-19.1, SD=3.7). Bioimpedance measurements (performed on TANITA MC-580 M S MDD,TANITA MC-780MA-N, TANITA MC-780 P MA) provided information about fat (FM, kg) and fat-free mass (FFM, kg). Spearman's rank correlation was used to estimate described associations. The threshold of statistical significance was p=0.05.

Results: FM was positively correlated with BMI (p=0.8), WHtR (p=0.3), SBP (p=0.3) and HOMA IR (p=0.1). FFM was associated with SBP (p=0.4), BMI (p=0.3), ALT and AST (p=0.3 for both), WHR (p=0.3) and triglycerides (p=0.1). BMI was positively correlated with systolic blood pressure (SBP) (p=0.3) and HOMA IR (p=0.2). WHtR was strongly correlated with BMI (p=0.6). There was no statistically significant correlation between WHR and BMI. WHR was positively associated with the liver enzymes (p=0.4) and triglycerides (p=0.2). ALT and AST were positively associated with triglycerides (p=0.3 and p=0.2 respectively). There was a positive correlation between WHtR and SBP (p=0.2).

Conclusions: Results have shown that bioimpedance is a useful tool for determining cardiometabolic risk factors in examined cohort. Associations between FM, FFM and cardiometabolic risk factors were found to be stronger, than when only BMI was considered. Increased BMI and FM were associated with the greater risk of AH and carbohydrate metabolism disorders. Increased FFM was associated with the greater risk of AH, MAFLD and hypertriglycerydemia development. WHtR seemed to be a better indicator of severe obesity than WHR, probably due to the obesity hormones enhancing growth rate. WHR was found to be a better predictor of MAFLD and hypertriglycerydemia, while WHtR was found to be a better predictor of AH.

P1-61

Incidental Sitosterolemia on Genetic testing in Saudi Youth Presenting with Bony lesions, A Case Study

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Background: Sitosterolemia, a rare autosomal recessive defect in lipid metabolism, is caused by mutations in the transporter genes ABCG5 and ABCG8 coding receptors on the luminal surface of enterocytes. Thus, hyperabsorption of non-digestible plant sterol in tissue and blood resulting in cardiovascular (CVD) sequalae.

Here we report a case of Sitosterolaemia incidentally diagnosed on whole exome sequencing (WES) for bony lesions in a young Saudi girl with asymptomatic presentation and good response to diet restriction and Ezetimibe on one year follow up.

Case Description: A healthy 6 years old girl, referred to the endocrine service, for assessment of bony lesions and café au lait spots noted by family after minimal trauma. Clinical examination and biochemical workup for McCune Albright was negative. WES showed a missense pathogenic heterozygous variant in EXT1 (c.1019G>A) p. (Arg340His) and incidental nonsense pathogenic homozygous variant in ABCG5 (c.1336C>T) p. (Arg446*). The former causing Hereditary Multiple Exostoses, explaining the bony lesions. Patient remained clinically asymptomatic, apart from mild self-resolving skin bruises. Skin examination was normal without cutaneous manifestations of hyperlipidaemia. Initial lipid screening showed[fn1]: (TC) 5.0 mmol/L, (LDL-C) 3.69 mmol/L, (HDL-C) 1.05 mmol/L and (TG) 1.67 mmol/L. Baseline cardiovascular evaluation; including ECG, echocardiography and intimal-media thickness via cervical vascular ultrasonography was normal. Initial haematological evaluation revealed no haemolytic anaemia with normal platelet count and function. Gradually increasing LDL-C trend, reaching 5.56 mmol/L, showed response to both plant-sterol restricted diet and Ezetimibe. Cascade screening of immediate family revealed heterozygous carrier state in parents and younger siblings, a homozygous mutation in older sister who was clinically asymptomatic but started on Ezetimibe and diet control for elevated LDL-C.

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Conclusion: Sitosterolaemia has variable expressivity, ranging from nearly asymptomatic to severe hypercholesterolemia, accelerating atherosclerosis and premature cardiac mortality risk. Diagnosis is challenging and should be confirmed by genetic testing. Dietary restriction and once-daily Ezetimibe medication were effective in our case. Monitoring plant sterol levels pre and post intervention would have been helpful, likely reducing CVD risk progression, if it had been readily available. Given that proper management can improve disease's prognosis, early detection and timely intervention are crucial.

Note: tables and figures will be provided in the poster.

P1-62

Effect of metreleptin on metabolic changes in patient with congenital generalized lipodystrophy

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Background: Congenital generalized lipodystrophy is a rare and serious genetic disorder that has a profound impact on the quality of life of individuals. The worldwide prevalence of disease is estimated at 1 in 12 million people. It causes significant metabolic abnormalities and may reduce the life expectancy of children and young adults due to the late diagnosis and absence of adequate treatment. Below, we report the case of an 8-year-old boy with Berardinelli-Seip syndrome in Kazakhstan and the results of using metreleptin replacement therapy, especially its positive effect on the lipid profile.

Clinical Case: The boy was admitted to the local hospital at 4 months of age with complaints of high growth but not weight gain, excessive appetite and sweating, skin hyperpigmentation, irritability, abdominal distention, absence of total subcutaneous body fat. At 5 months of age the genomic DNA was isolated from his blood, and full-exome sequencing revealed a homozygous mutation c. 823 C>T (p. R 275 *) on the 8 exons of the BSCL 2 gene. The nonsense mutation found confirms Berardinelli-Seip syndrome (OMIM: 269700). Objectively, he mainly had height SDS +2,75, severe features of acanthosis nigricans, a total absence of subcutaneous fat throughout the body, acromegaloid facial features, and hepatosplenonephromegaly.

Metreleptin was initiated in November 2021 as a pathogenetic therapy due to leptin deficiency. Dosage: 0.06 mg/kg/day-1.8 mg subcutaneously.

Conclusion: Metreleptin is the first drug available for the pathogenetic treatment of leptin deficiencies in generalized lipodystrophy. Follow-up after the initiation of the treatment reveals that metreleptin is more effective than supportive symptomatic treatment at significantly lowering HbA1c, triglyceride, and liver enzyme levels. The rarity of the long-term effect of such a specific treatment is uncertain, the findings in this study illustrate that metreleptin has metabolic and clinical benefits, improves mortality, reduces the risk of developing diabetes mellitus, and cardiovascular risks by reducing triglyceride levels and improving insulin sensitivity.

Table 1. Laboratory test results

	19.10.2016	21.12.2017	08.11.2018	09.02.2021	09.11.2021	19.11.2021	05.12.2022
Total cholesterol(mmol/l)	2,69	3,02	3,51	4,52	3,95	3,75	3,84
LDL (mmol/l)	1,34	1,57	2,04	1,84	2,26	2,45	2,75
HDL (mmol/l)	0,29	0,43	0,62	0,59	0,69	0,77	1,01
Triglycerides(mmol/l)	5,14	6,01	5,47	9,71	9,86	2,81	1,14
Glucose (mmol/l)	4,88	4,0	5,54	10,26	6,34	3,62	5,11
HbA1c (%)	4,3	5,09	5,0	7,76	5,12	5,03	5,14
Insulin (mcME/ml)	27,65	192,4	71,78	91,16	56,04	13,71	13,62
C-peptide (ng/ml)	5,06	14,63		8,01	6,9	3,12	2,59

P1-63

The effectiveness of novel E-Health applications for the management of obesity in childhood and adolescence during the COVID-19 outbreak in Greece

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Background: The prevalence of childhood obesity has recently increased, particularly during the COVID-19 pandemic, which has led to lifestyle changes as a result of public health regulations and guidelines introduced by governments worldwide.

Objective: To investigate the effectiveness of novel e-Health applications in addressing childhood obesity prior to and during the Covid-19 outbreak.

Patients and Methods: The study was carried out as part of the four-year European project BigO (http://bigoprogram.eu, Horizon2020, No.727688). Eighty-six (n=86) overweight and obese children and adolescents (mean age±SEM: 11.82±0.25 years; 49 males, 37 females) were studied prospectively for 1 year prior to the pandemic (non-Covid-19 group, n=50) and during the pandemic (Covid-19 group, n=36). The data collection system included the BigO technology platform, which interfaces with a Smartphone and Smartwatch, and records data on diet, sleep and exercise objectively for each patient. Participants used the BigO system for 4 weeks and wore the watch for specific periods during the week. Subsequently, they entered a personalized life-style intervention program for 4 months and used the system again for 4 weeks.

Results: When determining improvement as reduction in BMI category, the program was successful in 36% in the non-Covid-19 subjects versus 58.3% in the Covid-19 group. Body Mass Index (BMI), BMI z-score, insulin resistance indices (HOMA and QUICKI), blood pressure, γ-GT and insulin concentrations decreased, and HDL concentrations increased at 12 months follow-up in both groups ($p<0.01$). The BMI z-score at 12 months was significantly lower in the Covid-19 compared with the non-Covid-19 group ($p<0.05$).

Conclusion: Our results indicate better compliance with lifestyle interventions and improved cardiometabolic risk factors in the Covid-19 group. These novel e-Health applications were effective at managing childhood obesity despite the implications and lifestyle changes owing to the Covid-19 pandemic.

P1-64

WITHDRAWN

P1-65

Natural history of corpulence in patients carrying heterozygous pathogenic variants in the five major genes of the leptin-melanocortin pathway

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Introduction: The leptin-melanocortin pathway plays a key-role in weight control. Pathogenic variants in the five major genes (LEP, LEPR, POMC, PCSK1, MC4R) are associated with early severe obesity. However, the specific associated phenotype with presence of mono-allelic variants and especially BMI trajectories are not well known.

Objective: In order to identify specific profiles, we compared BMI trajectories during the first 6 years of life in subjects carrying pathogenic mono-allelic variant in one of the five major genes of the leptin-melanocortin pathway with those of subjects either carrying bi-allelic variant or no identified variant.

Methods: We retrospectively collected anthropometric data (weight, height, BMI) from 64 subjects carrying a pathogenic mono-allelic or bi-allelic variant in at least one of the 5 major genes of the pathway (LEP (n=3), LEPR (n=22), POMC (n=9), PCSK1 (n=8), and MC4R (n=22)) and from 24 subjects in whom no variant in the same genes were identified. BMI and BMI Z-score at each age between 0 and 6 years were compared between the groups (mono-allelic (HET) or bi-allelic (HOM) or no variant (NM)).

Results: The evolution of weight of HET patients (n=30) whatever the gene (LEP, LEPR, POMC, PCSK1, MC4R) were not significantly different before the age of 6 years. Similarly, the BMI trajectory of patients with a pathogenic mono-allelic MC4R variant was comparable to patients with one mono-allelic variant in one of the four other genes (age 3 years : BMI Zscore MC4R (n=12) 4.9 SD vs other genes (n=18) 3.7 SD (NS) ; age 5 years: BMI Zscore MC4R (n=10) 6.6 SD vs other genes (n=18) 6.6 SD (NS)). Between 1 and 5 years, HOM patients (n=14) had significantly higher BMI compared to HET patients with a difference of at least 2.5 SD at each age ($p<0.01$) and earlier obesity ($p<0.01$). The evolution of BMI before 6 years of age was not significantly different between patients carrying mono-allelic variant and patients without identified variant (age 3 years: BMI ZScore HET (n=29) 4,3 SD vs NM (n=16) 3.6 SD (NS); age 5 years: BMI Zscore HET (n=27) 5,2 vs NM (n=13) 6.3 (NS)).

Conclusion: Patients carrying bi-allelic variant develop more severe obesity in the early childhood than patients carrying mono-allelic variant or no variant. The lack of specific BMI profile in patients with a mono-alllelic variant in one of the 5 major of the leptin-melanocortin pathway requires systematic genetic exploration if the BMI is > 25 kg/m^2 at 2 years.

P1-66

Leptin treatment affects adipose progenitor cells physiology

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Introduction: Leptin, an adipokine secreted mainly by adipose tissue, is a regulator of energy balance acting through central mechanisms on the hypothalamus. However, leptin has many functions regulating e.g., immune system and reproduction. Leptin exerts its biological effects through its receptor, the expression of which has been demonstrated in several tissues. There are several leptin receptor isoforms, but activation of only one of them, the long form, results in signaling pathway activation. Nevertheless, there are conflicting results about peripheral effects of leptin on adipocytes.

Aim of the Study: Our purpose was to investigate how leptin affects the physiology of adipose progenitor cells.

Methods: Experiments were conducted on adipose progenitor cells (LipPD1) incubated with recombinant leptin (0-100 nM). We assessed cell proliferation after Hoechst staining. Cell viability was studied by incubating cells with WST-1 (water-soluble tetrazolium salt). Intracellular lipid content was measured using Oil Red O and Nile Red. To examine whether exogenous leptin can reverse the effects of leptin deficiency, we used siRNA to introduce leptin knockdown. The expression of leptin and leptin receptor isoforms was studied by qPCR.

Results: Leptin and leptin receptors were present in preadipocytes and adipocytes with higher expression in differentiated cells (respectively 1.6-fold and. 2-fold change compared to. preadipocytes). Leptin treatment (10, 100 nM) in the presence of 10% FCS in the culture medium decreased preadipocyte viability (approx. 0.8-fold change vs. control group, on day 1). No effect was observed after an incubation in a medium containing 0.1% BSA or 0.1% and 1% FCS. In addition, incubation with leptin (0-100 nM) did not affect preadipocyte number (on day 1 and 7) in medium with 0.1% BSA, 0.1%, 1% and 10% FCS. Leptin treatment did not alter lipid accumulation measured on day 8 (after differentiation onset) – demonstrated by Oil Red O and Nile Red staining. However, leptin incubation (1 nM) partially reversed the decreased lipid accumulation observed after leptin knockdown (1.6-fold change compared to leptin knockdown group).

Conclusion: Leptin receptor expression occurs in preadipocytes and adipocytes, suggesting that leptin may act directly on adipose tissue. Leptin treatment affects preadipocyte physiology by lowering their viability (in culture medium with 10% FCS conditions), without impacting their expansion. Moreover, leptin does not stimulate adipocyte differentiation but can restore this process in the presence of leptin deficiency.

P1-67

Percentage of Appendicular Skeletal Muscle Mass Reference and Association with Metabolic Syndrome in Korean Adolescents

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Purpose: The association between appendicular skeletal muscle mass (ASM) and cardiometabolic risk has been emphasized. We estimated reference values of the percentage of ASM (PASM) and investigated its association with metabolic syndrome (MS) in Korean adolescents.

Methods: Data from Korea National Health and Nutrition Examination Survey performed between 2009 and 2011 was used. Tables and graphs of reference PASM were generated using 1,522 subjects (807 boys) aged 10 to 18. The relationship between PASM and each component of MS in adolescents was further analyzed in 1,174 subjects (613 boys). Moreover, the pediatric simple metabolic syndrome score (PsiMS), homeostasis model assessment of insulin resistance (HOMA-IR), and the triglyceride glucose (TyG) index were analyzed. Multivariate linear and logistic regressions adjusting for age, sex, house income, and daily energy intake were performed.

Results: In boys, PASM increased with age, but girls showed a different trend that declines with age. PsiMS, HOMA-IR, and TyG index showed inverse associations with PASM (PsiMS, β –0.105, p-value <0.001; HOMA-IR, β -0.104, p-value <0.001; TyG index, β -0.013, p-value <0.001). PASM z-score was negatively associated with obesity (aOR 0.22, 95% CI 0.17-0.30), abdominal obesity (aOR 0.27, 95% CI 0.20-0.36), hypertension (aOR 0.65, 95% CI 0.52-0.80), and elevated triglycerides (aOR 0.67, 95% CI 0.56-0.79).

Conclusions: The probability of acquiring MS and insulin resistance decreased with higher PASM values. The reference range may offer clinicians information that aid the effective management of patients. It is urged that clinicians monitor the body composition using standard reference databases.

P1-68

The association of triglyceride glucose-body mass index with transient elastography in pediatric non-alcoholic fatty liver disease

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Background: Triglyceride glucose (TyG) index combined with body mass index (BMI) were reported to be superior to TyG index alone in predicting non-alcoholic fatty liver disease (NAFLD) in youths. Transient elastography (TE) uses pulsed echo ultrasound to measure the hardness of the liver, showing excellent accuracy in the assessment of fibrosis, and is considered a useful test in NAFLD. Objects: This study aims to investigate the association between TyG-BMI and TE and to evaluate its usefulness in NAFLD.

Methods: Alanine aminotransferase (ALT) was used as the screening method for NAFLD (>26IU/L in boys and >22IU/L in girls), and US-FLI was performed on children who met these criteria. The US-FLI is a scoring system ranging 2-8 that evaluates based on intensity of liver/kidney contrast, posterior attenuation of ultrasound beam, vessel blurring, difficult visualization of gallbladder wall, difficult visualization of the diaphragm and areas of focal sparing. NAFLD is diagnosed by the minimum score ≥2. TE was used to evaluate liver fibrosis in terms of liver stiffness measurement (LSM).

Results: A total of 130 NAFLD patients (90 boys and 40 girls) included in this study, with mean age of 11.5±2.29 years. The control group consisted of a total of 28 subjects (17 boys and 11 girls) with mean age of 8.39±1.60 years. The mean TE values of the NAFLD group and the control group were 4.40±0.91 kPa and 3.77±0.29 kPa, respectively, showing a statistically significant difference ($p<0.001$). The TE was significantly correlated with AST ($r=0.322$, $p=0.001$), ALT ($r=0.330$, $p=0.001$), BMI ($r=0.330$, $p=0.001$), US-FLI ($r=0.203$, $p=0.047$), and TyG-BMI ($r=0.356$, $p<0.001$) after controlling for sex and age. Multiple linear regression analysis showed that TE were significantly associated with TyG-BMI ($\beta=0.359$, $p=0.001$) after adjusting for confounders. In the receiver operating characteristic analysis, TE showed a superior ability to detect NASH (area under the curve [AUC]=0.831, $p<0.001$) than its ability to detect NAFLD (AUC=0.738, $p<0.001$).

Conclusions: TE was significantly associated with TyG-BMI and showed better detection ability in severe NAFLD, suggesting that it could be useful in the evaluation of NASH in children and adolescents.

P1-69

Difference of nafld frequency between younger and older children with obesity

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Background: Non-alcoholic Fatty Liver Disease (NAFLD) is a frequent complication of obesity in both adults and children and there is an alarming increase in prevalence of both. Studying of risk factors for NAFLD in children and adolescents might help to select vulnerable groups to start an early intervention.

Objectives: The aim of our study was to detect the prevalence of NAFLD in pediatric obese patients (0-18.9 years, separately for groups <10 and >10 years old) and its association with age, gender, BMI, and other risk factors of NAFLD.

Methods: 697 children and adolescents with obesity (313 girls and 384 boys), with average age12.3±3.9 years and BMI SDS 4.6±2.5were included to the study. The prevalence of NAFLD was evaluated on the base of hepatic transaminases in obese individuals. Risk factors (age, gender, BMI-SDS, waist circumference, fasting glycaemia, total and HDL cholesterol, insulin resistance) were statistically calculated via t-test, Pearson correlations and multiple logistic regressions.

Results: NAFLD prevalence based on ALT was 19.5% in the whole study group. There was significantly higher prevalence of increased ALT in the group of children >10 years in comparison to children <10 years (21.4% vs. 14.5%, $p=0.004$), while the most significant increase of prevalence was in adolescents. Most important risk factors of increased ALT in children is BMI-SDS ($\Delta R2=0.054$; $p=0.001$), male gender ($\Delta R2=0.043$, $p<0.001$) and insulin resistance ($\Delta R2=0.014$, $p=0.028$) in the forward stepwise multiple logistic regression analysis.

Conclusions: Almost every 5th child with obesity has NAFLD based on the increased ALT, while the highest prevalence is in adolescents. Alarming is relatively high prevalence of NAFLD in children <10 years, that's why also in this group should be screening and management of obesity and NAFLD very important. Risk of NAFLD is higher in boys and increases with severity of obesity and presence of insulin resistance.

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P1-70

Association of Serum Uric Acid Levels with Metabolic Syndromes in Children and Young Adolescents

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Purpose: We investigated uric acid reference values and their association with cardiometabolic risk among children and adolescents using the Korea National Health and Nutrition Examination Survey (KNHANES).

Methods: A total of 2,462 participants, aged 10-18 years, from the KNHANES 2016-2018 were included.

Results: Serum uric acid (SUA) levels varied with sex and age. In male subjects, SUA levels tended to increase from 10 to 14 years of age and plateaued after 14 years of age. Moreover, the overall uric acid level in females was found to be lower than that in males; the levels tended to increase at approximately 10 to 12 years old but were relatively consistent according to age. Mean uric acid levels increased according to obesity status in both males and females. However, correlation analysis revealed that SUA levels were associated with several metabolic risks even after adjusting for obesity. The detailed metabolic syndrome (MetS) components that were observed to be associated with an increase in uric acid levels were different between males and females, but overall, high uric acid levels increased MetS risk. Additionally, a statistically significant increase in the OR for MetS and its components, such as waist circumference (WC), triglyceride (TG) levels, and low high-density lipoprotein cholesterol (HDL-C) levels, was observed.

Conclusion: SUA levels were closely associated with MetS and its components, even in non-obese subjects. Therefore, high SUA levels in children and young adolescents should be closely monitored to prevent MetS.

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P1-71

Obesity prevalence and gender incongruence – Results from a systematic literature review

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Introduction: Elevated obesity prevalence among transgender individuals compared to cisgender control groups or general population have been reported in some studies. Whether there is a higher prevalence for obesity in transfeminine and transmasculine persons at different age groups has not yet been systematically studied.

Methods: We performed a systematic literature search using Pubmed and Google Scholar. Following search terms were used "Obesity", "BMI", "Overweight" AND "Gender dysphoria", "Gender identity disorder", "Transgender*" and "Transsexual*". Inclusion criteria was that data on the proportion of participants with gender dysphoria and obesity (OB) had been reported. 1,552 records were screened (116 duplicates). 1.380 records were removed after title and abstract screening (n=898), and after full-text screening and bias risk assessment (n=482). 56 records were included in analysis. The published obesity prevalence of the study populations was extracted. Comparisons were either drawn to cisgender control groups included in the study or descriptive comparisons to general population data (World Obesity Federation). We categorized a record to have: higher, lower or similar obesity prevalence as comparative populations. In a further step, we looked whether there were differences in the reported obesity prevalence depending on gender (transmasculine (TM) versus transfeminine (TF)), treatment status (treatment-naïve), sample type (treatment-seeking, i.e. diagnosis-based versus non-treatment seeking samples (nTS), e.g. community-based and probability samples), countries of origin (USA versus Non-USA) and sample size (n>200, n>1000).

Results: 21/37 TM cohorts had a higher OB prevalence than comparative populations, in contrast to only 6/31 TF cohorts. Cohorts with mixed genders showed higher prevalence in 8/14 reports. nTS were not associated with higher OB prevalence among TM study populations. 12/16 treatment-naïve TM cohorts had higher than expected obesity rates. 11/20 youth cohorts (all genders) and 6/9 TM youth cohorts had higher OB proportions than comparative populations. The observation of higher OB prevalence in TM samples was more pronounced in cohorts with a sample size>200 (12/19) and among Non-US cohorts (9/13).

Conclusion: No differences in obesity prevalence were observed for transgender women compared to control group. Obesity is more common among transgender boys and men compared to general population data or cisgender control groups. Hormonal treatment is not likely to be the cause as reports of treatment-naïve patients already show elevated obesity rates compared to control group. Healthcare providers working with transgender men should be aware of the increased rate of obesity in this population compared to general population and incorporate appropriate management strategies into their care.

P1-72

GLP-1 analogues in therapy of obese adolescents. Early real-life experience with liraglutide treatment

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Introduction: GLP-1 analogues are promising agents for the pharmacotherapy of obesity due to their combined effect on metabolic signalization and eating behavior. The GLP-1 analog liraglutide is registered in Europe for therapy of obese adolescents aged 12-17 years since 2021. According to clinical studies, liraglutide administration leads to a mean weight loss 4.6%. We summarize early real-life experience with this novel therapy.

Patients and Methods: Nine boys were treated with liraglutide under the supervision of out-patient clinic for obesity of Department of Pediatrics, University Hospital Motol, between September 2021 and January 2023. At treatment onset, they were 12.0-16.5 years old (median 15), and had body weight 74-188 Kg (median 123) and BMI 30.7-65.9 Kg/m^2 (median 38.6). Therapy was initiated following failure of conventional treatment including behavioral and psychological intervention.

Results: After the early-phase dose escalation, the long-term daily treatment dose stabilized at 1.8-3.0 mg (median 2.4). Therapy was accompanied by nutritional and behavioral intervention. By the latest check-up following 4-15 months on therapy (median 6), BMI declined to 31.5-61.6 Kg/m^2 (median 35.6; $p<0.05$ vs. treatment onset). BMI dropped by 6.5% (median; range -12.7 to +3.0%; $p<0.05$). The current body weight ranges from 79 to 177 Kg (median 114). Therapy was discontinued in two boys due to limited success, and is ongoing in all others. Treatment related adverse events were minimal.

Conclusion: Liraglutide may contribute to stabilization or reduction of body weight and BMI in a significant proportion of severely obese adolescents, and may serve as a starting point for the further life-long obesity management. The real-life experience is mimicking the previous results from clinical studies, with a modest albeit significant positive effect on decreasing BMI, and just a few patients escaping from the treatment effect, apparently due to limited compliance.

P1-73

Insulin as a treatment modality for familial chylomicronemia syndrome in resource-limited settings- A Case series

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Introduction: Familial chylomicronemia syndrome (FCS) is an extremely rare monogenic disease with a prevalence of

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1-2:1,000,000. Defects in lipoprotein lipase (LPL) are the main cause. Recurrent acute pancreatitis is a life-threatening complication of FCS. Insulin therapy is known to be a mode of treatment for hypertriglyceridemia.

Case Series: We present four children with genetically confirmed LPL deficiency followed up in our clinic who showed favorable responses to insulin.

The first patient presented at 35 days with incidental findings of a lipemic sample. Initial triglyceride (TG) was 6531mg/dl. She had hepatosplenomegaly and was started on fenofibrate and statins with a minimum biochemical response. At 4 years and 6 months of age, she was started on subcutaneous(S/C) soluble insulin.

Patient 2 presented at 3 years with a lipemic sample (TG 668mg/dl). He was started on intermittent insulin dextrose infusion and S/C long-acting insulin 6 months later due to recurrent acute pancreatitis (RAP). After the initial response, he continued to have frequent RAP and needed plasmapheresis 4 years later.

Patient 3 presented at 7 years of age and was started on insulin-dextrose infusion followed by S/C long-acting insulin after the failure of oral drugs. She is clinically stable to date.

Patient 4 presented at 2 months with vomiting and was started on insulin infusion along with fibrates from the beginning with clinical and biochemical improvement.

Discussion and Conclusions: Cases 1, 2, and 4 had biochemical as well as clinical improvement after insulin therapy. Despite an initial response to insulin, patient 3 needed plasmapheresis.

Insulin therapy should be considered in patients with difficult to treat hypertriglyceridemia. It's equivalent in efficacy to plasmapheresis, cost-effective, and associated with fewer complications.

P1-74

A novel mutation of leptin gene in two siblings with early onset obesity

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Background: Congenital leptin deficiency is a rare cause of early-onset severe obesity. Clinical features of congenital leptin deficiency include early-onset severe obesity, marked hyperphagia, endocrine and metabolic alterations. Some patients have immune dysregulation.

Case Report: We describe two siblings from Libya referred for severe obesity. A boy (patient 1) referred at the age of 4 years and 3 months and a girl (patient 2) at the age of 2 years and 3 months. The parents were consanguineous and normal weighted. Both children started developing severe obesity at the age of 6 months, associated with food seeking behaviour, recurrent respiratory infections, sleeping disorders, psychomotor delay. Weight of patient 1 was 45.7 kg (+5.2 SDS) and height 111 cm (+1.5 SDS). Weight of patient 2 was 25 kg (+ 4.9 SDS) and height was 90 cm (+ 0.4 SDS). At physical examination severe acanthosis nigricans and brachydactyly were present. Both children showed undetectable serum concentrations of leptin. Immunological investigations documented a significant reduction in transitional B Lymphocyte and a mild deficiency of CD16+CD56+ cells. Both patients had dyslipidemia and insulin resistance. Next generation sequencing revealed a frameshift novel variant in the leptin gene located in c.150_153delCAGT causing the introduction of the premature stop codon p.Val51ProfsTer19 at the protein level.

Conclusions: A novel mutation of leptin gene causing early onset severe obesity associated with metabolic alterations and immune dysfunction was identified. Early diagnosis leptin deficiency leads replacement therapy with recombinant human leptin (metreleptin) which modifies the natural history of this condition.

P1-75

Newer anthropometric indexes predicting insulin resistance in Greek children and adolescents with overweight and obesity

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Introduction: Body mass index (BMI) and waist circumference (WC) are the main anthropometric measures of obesity. However, their inability to take into account body fat distribution raises queries for their predictive value of insulin resistance (IR) in youth.

Aim: The aim of this study is to compare BMI and WC with latest anthropometric indices in the assessment of IR in a paediatric Greek population with overweight and obesity.

Materials & Methods: One hundred and two children and adolescents (age range 2,80-14,80, mean 11,75, standard deviation 2,77 years) of Greek origin having overweight and obesity were enrolled in the study. The correlation between adiposity indexes, including body mass index (BMI), waist circumference to height ratio (WtHR) a body shape index (ABSI), body roundness index (BRI), Conicity-index (C-index) and various measures of IR, not only homeostatic assessment of insulin resistance (HOMA-IR) but also HOMA-2IR, quantitative insulin-sensitivity check index (QUICKI), fasting serum insulin (FSI), fasting plasma glucose (FPG)/FSI, and triglycerides to high density lipoprotein ratio (Trig/HDL) were investigated. Statistical analysis was performed using the IBM SPSS Statistics 27.

Results: BMI adjusted for age and sex and WC correlates similarly to many of the newer anthropometric indexes with IR as assessed by HOMA-IR and other main surrogate markers. The highest correlation with HOMA-IR, HOMA-2IR, QUICKI, FSI, FPG/FSI and Trig/HDL was recorded for BMI and WC (R=0,495 p<0,0001, R=0,494 p<0,0001, R=0,481, p<0,0001, R=-0,494 p<0,0001, R=-0,444 p<0,0001, R=0,283 p=0,004 and R=0,426 p<0,0001, R=0,424 p<0,0001, R=0,415 p<0,0001, R=-0,424 p<0,0001, R=-0,387 p<0,0001, R=0,318 p=0,001, respectively).

WtHR and BRI presented an identical degree of correlation with all of the previously mentioned IR indexes (R=0,296 p=0,003, R=0,299 p=0,002, R=0,282 p=0,005, R=-0,299 p=0,002, R=-0,267 p=0,007, R=0,259 p=0,008, respectively). On the other hand, ABSI and C-index did not correlate with any of the IR indexes.

Conclusions: BMI adjusted for age and sex and WC reserve their predictive value of IR. WtHR and BRI, more representative of body fat distribution, emerge as reliable anthropometric indexes assessing IR. However, ABSI and C-index, usually applied in adults, appear to have low clinical applicability in the pediatric population. Furthermore, except for HOMA-IR, other IR indexes were proved to be valuable. Larger studies need to further support the usage of new anthropometric and IR indexes in the pediatric population.

P1-76

Evaluation of Clinical Characteristics of Patients Diagnosed with Syndromic Obesity

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Keywords: Syndromic Obesity, Child, Genetics

Objective: Syndromic obesity is accompanied by dysmorphic findings, motor and mental retardation, and organ anomalies. In this study, we aimed to evaluate the patients who were followed up with a diagnosis of syndromic obesity in our clinic.

Materials and Methods: Demographic, clinical, and biochemical data of the patients followed up between 2003 and 2022 were analyzed retrospectively. Dysmorphic findings, organ anomalies, and obesity-related comorbidities were recorded.

Results: The study included 20 patients. Eight (40%) of them were female, and 12 (60%) were male, with a median age of 4 years (1-13.5) at presentation and 11.9 years (3-21.1) at the last follow-up. There was a family history of obesity in 25% and consanguinity between parents in 50% of patients. The median value of body mass index (BMI) SDS at presentation was 2.6 (-0.72-4.9). Fourteen (70%) patients had hyperphagia. In terms of syndrome diagnosis, Prader-Willi Syndrome (PWS), Bardet-Biedel Syndrome (BBS), and Alström Syndrome (AS) were found in 8, 6, and 1 patients, respectively. Disease-associated variants were identified in the CPE gene of 2 patients with BDV syndrome, SETD2 gene in 1 patient with Luscan-Lumish syndrome, MAGEL2 gene in 1 patient with Schaaf-Yang syndrome and SMAD4 gene in 1 patient with Mhyre syndrome.

In patients with PWS, concomitant hepatosteatosis, hypogonadism, cardiomyopathy, tricuspid insufficiency, attention deficit hyperactivity disorder (ADHD), and epilepsy were all present. Patients with BBS had retinitis pigmentosa, optic atrophy, grade 1 hydronephrosis, cholelithiasis, hepatosteatosis, and hypertension, and one patient had phenylketonuria. Patient with AS had optic atrophy, sensorineural hearing loss, hepatosteatosis, hypertension, type 2 diabetes, and hypergonadotropic hypogonadism. Two patients with variants in the CPE gene and considered as BDV syndrome both had central hypothyroidism, with one also having hypoxic-ischemic encephalopathy. The patient with Luscan-Lumish syndrome with SETD2 variant had autism. The patient with Schaaf-Yang syndrome with MAGEL2 gene variant had ADHD, type 2 diabetes mellitus, and hepatosteatosis. The patient with Mhyre syndrome with a variant in the SMAD4 gene had prococious puberty and hepatosteatosis.

Conclusions: Additional dysmorphic features should be considered for the differential diagnosis of syndromic obesity. A confirmed genetic diagnosis will offer higher-quality family counseling and more effective treatment protocols in suspected cases.

P1-77

Association between Steroid Therapy and Lipid Profiles in Children with Chronic Disease

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Background: Steroid is a standard treatment for several chronic diseases in children, such as autoimmune or rheumatology disease. However, despite its benefit, steroids have many side effects, including dyslipidemia. Dyslipidemia in childhood increases the risk of atherosclerosis development that can progress into cardiovascular disease. Dyslipidemia is diagnosed using the lipid profile of the patient. The aim of this study was to determine the association between steroid therapy (dose, duration, and type) and lipid profiles (total cholesterol, HDL, LDL, and triglyceride) in children with chronic disease.

Methods: This retrospective study included 18 children aged 0-18 years who consumed steroids due to their chronic disease and consulted to the endocrinology specialist from January 2022 – February 2023. Anthropometric measurements and lipid profile examination were performed. We converted the steroid dose from other types of steroid equivalent to prednisone. The association between the type of steroid, duration, and steroid dose with lipid profiles was assessed using one-way ANOVA. A P-value of <0.05 is considered to be significant.

Results: Ten girls and eight boys were included in this study. Most children in this study were treated with steroids because of nephrotic syndrome (n=6), followed by ITP (n=5) and SLE (n=2). Six children use steroids in low-moderate doses daily; 12 children use steroids in high doses daily. The type of steroids used as a treatment in this study were methylprednisolone, prednisone, and betamethasone. There was no association between the type of steroid with the patients' lipid profiles. This study found a significant difference between the duration of steroid use and triglyceride levels (p-value 0.036). The dose of steroids was found to be significant in influencing LDL levels (p-value 0.003) and total cholesterol levels (p-value 0.002) in the subjects.

Conclusion: Steroid use in children with chronic disease could affect their lipid profile. This study found that the duration of steroids is associated with triglyceride levels, while the dose of steroids was associated with LDL and total cholesterol levels. Routine monitoring of lipid profiles and any dyslipidemia signs in children treated with steroids is recommended.

P1-78

Evaluation of Tri-Ponderal Mass Index as a reflector of adiposity among pediatric cancer survivors

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Objectives: Modern treatments lead to increased survival rates from childhood cancer. Childhood cancer survivors (CCS) are a growing population group, which is at high risk for cardiometabolic disorders including metabolic syndrome, type 2 diabetes and cardiovascular disease. Obesity is one of the major drivers of these adverse outcomes, resulted from corticosteroids, radiotherapy, sedentary behavior, and precancer obesity. Assessment of obesity could identify CCS at risk and predict cardiometabolic risk. Dual-Energy X-ray Absorptiometry (DEXA) scans incorporate measurements of adipose tissue mass but are not feasible because they require special equipment, expertised personnel and are expensive. The Tri-Ponderal Mass Index (TMI: kg/m^3) has recently been validated as an accurate measure of obesity than the widely used Body Mass Index (BMI). The aim of the study was to investigate TMI as a measure of obesity versus DEXA compared with BMI z-score in CCS.

Methods: A single-center retrospective study enrolled thirty CCS (17 boys) of Caucasian origin, aged 12.38±3.99 years, was conducted. Anthropometric data were recorded and DEXA scan measurements of body composition were performed to assess obesity. TMI was calculated as weight (kg) divided by height cubic meters (m^3).

Results: Participants had a mean age at diagnosis of 7.95±4.07 years, 20/30 (66.7%) had survived of acute lymphoblastic leukemia, all received chemotherapy, 46.7% had received radiotherapy and 6.7% underwent bone marrow transplantation. Recurrence was recorded in 23.3%. Cancer treatment was terminated at a mean age of 9.32±4.07. Mean BMI z-score was 0.62±1.17, weight (kg) 49.05±18.2, height (m) 1.50±0.20. Mean Fat Mass (FM)% measured by DEXA was 39.12±7.74. The mean TMI (kg/m^3) was 14.18±3.18.

TMI is significantly correlated with FM% measured by DEXA (r=0.519, p-value=0.004), even after adjustment for age and gender (r=0.368, p-value=0.05). However, BMI z-score remains largely correlated to FM% in the studied sample, after adjustments for age and gender (r=0.641, p-value<0.001).

Regression analysis, revealed that the association of TMI alone was not significant for obesity (TMI vs FM% estimated unstandardized B=0.711; p-value=0.117), however, the combination of TMI and BMI z-score could reliably predict FM% distribution among CCS (model R^2=0.49, p-value<0.001; TMI unstandardized B=-2.25, p-value=0.005; BMI z-score unstandardized B=9.04, p-value< 0.001).

Conclusion: TMI constitutes a reliable, easy applicable and clinical obesity-specific index among CCS.

P1-79

Features of exogenous-constitutional obesity in children and adolescents of the Uzbek population depending on age

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Objective of the Study: To study the characteristics of carbohydrate and lipid metabolism in obese children and adolescents depending on the age.

Materials and Methods: We examined 171 children and adolescents aged from 6 to 16. Among them, there were 100 children and adolescents with ECO and 71 healthy children and adolescents. ECO patients were divided into 2 groups: group 1 including children with ECO aged 6-<10 years old, group 2 with adolescents aged 10-<16 years old.

All the children and adolescents were checked for lipids, carbohydrate metabolism, insulin resistance using HOMA-IR.

Results and Discussion: In children aged from 6 to 10 years old, the indicators of carbohydrate metabolism differed significantly from the control, while the level of activity in 2 hours (11.6%) and HbA1c (15.2%) in patients of the second group was higher. Impaired fasting glycemia (fasting ≥5.6<6.1 mmol/l; in 2 hours <7.8 mmol/l) caces were not identified in 1 (5.0%) 7 years old girl and 3 (3.8%) adolescents with ECO.

Analysis of the lipid spectrum indicators showed that both in the 1st and 2nd groups were patients with total cholesterol ≥5.2 mmol / l (25.0% and 37.5%, respectively), TG ≥ 1.7 mmol /l (60.0% and 70.0%, respectively), LDL ≥3.5 mmol/l (30.0% and 23.8%, respectively) and HDL < 1.03 mmol/l (15.0% and 33.8%). In children under 10 years old, the level of total cholesterol and HDL did not differ significantly from the control. LDL in patients of this group was 2.4 times (p=0.0001), TG 1.8 times (p=0.0001) and AI 1.4 times (p=0.04) higher, than in the children of the control group. In the group of adolescents, the data of the lipid spectrum differed significantly from the control. So, the level of total cholesterol was increased by 34.2%, LDL by 76.4%, TG by 66.7% and AI by 42.1% compared to adolescents from the control group.

HOMA-IR reference values for children (1.2) and adolescents (1.8) were calculated. HOMA-IR index ≥97 peppers (≥1.2 for children) was detected in 5 (29.4%) of 17 children. Cases of HOMA-IR≥97pp. (≥1.8 for adolescents) were registered in 47 (70.1%) of 67 adolescents.

Conclusions: 1. HOMA index > 97 percentile (>1.2 for children) was detected in 75% of the children of group 1) Cases with HOMA>97 percentile (>1.8 for adolescents) were registered in 70.1% of adolescents of 2nd group.

P1-80

Leukocyte, platelet counts and the neutrophil-to-lymphocyte ratio (NLR) are related to insulin resistance in obese and overweight children

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Background and Aims: The development of insulin resistance (IR) may be influenced by inflammation in overweight/obese individuals. To identify indicators of IR, new markers of inflammation and systemic inflammation such as leukocyte (WBC) and platelet counts (PLT), the neutrophil-to-lymphocyte ratio (NLR) have been suggested. This study aims to investigate the association between these markers and IR in a group of overweight and obese.

Materials and Methods: A total of 247 overweight/obese school-children were studied (119 males and 128 females; 109 prepubertal and 138 pubertal). Anthropometric, hematological and biochemical measurements were collected. HOMA-IR values were calculated as insulin resistance index. According to HOMA-IR values, the study population was divided into tertiles (1st tertile: < 2.58; 2nd tertile: between 2.58 and 4.08; 3rd tertile: >4.08) and differences across tertiles in terms of blood count values were investigated. In addition, a Spearman test was performed to evaluate a correlation between blood counts and insulin resistance indexes.

Results: The three tertile groups were similar in terms of age (10.8, 11.3 and 11.8, years respectively), and gender (M/F, 40/43, 40/42 and 39/43 respectively). As expected, Weight-SDS, BMI-SDS, fasting glucose and insulin values, and HOMA-IR increased across the three tertile groups, showing higher values in the third tertile. Interestingly, WBC, PLT and NLR significantly and progressively increased across the three tertile groups, showing higher values in the third tertile. The Spearman analysis in the entire study population showed a significant correlation between both WBC and PLT with fasting insulin and HOMA-IR values.

Conclusion: White blood cell values, PLT and NLR increased progressively across insulin resistance tercile in overweight/obese children. Therefore, these markers may serve as indicators of the presence of IR in these subjects and should be taken into account when predicting potential complications such as type II diabetes mellitus.

P1-81

Comparison of HbA1c and OGTT for the identification of type 2 diabetes in obese children above 10 years of age

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Background: Childhood obesity is a growing global problem that linked with health issues including type II diabetes. Early screening and diagnosis using OGTT and/or HbA1c of obese children is recommended in order to minimize type II diabetic risk. OGTT requires fasting and two venesections impeding the child's compliance. In contrast, hemoglobin A1c (HbA1c) is a convenient test and evaluation of HbA1C as a diagnostic tool of type II diabetes in the obese children compared to OGTT is momentous.

Objectives: To evaluate the correlation between HbA1c and 2h-OGTT level for the diagnosis of type II diabetes in obese children above10 years of age who attended the Endocrine and Diabetes clinic.

Method: A descriptive analytical study was conducted using routine simultaneous screening results of OGTT and HbA1c of all the obese (Age and gender specific BMI ≥95th percentile) children over 10 years visiting Endocrine and Diabetes Unit Lady Ridgeway Hospital for Children, Colombo, Sri Lanka from 1st of February 2021 to 31st of August 2021.

Results: A total number of 189 children were recruited to the study. The mean age 11.8 years (male 68% and female 32%), mean weight and the mean BMI were 60 kg and 26.15, respectively. The majority (79%) of the children were between 10 to 12 years of age and the most of them (76%) had a family history of obesity. The mean 2h-OGTT was 6.44 and according to OGTT criteria 3.7% were in the diabetes group,14.81% were in the impaired glucose tolerance group and 81.48% were in the normal glucose tolerance group. Mean HbA1c was 5.5 and HbA1c categorized the 4.23%, 28.57%, and 67.2% of children into diabetes, pre diabetic and normal, respectively. A significant correlation between 2h-OGTT and HbA1c was observed by Fisher's Exact test($P<0.001$).

Discussion: Correlation between HbA1c and OGTT level for the screening of type II diabetes in obese children was observed. Other studies also showed HbA1c is a reliable indicator of diabetes risk in the paediatric population. Some studies concluded that HbA1c alone is a substandard determinant of paediatric prediabetes population unless it is collaborated with other clinical evidence. Therefore, data verifying HbA1c in predicting type II diabetes among children necessitate further large-scale studies.

Conclusion: Our findings indicate the potential use of HbA1c for the diagnosis of type II diabetes in Sri Lankan obese children. However, HbA1c alone is a poor discriminator of prediabetes in the same population.

P1-82

Leptin receptor's mutation in a patient with childhood obesity and hyperphagia

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Introduction: Genetic factors play an important role in determining individual susceptibility to weight gain and obesity. In the last few years, several genetic variants have been identified as monogenic forms of obesity. Among them, Leptin (LEP) and its receptor on hypothalamic neurons (LEPR) are key players in the regulation of body weight, food intake and energy homeostasis. Pathogenic variants in the LEPR gene cause severe childhood-onset obesity with an autosomal recessive inheritance.

Case Presentation: N.Y, male, aged 1.73 years, was referred to our Centre for excessive weight and hyperphagia. He was born at full term from Egyptian non consanguineous parents. Birth weight was 3920 g, length 53 cm and head circumference 34.5 cm (adequate for gestational age). He was breastfed for 15 months and he was regularly weaned at 6 months. He had normal psychomotor development. He had a significant weight gain within the first months of life (+ 1 kg per month). His diet was varied but with many snacks between meals. He ate every couple of hours. At 1.73 years old his length was 84.4 cm (-0.19 SDS), his weight 21 kg (+5.4 SDS), his BMI 29.48 kg/m2 (+6.59 SDS) and his head circumference 49.5 cm. Blood tests showed microcytic, hypochromic anemia, hypovitaminosis D and hypertriglyceridemia. Liver and renal function, thyroid function tests and adrenal function were within normal limits. At examination, adipomastia and acanthosis were detected. Considering the clinical picture, we performed NGS genetic test. Two variants of unknown clinical significance (VUS) c.3G>A p.Met1? and c.1345T>G p.(Trp449Gly) were detected, both in heterozigosity in the LEPR gene. Additionally, the variant of unknown significance c.661A>G p.(Asn221Asp) was detected in heterozygosity in the PCSK1 gene. The c.1345T>G p.(Trp449Gly) variant of the LEPR gene has not been described previously. The bioinformatic analysis predicts it to have a deleterious effect. Therefore, this should be classified as a VUS, suspected to be pathogenic. The variant in PCSK1 gene is described in the literature as a polygenic risk variant for obesity. Finally, we tested the patient's parents. Father carried the c.1345T>G p.(Trp449Gly) variant, whereas mother carried the c.3G>T p.Met1? variant. Clinical and endocrinological follow-up of the patient is still ongoing.

Conclusion: The presence of monogenic mutations should be suspected in children with early onset obesity and hyperphagia. It is crucial to recognize pediatric obese patients to set a specific diagnostic path and management.

P1-83

Improvement in Health-Related Quality of Life scores in Children and Young people with Obesity following intervention and support from a Tertiary MDT Weight Management Service

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Introduction: Obesity is a significant public health concern affecting children and young people (CYP) worldwide. The impact of obesity on CYP is multi-faceted and can have a significant effect on their lives. They are at risk of being stigmatized and discriminated against, leading to poor academic performance and social functioning. It is crucial to assess the impact of obesity on the lives of CYP through tools such as Health-related quality of life (HRQOL) questionnaires.

Aim: The aim of this study was to conduct a retrospective review of the baseline and three-month follow-up HRQOL scores in a group of CYP with obesity, who are being managed as part of the tertiary multidisciplinary (MDT) weight management service.

Methods: 31 patients with a mean age of 14.2 years (M:F, 14:17) and a mean BMI of 44.1kg/m^2 completed the paediatric QOL questionnaire [PedsQL 4.0 Generic Core Scales] at baseline and 3 months after intervention from the MDT team. Scores were categorised under four individual sections and the summary scores were also calculated. Psychosocial health summary score compiled scores on emotional, social, and school functioning results and the physical health summary score complied scores on physical function. The mean score for all items were evaluated.

Results: Overall, the total score improved from a baseline of 52.11/100 to 55.37/100 after 3 months of intervention from MDT team. The subdomains most impacted were school function and emotional score, with baseline scores of 44.69/100 and 47.80/100, respectively. With active intervention and support, school and emotional scores improved to 49.06/100 and 50.625/100. The social function score also improved from 53.84/100 to 61.15/100 within the same period. Overall, the psychosocial score summary showed improvement from 49.35/100 to 53.82/100.

Conclusion: Our study highlights that targeted intervention by MDT weight management service could improve the HRQOL in CYP with obesity. The PedsQL questionnaire helps healthcare professionals to identify the specific issues and offer focussed support. The study provides compelling evidence for investment in MDT teams to provide ongoing support to manage the obesity-related complications, including mental health issues, thereby improving the long-term outcomes and overall well-being.

P1-246

Obesity Caused by Mutations in the Melanocortin 4 Pathway: Experience From a Teaching Hospital

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Introduction: The role of genetics in obesity is a much under discussed area. Whilst it is undeniable that environmental factors play a major role in obesity in most cases, there is a small proportion of cases where genetic mutations are the main underlying cause. This includes novel monogenic conditions involving mutations in the Melanocortin-4 receptor (MC4R) signalling pathway. In a healthy individual, the post-meal increase in leptin (LEP) stimulates melanocyte stimulating hormone (MSH) production from Proopiomelanocortin (POMC), and MSH binds MC4Rs to induce satiety and increase energy expenditure. Malfunction of this pathway can lead to obesity.

Aim: The aim of this retrospective study was to look for common features in children and young people (CYP) with MC4R/LEP mutations, which could prompt early specialist referral to establish a genetic diagnosis and help formulate a management plan.

Methods: We carried out a retrospective data collection using LORENZO which is the Hull University Teaching Hospitals (HUTH) trust main database and the HUTH paediatric departmental database. We identified 5 patients with known MC4R/LEP mutations managed by the HUTH trust for obesity, with initial presentations between 1999–2017. The Cambridge Genetics of Obesity Study (GOOS) request form was used as a model to create the data collection template.

Results: 4 patients had MC4R mutations and 1 had a LEP mutation. The CYP presented between ages of 7 months and 11 years, with BMIs over +3SDs for their ages. 2 had heights over +2SDs for their ages. Birth weights for 4 of the patients were low or appropriate for gestation, whilst 1 was large for gestation. All 4 patients with the MC4R mutations had family history of significant obesity in one of the parents. All patients exhibited food seeking behaviours and hyperphagia from early childhood (1–4 years of age). None of the participants had dysmorphic facies or hypogonadism. 3 patients had mental health problems, including self-harming behaviours.

Conclusions: CYP with MC4R mutations may not always be identifiable based on birth weight or tall stature. Although autosomal dominant history of obesity is present among parents, this may not be a distinguishing feature. Early onset food-seeking behaviour and lack of satiation should alert primary care practitioners and general paediatricians towards the possibility of a genetic cause of obesity. Clinicians should also be aware of the high incidence of mental health problems in this cohort of CYP, and consider early referral for psychological support.

P1-247

Th17 lymphocytes and peripheral complete blood count alterations in obese children

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Introduction: Obesity is considered one of the most common chronic diseases worldwide which is associated with chronic, low-grade, sterile inflammation. It leads to variable changes in metabolic and hormonal homeostasis. The aim of our study was to evaluate the impact of obesity associated chronic inflammation on peripheral complete blood count alterations.

Material and Methods: 27 overweight/obese and 15 normal-weight children aged 8–18 years were enrolled in the study. The analysis included anthropometric measurements, CBC parameters, biochemical parameters. Inflammation was evaluated by CRP concentration and Th17 cells' frequency. Th17 cells were identified by flow cytometry and defined as CD3+CD4+CD196+IL-17Aic+. Obesity was defined by BMI >+2 SDS, and overweight was defined as BMI between +1 to +1.9 SDS.

Results: The overweight and obese group had significantly higher leukocyte ($p = 0.04$), lymphocyte ($p = 0.03$), monocyte ($p = 0.02$) and erythrocyte counts ($p < 0.001$), haemoglobin concentration ($p = 0.005$) and frequency of Th17 cells ($p = 0.048$). We detected significant relationships between anthropometric parameters, and CRP concentration, Th17 cells frequency and CBC parameters. The Th17 cell' frequency correlated positively with erythrocyte value ($p = 0.01$, $r = 0.38$). Additionally, in the overweight/obese group the erythrocyte correlated positively with CRP ($p = 0.02$, $r = 0.44$).Moreover, in all children the correlation was found between erythrocyte and: fasting insulin ($p = 0.00005$, $r = 0.58$), HOMA-IR ($p = 0.00005$, $r = 0.58$), QUICKI ($p = 0.000042$, $r = -0.59$), as well as between haemoglobin and: fasting insulin ($p = 0.037$, $r = 0.32$), HOMA-IR ($p =0.37$, $r = 0.32$), QUICKI ($p = 0.049$, $r = -0.31$). In the overweight/obese children the significant correlation was found between glucose 2 h after OGTT and HGB ($p = 0.018$, $r = 0.45$) and insulin 2 h after OGTT and erythrocyte ($p = 0.04$, $r = 0.4$), and HGB ($p = 0.04$, $r = 0.44$), also Matsuda Index with erythrocyte ($p = 0.01$, $r = 0.48$).

Conclusions: Obesity change CBC picture in white and red blood cell lineages. The finding of significant relationships between proinflammatory Th17 lymphocytes, CRP, and CBC as well as metabolic parameters may indicate that both obesity-induced inflammation and insulin resistance markers can influence on peripheral blood morphology in obese children. Our results suggest that obesity-induced carbohydrate complications primarily affect red blood cell lineage.

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P1-248

Single Gene Variations in Etiology in Children with Severe Obesity

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Background: Obesity is a multifactorial disease caused by environmental and genetic factors. Single gene defects explain approximately 5-13% of early-onset obesity and these rates vary according to genetic panel used and the rate of consanguinity in the population studied. As the new treatment modalities emerge for monogenic obesity, it is important to identify the molecular etiology of obesity.

Materials and Methods: Buccal swab samples were taken for genetic analysis from 27 obese chidren with a body mass index of over 120% and a history of early-onset obesity (<5 years old) between August 2022 and January 2023. ROAD gene panel containing 79 genes and 1 chromosome region. (ADCY3, AFF4, ALMS1,ARL6, BBIP1, BBS1,BBS10, BBS12,BBS2,BBS4,BBS5,BBS7, BBS9,BDNF, CEP290,CFAP418, CPE,CREBBP, CUL4B,DNMT3A,DYRK1B, EP300,GNAS, HTR2C,IFT172, IFT27,IFT74,INPP5E,ISL1, KIDINS220, KSR2, LEP,LEPR, LZTFL1,MAGEL2, MC3R, MC4R,MECP2, MKKS, MKS1, MRAP2, NCOA1,NR0B2, NRP1,NRP2, NTRK2, PCNT,PCSK1, PHF6,PHIP,PLXNA1, PLXNA2,PLXNA3, PLXNA4,POMC, PPARG,PROK2, RAB23, RAI1, RPGRIP1L, RPS6KA3,SDCCAG8,SEMA3A,SEMA3B, SEMA3C,SEMA3D, SEMA3E,SEMA3F, SEMAB3G,SH2B1,SIM1, TBX3,TRIM32,TRPC5,TTC8,TUB,UCP3,VPS13B,WDPCP + 16p11.2) were applied to these samples.

Segregation analyses were performed in patients who had variations classified as unknown clinical significance (VUS), likely pathogenic (LP) and pathogenic acccording to ACMG classification.

Results: The mean age of 24 patients (50% male)whose analyzes were completed was 12.64 years. While no variation was detected in 8 of the patients,30 changes were detected in 17 genes in 18 patients. While 5 of them were classified as benign or likely benign,18 (58.6%) were classified as VUS,4 as likely pathogenic (13.7%), and 3 as pathogenic (10.3%). More than one variation was detected in eight cases. All variants were heterozygous. In 6 of the index patients whose results were completed, LEPR,PCSK1, PLXNA2,PLXNA3,GNAS mutations and dup(19)(q13.2)chr19 were detected as the etiology of obesity. Detection rate of a monogenic cause in our cohort was 25%.

Conclusion: A monogenic cause for obesity was detected in approximately one in every four children with early-onset obesity in our cohort which is higher then previously reported cohorts.

Gene Name	Number of Variations	Variations	ACMG Classification
MECP2	2	c.-99+2T>G c.1214C>T	1Pathogenic,1VUS
PCSK1	3	c.661A>G c.1381G>A	2Pathogenic,1VUS
GNAS	1	c.793C>T	1LP
PLXNA2	4	c.1451G>A c.5593A>T c.5593A>T	1LP,Pathogenic,2 VUS
PLXNA3	3	c.3680G>T c.1249G>A c.263A>G	1LP,2 VUS
SDCCAG8	1	c.(675+1_676-1)_(740+1_741-1)del	1LP
dup(19)(q13.2)chr19	1		1VUS
BBS9	2	c.890G>C c.2134G>A	2VUS
CREBBP	1	c.6034G>A	VUS
DYRK1B	1	c.289G>A	VUS
LEP	1	c.(?_1)_(144+1_145-1)dup	VUS
LEPR	2	c.946C>A c.1938G>T	2VUS
NRP2	1	c1799C>T	VUS
POMC	1	c.423G>A	VUS
TBX3	1	c.1219C>T	VUS
RPGRIP1L	1	c.2537T>C	VUS

P1-249

Association of chemokine network profile with albuminuria in obese children

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Childhood obesity has increased in epidemic proportions worldwide. Complications of obesity represent a growing proportion of childhood morbidity. Albuminuria resulting from endothelial damage was recognized as a complication of obesity, implying higher cardiovascular risk.

Aim: to investigate the association of albuminuria in obese children with metabolic and inflammatory parameters.

Materials and Methods: The study included 29 healthy controls (HC, 14 M, age 15.46+/-1.51 years, BMI-z 0.1 SD (IQR -0.68 – 0.55)) and 34 obese children (OB; 19 M, age 14,69+/-1.60 years, BMI-z 2.35 SD (IQR 2.16 – 2.52)). Albuminuria was reported as the mean of albumin to creatinine ratio (ACR) from two first-morning urine samples. It was correlated with clinical parameters, parameters of metabolic complications (HOMA-IR, ALT, lipid profile), and inflammation (CRP and fibrinogen, chemokine/chemokine receptors). B-cell (CD19+), T-cell (CD3+), and monocyte (CD14+) phenotype and CCR2, CCR4, CXCR3, and CXCR4 expression was determined from peripheral blood mononuclear cells using flow cytometry. Chemokines CCL2, CCL5, and CXCL10 were determined using BioLegend LEGENDplex™, and CXCL12 was analyzed by ELISA. Results are reported as the median and interquartile range (IQR).

Results: Obese children had higher ACR than lean controls (ACR (OB) 0.5 mg/mmol (IQR 0.275 – 0.8) v.s. ACR (HC) 0.2 mg/mmol (IQR 0.0-0.4), p=0.0035), and higher inflammatory markers (CRP(OB) 2.2 mg/L (IQR 1.0 - 4.1) v.s. CRP(HC) 0.1 mg/L (IQR 0.1 – 0.5), p<0,001; fibrinogen (OB) 3.4 g/L (IQR 2.9-4.0) v.s. fibrinogen (HC) 2.6 g/L (IQR 2.3 – 2.9), p<0,001). In all subjects included, ACR positively correlated with BMI-SDS, insulin concentration, HOMA-IR, and diastolic blood pressure (DBP). However, no correlations with metabolic or inflammatory markers were found in the obese group. Obese subjects showed a positive correlation of ACR with monocyte proportion, and an inverse association with monocytes expressing CCR2, CCR5 CXCR3, and CXCR4, but no correlations with chemokine ligands. In healthy subjects, ACR positively correlated with all CCR2-expressing lymphocyte subsets and ligand CXCL10 but reversely with CCL5.

Conclusion: Obese children had a higher rate of albumin excretion and inflammatory markers, but no associations of ACR with metabolic and inflammatory markers. When all subgroups were included, ACR showed a significant positive correlation with the degree of obesity, insulin resistance markers, and DBP. However, there are significant associations of ACR with monocyte subsets suggesting a monocyte role in renal endothelial damage. Albuminuria might be a complication of obesity observed even at a young age, associated with particular chemokine network activation.

P1-250

Sitosterolemia – An underdiagnosed and heterogeneous lipid disorder. A Case Series from The Children's Hospital at Westmead NSW Australia

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Background: Sitosterolaemia, or phytosterolaemia, is a disorder of increased plant sterol levels in the body leading to a variable presentation including hypercholesteremia, xanthoma, atherosclerosis and haematological manifestations. Although considered rare, the prevalence is likely underestimated due to the variable phenotype. It is caused by recessively inherited mutations in ABCG5 or ABCG8 which encode the sterol efflux transporters in the gut. Hypercholesterolaemia is often mild in adults but more marked in young children. The diagnosis may be missed unless plant sterol levels are checked using gas spectrometry or liquid spectrometry or genetic testing is performed based on clinical suspicion. The delayed diagnosis may lead to cardiovascular disease. Management is with dietary modification to reduce foods high in plant sterols in addition to Ezetimibe which inhibits sterol absorption. Statins are not usually indicated. Reduction in plant sterol levels can lead to improvement in cardiovascular outcome and haematological manifestations.

Case Series: We report 4 children aged 18 months to 18 years who presented to our lipid clinic with variable manifestations from xanthmoas to haemolytic anaemia and were subsequently confirmed to have sitosterolaemia on genetic testing. All patients had a strong family history of lipid disorders and cardiovascular disease at a young age. All have responded to dietary modifications and Ezetimibe.

Conclusion: Sitosterolaemia may be missed or underdiagnosed due to the spectrum of clinical presentation ranging from asymptomatic to cardiovascular and haematological complications. Specialised testing for plant sterol levels and genetic mutations are needed to confirm the diagnosis. The clinical features can be fully reversed by dietary modification and Ezetimibe.

Patient	Age at diagnosis	Clinical manifestation at presentation	Lipid levels at diagnosis	Genetic mutation	Management
1	18 months	Xanthomas over the wrist and Achilles tendon	TC 9.8mmol/l LDL 8mmol/l Plant sterol 0.2mmo/l	Compound heterozygous ABCG5	Ezetimibe Low sterol diet
2	11 years	Incidentally detected fatty liver on US.	TC 8.5mmol/l LDL 4.6mmol/l Plant sterols	Homozygous ABCG5	Ezetimibe Low sterol diet
3	18 years	Menorrhagia associated with macrothrombocytopaenia and haemolytic anaemia	TC 5.2mmo/l LDL3.5mmol/l Plant sterols 0.9mmol/l	Homozygous ABCG5	Ezetimibe Low sterol diet
4	15 years	Incidentally detected macrothrombocytopaenia and haemolytic anaemia following investigation for underweight status.	TC 3.1mmol/l LDL1.9mmol/l Plant sterols 1.2mmol/l	Homozygous ABCG5	Ezetimibe Low sterol diet

Normal plant sterol level <0.02mmol/l

P1-251

Overweight and obesity in childhood and adolescence is associated with an increased fracture risk - Results of a systematic literature review

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Introduction: Up to now, no systematic literature review has studied whether overweight or obesity compared to normal weight in childhood and adolescence is associated with an increased fracture risk (fractures overall and by site).

Methods: The systematic literature search was conducted in PubMed/Medline, Embase, Cochrane Library, BIOSIS databases using defined keywords and MeSH terms. 1,677 publications were identified (N=320 duplicates). 1,295 publications were excluded after screening the title/abstract and full text. 62 publications were included in the analysis.

Results: 7/10 studies showed an increased fracture risk in children and adolescents with obesity compared to children and adolescents with normal weight (range reported OR/RR: 1.1-4.4). In 8/12 studies, obesity was associated with a significantly increased risk of fractures compared to children and adolescents with normal weight (range reported OR/RR: 1.1-13.2). Children and adolescents with extreme obesity had a 1.4 to 1.5-fold increased risk of fractures compared to children and adolescents with normal weight (2/2 studies). In 5/16 studies, the percentage of children and adolescents with overweight and/or obesity was higher than the percentage of children and adolescents with normal weight in the group of children and adolescents who suffered a fracture. In n=7 studies, a trend for higher BMIz/fat mass was observed in children and adolescents with fractures compared to children without fractures. The remaining publications reported only the percentage of children and adolescents with obesity in the presence of a fracture, without the comparison with a control group. Another result of this systematic literature review was that we identified factors discussed in the literature as increasing the risk of fractures in children and adolescents with overweight and/or obesity. These factors include: lower physical activity, poorer balance, lower serum vitamin D concentrations, higher leptin and lower adiponectin concentrations in children and adolescents with overweight and/or obesity compared to children and adolescents with normal weight.

Conclusion: Compared to normal weight, overweight or obesity in childhood and adolescence is associated with a 2-fold increased fracture risk (fractures overall and by site). Treating physicians should be aware of this increased risk of fractures in children and adolescents with overweight or obesity and encourage an increase in physical activity in them and regularly determine parameters of bone metabolism such as serum vitamin D concentration.

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Dietary and physical activity habits of children and adolescents after a personalized intervention for the management of obesity

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Introduction: Obesity in childhood and adolescence has been recognized by the WHO as a global epidemic and a major public health problem. Greece, is one of the main countries in Europe where the problem of childhood obesity has increased rapidly. This rise can be attributed to dietary and physical activity risk factors. Recently, there has been a need for a detailed recording and assessment of the lifestyle habits of children and adolescents receiving personalized intervention for the management of obesity.

Aim: To determine the dietary and exercise habits of children and adolescents before and after their participation in an interventional program within the context of the study 'BigO: Big Data against Childhood Obesity'(http://bigoprogram.eu, Horizon2020, No. 727688).

Methods: Three hundred ninety-four (n=394) children and adolescents, aged 8-18 years, attending our Out-patient Clinic for the Prevention and Management of Overweight and Obesity in Childhood and Adolescence participated in the study prospectively. All subjects underwent a personalized management intervention program that provided guidance on diet, sleep and physical activity. The data collection system included the BigO technology platform, which interfaces with a Smartphone and Smartwatch, and records data on diet, sleep and exercise objectively for each patient. Participants used the BigO system for 4 weeks and wore the watch for specific periods during the week. Subsequently, they entered a personalized life-style intervention program for 4 months and used the system again for 4 weeks.

Results: Of all participants, 74.4% were obese, 25.1% overweight and 0.5% had normal BMI. Following the intervention, a statistically significant decrease was observed in the amount of cheese, cereal with added sugar, savory snacks, pasta and fried potatoes consumption in all BMI categories. Also, an increase in the number of children who drank water between the meals daily was noted in all BMI categories (p-value=0.001). Furthermore, there was a decrease in the consumption of evening snack or dinner watching television (p-value<0.05). Boys showed a decrease in the amount of savory snacks and pasta (p-value<0.05) and drank more water between meals daily (p-value<0.001).

Conclusion: A personalized and multidisciplinary intervention based on the BigO study improves dietary and physical activity habits of children and adolescents.

P1-253

Effect of growth hormone on thermogenic and endocrine activity of brown adipose tissue and on the lipidome of children born small for gestational age

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Introduction: Brown adipose tissue (BAT) secretes molecules capable of modulating systemic metabolism. Growth hormone (GH) has hyperglycemic action, produces lipolysis and increases muscle mass. However, there are no human studies on its effect on the BAT and lipidome.

Aim: To evaluate the effect of GH on BAT and lipidome in small for gestational age (SGA) patients and its relationship with adherence to treatment.

Material and Methods: Eleven prepubertal SGA patients between 3-9 years of age were recruited. They were classified into two groups: a) treated with GH (SGA-GH: 7 patients) and b) not treated with GH (SGA: 4 patients). The indicated GH was somatropin (Saizen® from Merck-Serono) using the EasyPodSystem device at a dose of 0.035mg/kg/day.

A baseline visit to all patients and follow-up were done in the SGA-GH group at 3 and 12 months of treatment. At each visit (baseline, 3 and 12 months post-treatment) anthropometric and adherence data were collected using the EasypodConnect® app, as well as a fasting blood sample. Basic blood count and biochemistry, hormone levels, and concentrations of molecules of interest were measured. The thermogenic capacity of the supraclavicular BAT was also determined by infrared thermography after cold stimulation. Finally, a lipidomic analysis by mass spectrometry was performed on the serum of these patients. Statistical analysis was performed using IBMSPSS-Statistics19.0.

Results: The adherence to GH was correct. At the lipidomic level, 42 lipid species appeared modulated in SGA vs. SGA-GH at baseline. SGA-GH group showed increased levels of odd-chain fatty acids (OCSFAs) that are associated with cardiovascular protection. Some lipid species related to cellular senescence appeared elevated in the SGA-GH serum after the treatment.

After GH treatment, there was a trend of increasing concentrations of CXCL14, FGF21, IL-8, leptin, and MCP1, and a slight decrease in GDF15, adiponectin, and resistin. The SGA group showed lower basal resting temperature of the supraclavicular BAT than the SGA-GH group. Treatment with GH did not produce remarkable changes in the thermogenic capacity except in one patient whose low growth response to GH coincided with a worsening of the thermogenic capacity of BAT.

Conclusions: GH treatment increases some lipid species related to cardiovascular protection and markers of cellular senescence. This study opens a door about the GH effect on BAT activity by modulating the levels of some batokines with a systemic effect.

P1-254

The early identification of glycaemic dysregulation with the use of continuous glucose monitoring in children and young people with obesity

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Introduction: Impaired glucose tolerance and type 2 diabetes mellitus are known complications associated with childhood obesity. At present, an oral glucose tolerance test (OGTT) is the gold standard investigation. Continuous glucose monitors (CGM) are used in children and young people (CYP) with type 1 diabetes mellitus. The aim of our study is to investigate whether the use of a CGM is more effective in identifying glycaemic dysregulation, compared to an OGTT.

Method: In total, 32 paediatric patients who are under the care of a tier 3 multidisciplinary weight management service were included. Blinded Dexcom G6 CGM devices were inserted into the upper arm for a minimum of three days to obtain free-living glucose readings on 51 occasions. On each of these, the patient had a recent normal OGTT prior to the CGM being inserted. None of the patients were on any medicines which effect glucose levels.

Results: The mean age of the patients was 14.2 years (range: 10.1-16.7) with 53.1% (17/32) being female. The mean weight was 112.5kg (±22.2 SD), mean BMI was 40.8kg/m^2 (±7.6 SD) and average BMI SDS was +3.6 (±0.5 SD). The CGM devices were worn for an average of 8.0 days (range: 3-10) and the mean glucose over this duration was 6.5mmol (+1.0 SD). The coefficient of variation was normal (16.8%; NR <36%). The mean percentage time that the glucose levels were within range (3.9-7.8mmol/L; 70-140mg/dL) was 82.4% (±17.3 SD). The average percentage glucose levels over 7.8mmol/L (140mg/dL) was 14.7% (±17.1 SD) and over 10mmol/L (180mg/dL) was 1.7% (±5.4 SD).

Conclusion: The results have shown that the percentage time in range on CGM for CYP with obesity (82.4%) is lower than that seen in healthy, non-diabetic participants (95%)[1]. Interestingly, 1.7% of our readings were glucose levels over 10mmol/L, which was not seen in the healthy cohort[1]. Therefore, glycaemic dysregulation was identified in CYP with obesity despite normal OGTT results. This highlights the potential use of CGM devices in the early identification of glycaemic dysregulation, which would enable healthcare professionals to manage in a timely manner and prevent long-term complications.

Reference

[1] Shah VN et al., Continuous Glucose Monitoring Profiles in Healthy Nondiabetic Participants: A Multicenter Prospective Study. J Clin Endocrinol Metab. 2019.

P1-255

Comparison of triglyceride-glucose index and HOMA-IR for predicting severity of nonalcoholic fatty liver disease in Korean children and adolescents

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Background: Triglyceride-glucose (TyG) index is known as a reliable insulin resistance surrogate marker to identify nonalcoholic fatty liver disease (NAFLD). Ultrasonographic fatty liver indicator (US-FLI) is proposed as a non-invasive, semi-quantitative method for predicting hepatitis in patients with NAFLD and accurately identifies histological severity. Few studies have compared the TyG index to homeostasis model assessment of insulin resistance (HOMA-IR) in the detection of NAFLD in children and adolescents. Additionally, there were no studies comparing the ability of TyG index and HOMA-IR to assess the severity of NAFLD.

Objects: We investigated the relationship between TyG index and NAFLD compared to HOMA-IR in identifying and assessing the severity of NAFLD in children and adolescents.

Methods: Alanine aminotransferase (ALT) was used as the screening method for NAFLD (>26IU/L in boys and >22IU/L in girls), and US-FLI was performed on children who met these criteria. The US-FLI is a scoring system ranging 2-8 that evaluates based on intensity of liver/kidney contrast, posterior attenuation of ultrasound beam, vessel blurring, difficult visualization of gallbladder wall, difficult visualization of the diaphragm and areas of focal sparing. NAFLD is diagnosed by the minimum score ≥2. Healthy children of normal weight (body mass index 5-85th percentile) without metabolic comorbidities and no steatosis on ultrasound participated as a control group. TyG index was calculated as ln(fasting triglyceride (TG) [mg/dL] × fasting glucose [mg/dL]/2).

Results: A total of 130 NAFLD patients (90 boys and 40 girls) included in this study, with mean age of 11.5±2.29 years. The control group consisted of a total of 28 subjects (17 boys and 11 girls) with mean age of 8.39±1.60 years. The US-FLI was significantly correlated with TyG index (r=0.264, p=0.003) but not with HOMA-IR after controlling for sex, age, and BMI. Multiple linear regression analysis showed that TyG index were significantly associated with US-FLI (β=0.202, p=0.002) not with HOMA-IR after controlling for sex, age, and BMI. The TyG index was superior to HOMA-IR in its ability to detect the severity of NAFLD in US-FLI ≥4, ≥5, and ≥6.

Conclusion: TyG index and HOMA-IR were useful for detecting pediatric NAFLD. However, the TyG index was useful for detecting the severity of NAFLD, whereas HOMA-IR was not. Therefore, we propose to use the TyG index to predict and evaluate the severity of NAFLD in children.

P1-256

Serum leptin concentrations in a pooled cohort of 6.105 children and adolescents: Reference values as a function of dependence on sex, age, pubertal stage and BMI-SDS

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Background: Current reference values for leptin in childhood and adolescence are presented separately for girls and boys, and as a function of age without considering the variability of fat mass. This complicates the interpretation of measured serum leptin concentrations since fat mass is the major determinant of circulating leptin concentrations. To fill this gap, we aimed at pooling existing data (age, BMI, sex, tanner stage (TS), serum leptin concentrations) from cohorts of children and adolescents to establish reference values in dependence of sex, age, pubertal stage and the surrogate parameter for fat mass, BMI.

Methods: The total study group consisted of 11 cohorts with a total of n=6.105 children and adolescents (49.9% females; age range:0.14 - 19.9 years, BMI-SDS range: -4.4 to +6.3). Serum leptin concentrations were measured with the ELISA from Mediagnost, Reutlingen, Germany.

Results: Serum leptin concentrations ranged between 0.01 and 207 ng/ml. We observed an increase in serum leptin concentrations (ln) with increasing BMI-SDS in both sexes (males: r=0.82; females: r=0.83). When serum leptin concentrations were related to age, higher concentrations in girls than in boys were observed. A minimal variance of leptin concentrations was observed in the first three years of age (males: 0.2-14.4 ng/ml; females: 0.2-40.8 ng/ml). From age three to 10 years, the variance of leptin concentrations became wider (males: 0.07-68.8 ng/ml; females: 0.16-74.6 ng/ml) and a wider variance of leptin concentrations was present between 10 and 19.9 years of age (males: 0.11-207 ng/ml; females: 0.2-183.6 ng/ml). Leptin concentrations (median) increased in girls continuously with progression of puberty (2.58 ng/ml at T1 to 29.1 ng/ml at TS5), while in boys, leptin concentrations were highest at TS2 (15.2 ng/ml), declined to 7.68 ng/ml at TS4 and increased again to 8.44 ng/ml at T5.

Conclusion: We describe clear associations between sex, age, pubertal stage, BMI-SDS and leptin concentrations in a large cohort of children and adolescents. We present reference values for leptin concentrations in childhood and adolescence as a function of sex, age, pubertal stage and BMI-SDS.

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Risk Factors for becoming adult with obesity in survivors of childhoodcancer

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Purpose: The aim of this study was to identify risk factors for adult obesity in childhood solid cancer or lymphoma survivors (CCS).

Patients and Methods: The study included 3199 patients of the French Childhood Cancer Survivor Study Cohort (FCCS) with 303 obese patients who had returned self-questionnaire. Analyses were adjusted on social deprivation index and sex.

Results: CCS being less frequently obese (9.5%, 95% confidence interval [CI] 8.5% to 10.5%) than expected from the GFP rates (12.5%; P = 0.0001). Nevertheless, brain tumor survivors were significantly more obese than the GFP (P = 0.0001). Compared with patients who did not receive radiotherapy, for those who received < 1, 1 to 5, 5 to 20, 20 to 40, or ≥ 40 Gy of radiation to the pituitary gland, the RR of obesity was 0.8 (95% CI 0.5 to 1.1), 1.1

(95% CI 0.6 to 1.8), 1.09 (95% CI 1.2 to 3.1), 2.5 (95% CI 1.7 to 3.7), and 2.6 (95% CI 1.6 to 4.3), respectively. Etoposide administration appeared to significantly increase the risk of obesity (RR 1.7, 95% CI 1.1 to 2.6). High social deprivation index was also a risk factors for adult obesity, just like BMI at diagnosis.

Conclusion: Long-term follow-up of CCS should include weight follow-up during adulthood, especially in patients who had received pituitary gland irradiation.

P1-258

An interesting case of combined familial hyperlipidaemia and high lipoprotein (a) in a 20-month-old girl

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Introduction: Familial hypercholesterolaemia(FH) is a genetic disorder affecting approximately 1 in 250 people, resulting in high levels of low-density lipoprotein Cholesterol(LDL-C), increasing the likelihood of developing cardiovascular disease(CVD) at a younger age. Lipoprotein (a)(Lp(a)) is another risk factor for atherosclerosis, elevated in 20-25% of people and 90% genetically determined, only slightly reduced by diet, exercise and medication.

Aim: We describe a 20-month-old girl with a positive family history and a particularly abnormal lipid profile.

Subjects and Methods: Fasting lipids profiles were obtained from the whole family. Clinical diagnosis was made according to the Dutch Lipid Clinic Network criteria. Isolation of genetic material (Macherey Nagel) from whole blood, amplification(PCR-Qiagen) and sequencing(Sanger) of the LDL-r gene were performed.

Results: The family's lipid profiles are shown in table 1. Sudden deaths at <50 years of age due to CVD were reported in the paternal and maternal relatives of the patient at a depth of four generations. Genetic analysis showed that the mother carries the mutation c.902A>G(p.Asp301Gly) in the LDLR gene(NM_000527.5) in heterozygosity belonging to the LDL-receptor class A7 and results in reduced binding of LDL particles by the receptor. The mutation was confirmed in the patient. Analysis continues on the Lp(a) gene.

Conclusions: Elevated Lp(a) is a genetic risk factor for CVD, independent of conventional risk factors such as elevated LDL-C. Although no pharmacologic treatment is available to lower Lp(a) levels in children, measurement of Lp(a) levels is important to further optimize other CVD risk factors, including more aggressive LDL-C reduction and lifelong adoption of balanced lifestyle habits. First-degree relatives of a patient with FH should be screened so that other gene carriers can be identified and treated. All patients with FH and their families should receive education about lifestyle management, including healthy eating, smoking cessation and physical activity.

Table 1. Family's lipid profiles

	Patient	Mother	Father	Brother
TChol <170mg/dl (4.4mmol/L)	392 (10.14)	281 (7.27)	232 (6)	92 (2.38)
HDL-C ≥60mg/dl (≥1.55mmol/L)	47 (1.22)	54 (1.4)	72 (1.86)	41 (1.06)
LDL-C <130mg/dl (<3.36 mmol/L)	326 (8.43)	160 (4.14)	142 (3.67)	44 (1.14)
Tg <150mg/ dl(<1.69mmol/L)	66 (0.75)	63 (0.71)	88 (0.99)	35 (0.4)
Lp(a) <64 nmol/L	90.25	85.8	108.8	13.4
Apolipoprotein A 101-223mg/ dl(1.01-2.23g/L)	126 (1.26)	119 (1.19)	180 (1.8)	94 (0.94)
Apolipoprotein B 53-182mg/dl (0.53-1.82g/L)	193 (1.93)	86 (0.86)	93 (0.93)	39 (0.39)

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Exploring the Relationship between Muscle-to-Fat Ratio and Surrogate Markers of Nonalcoholic Fatty Liver Disease in Children with Overweight and Obesity

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Background: We previously reported on the strong predictive value of the muscle-to-fat ratio (MFR) z-score in the development of early-onset metabolic syndrome components in children with overweight/obesity. Data on the role of the balance between muscle and fat in the development of childhood onset nonalcoholic fatty liver disease (NAFLD) are sparse. In the current study we explored the interplay between MFR and surrogate markers of NAFLD in children with overweight/obesity.

Methods: An observational study of 136 pediatric subjects (56 boys, mean age 12.7±3.4 years, median BMI z-score 2.03 [range:

1.04-4.04]) from March 2022 to March 2023. Body composition was measured by bioelectrical impedance analysis (BIA, Tanita MC-780 MA and GMON Professional Software), and MFR z-scores were calculated. Outcome measures included: aspartate aminotransferase (AST)/alanine transaminase (ALT) ratio, AST to platelet ratio index (APRI), Fibrosis-4 index, NAFLD score, and steatosis (abdominal ultrasonography). Ultrasonography was performed in 62 out of 110 children with obesity (BMI z-score > 1.645).

Results: Strong negative correlations were found between the MFR z-score and the BMI z-score (r=-0.708, P<0.001) and fat percentage (r=-0.675, P<0.001). The MFR z-score showed a positive correlation with AST/ALT ratio (r=0.35, P<0.001), and a negative correlation with ALT (r=-0.294, P<0.001), HOMA-IR (r=-0.26, P=0.022) and age (r=-0.196, P = 0.023). No significant correlations were found between the MFR z-score and APRI, Fibrosis-4 index, and NAFLD score. Among the children who performed ultrasonography, 72.5% (n=45/62) showed evidence of steatosis. These children were older (14.1±2.9 vs. 12.1±2.8 years, P=0.019) and had significant differences in AST/ALT ratio (0.82 [IQR 0.66, 1.18] vs. 1.13 [IQR 1, 1.25], P=0.006), APRI (0.23 [IQR 0.16, 0.32] vs. 0.16 [IQR 0.15, 0.19, P=0.025), Fibrosis-4 index (0.23 [IQR 0.16, 0.30] vs. 0.18 [IQR 0.15, 0.19, P=0.026) and HOMA-IR (6 [IQR 3.8, 8.8] vs. 3.8 [IQR 2.25, 5.75], P=0.05) as compared to those without evidence of steatosis. In a logistic regression model, the only variable that showed a negative association with steatosis was the AST/ALT ratio (OR=0.011 [95%CI 0.001, 0.284], P<0.001).

Conclusions: This study highlights the potential role of an unfavorable body composition in the development of NAFLD in children with overweight or obesity. Preventive strategies should apply interventions for improving not only weight status but also the body composition parameters of both adiposity and muscle. However, further research is needed to determine the clinical significance of MFR in the development of NAFLD in children.

P1-260

Early onset obesity due to Melanocortin 4 receptor (MC4R) defect; Successful treatment with Semaglutide

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Introduction: Childhood obesity is a growing concern worldwide, and it has been linked to several nutritional and genetic factors. In some patients, monogenic causes can be identified, which are due to single gene mutations in specific pathways related to appetite regulation. One of the most common monogenic causes of obesity is heterozygous mutations in Melanocortin 4 receptor (MC4R), with a prevalence ranging from 2% to 6% in juvenile-onset obesity. We report the effect of Semaglutide (GLP1 analogue) in an adolescent boy with severe obesity due to heterozygous MCR4 mutation.

Discussion: A twelve-year-old boy was referred to the tertiary MDT weight management team for concerns of excessive weight gain since one year of age. He was born at term with a birth weight 3.57kg (50th centile). Weight was always above 99.6th centile after 1 year of age. He was diagnosed with autism at the age of 5 years. His mobility was hampered by his weight gain. The investigations revealed insulin resistance, normal fasting glucose and HbA1c, dyslipidemia and fatty liver. The genetic workup confirmed a heterozygous alteration in MCR4 [E61K] (inherited from mother). His management was particularly challenging in view of his exponential weight gain, needle phobia and behaviour difficulties. Intense multidisciplinary lifestyle intervention was not successful, and the patient continued to gain weight to a peak of 187.5kg (BMI 56.5kg/m2; body fat: 63.9%) at the age of 13 years. He was started on weekly Semaglutide at a dose of 0.5mg and gradually increased to 1mg weekly. Due to his severe autism and needle phobia, it was agreed that weekly injections would be the most suitable treatment option alongside lifestyle modification. After 12 weeks of Semaglutide treatment, his BMI decreased to 52.2kg/m2 (weight 176.8kg, body fat: 52.7%). Weight loss of 5.7% and 9.8% was recorded at 3- and 6-months post Semaglutide respectively.

Conclusion: We report a significant weight loss following weekly GLP1 analogue therapy in a patient with MC4R mutation and rapid weight gain leading to complications. MC4R receptor has been considered as a potential drug target for the treatment of monogenic obesity. GLP-1 analogues could circumvent MC4R-induced appetite regulation and thereby constitute a treatment option for individuals with MC4R mutations. A holistic approach that combines lifestyle modification, behavioural intervention, and pharmacological treatment is required to manage severe obesity in children and young people.

P1-261

Decreased physical fitness in children is associated with increased cardiovascular risk determined by increased carotid intima-media thickness

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Background: Early vascular aging is driven by modifiable lifestyle risk factors, including physical inactivity. Early identification of children at risk of atherosclerosis (AS) is needed for implementing primary preventive measures addressing vascular health. The aim of the study was to determine the association between objectively determined physical fitness (PF) and carotid intima-media thickness (cIMT), used as a reliable noninvasive biomarker of AS in a population of healthy children.

Methods: 784 healthy children (49.9% male) between the ages of 6 and 15 (mean +/. SD; 8.89 +/- 3.52 years) were included. cIMT measurement was performed by a linear probe with a frequency range of 3 to 13 MHz and the radiofrequency-based software-guided technique (RFQIMT, Esaote®). Device-specific percentile values for age and sex were used. The dataset on PF was obtained from the national physical activity surveillance system in collaboration with the Faculty of Sports (https://en.slofit.org/). An overall PF score is calculated from eight tests (arm plate tapping, standing broad jump, backward obstacle course, sit-ups in 60 s, stand and reach, bent-arm hang, 60-m dash, 600-m run). Low PF was determined if their score was < 10th percentile and high if the score was > 90th percentile. Percentile values are age- and sex-specific, based on the ranking of every child in the population of all Slovenian children in the 1989–2019 period. The PF results are not adjusted to weight, height, triceps skinfold thickness, or BMI. Statistical analysis of the pairwise comparison of cIMT in low and high PF performance groups was done using the Wilcoxon rank sum test with continuity correction.

Results: Children with PF < 10th percentile had higher cIMT (N= 58; mean 593 +/- .31 µm) than those with PF > 90th percentile (N=178; mean 480 +/- .29 µm) as was determined by the Wilcoxon rank sum test with continuity correction (p = .012).

Conclusion: Decreased PF was linked to an increased cITM, as a marker of early AS in a healthy population of children and adolescents. These results suggest that objectively determined PF in healthy children could be used as an additional screening tool to determine those at an increased cardiovascular risk already in childhood.

P1-262

16p11.2 microdeletion: a common copy number variation (CNV) identified in a Portuguese pediatric cohort with syndromic obesity

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Background: 16p11.2 microdeletion is most common chromosomal anomaly associated with syndromic obesity. The presence of a large number of flanking segmental duplications/low-copy repeat sequences with a high degree of sequence identity in the short arm of chromosome 16 (16p) leads to recurrent deletions and duplications as a consequence of non-allelic homologous recombination. A recurrent 600kb microdeletion is one of the most frequent genomic imbalances in 16p11.2 (~600kb) associated with abnormal phenotypes including neurodevelopmental disorders, autism spectrum disorder (ASD) and obesity. The 16p11.2 microdeletion (OMIM ID:611913; ORPHA:261211) is one of the major causes of syndromic obesity.

Material and Methods: it was performed a retrospective analysis of patient medical records of 45 patients with 16p11.2 deletions obtained by Agilent 180K oligonucleotide array-comparative genomic hybridization (array-CGC) and/or multiplex ligation-dependent probe amplification (MLPA). The study was performed at Pediatrics Hospital of Coimbra during the period of 2010-2022.

Results: From a total of 45 patients, 37 (82%) were under 18 years old, and 33 (91.6%) showed a deletion in the classical region of 16p11.2 (29,562-30,192bp). Thirty one (84.6%) were referred to our consultation from intellectual disability/learning difficulties and in those, only 6 (18%) was also reported to have obesity. Although the phenotype of individuals with the deletion can be variable, all patients showed at least one clinical finding typical of 16p11.2 deletion: cognitive impairment, language delay, autism or obesity. Seven from 28 (25%) individuals between 5 and 19 years old (WHO reference 2007) have body mass index (BMI) >2 standard deviation (SD) and 7 (25%) were overweight with BMI>1 SD. One (11,1%) from 9 individuals under 5 years old was obese (BMI>3SD).

Conclusion: Although the phenotype of 16p11.2 microdeletion syndrome shows a high variability, it represents the second most frequent genetic cause of obesity. In our cohort 21.6% were obese and 25% were overweight. The obesity observed in this population may be explained by the haploinsufficiency of one or more of the 30 genes present in this region. On the other hand, it is known that individuals with intellectual disability or autism have a higher predisposition for obesity, possibly due to the involvement of one or more pathways.

P1-263

Evaluating genotype-phenotype relations in pediatric obesity: a single centre experience

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Background: Childhood-onset obesity is a multifactorial disease with a lifelong health burden. In many cases, obesity is the result of the interaction between genetic predisposition and environmental factors. Aim of our study was to define phenotypic features of obese children and adolescents and to find possible associations between clinical phenotype and genetic variants.

Patients and Methods: We recruited obese children followed at our centre, who underwent obesity NGS panel (roadgenetics.unilabsweb.com). Genetic variants were defined as pathogenetic or variants of unknown significance (VOUS); VOUS were classified into 3 categories: suspected pathogenetic, uncertain, and suspected benign. We defined as "negative" patients with no variant, "positive" patients with any potentially relevant variant; we then defined as "suspected pathological" patients carrying pathogenetic variant(s) or suspected pathogenetic or uncertain VOUS, while patients with negative test or suspected benign VOUS were defined as “normal”. Clinical data were analyzed and compared to genetic findings.

Results: 25 patients (12M,3F) were enrolled between May, 2022 and March, 2023. Median age at blood sampling was 10.78 years (1st-3rd quartile 7.47-13.07years). Median age at obesity onset was 3.2 years (1.4-4.4years). Hyperphagia was reported by only 9 subjects. Median BMI was 33.8Kg/m^2 (27.6-38.8), median BMI SDS +3.60 (3.17-4.10). Median height SDS was +0.5 (-0.5-+2.0), while median delta between height and mid-parental height was +0.9 SDS (0.2-1.4)

A positive genetic test was found in 18 patients(72%), while 11 patients(44%) had a suspected pathological genetic test.

Median BMI SDS did not differ significantly between patients with a positive genetic test compared to negative genetic test (3.65 vs 3.58, P=0.16), nor between patients with suspected pathological findings and patients with normal result (3.68 vs 3.51, P=0.67). A trend towards higher height SDS was found in subjects with a suspected pathological test compared to normal tests (2.00 vs 0.25, P=0.07). No significant relation was found between height-mid-parental height SDS delta and genetic findings. Age at obesity onset did not differ significantly in patients with positive or negative genetic test(2.0 vs 4.7years,P=0.14), or in patients with suspected pathological or normal genetic test(3.0 vs 4.0 years, P=0.65)

Conclusions: Our preliminary findings in a small cohort of obese children support the hypothesis that no clinical feature – e.g. degree of obesity, age at disease onset, stature, or difference between stature and mid-parental height – predicts the presence of genetic variants in obese children.

P1-264

Implementation of the EOSS-P Risk Scale in children and adolescents living with obesity

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Body Mass Index (BMI) has a high association with body fat percentage and direct association with a higher degree of comorbidities. Categorizing patients only by the degree of obesity, as has been done over time, restricts the possibility of detecting and giving timely treatment to other aspects.

The Edmonton Obesity Staging System for Pediatrics (EOSS-P) has been proposed as a tool to categorize obesity not only by BMI, but also by assessing metabolic complications, functional/mechanical limitations, mental health and social environment, thereby helping to create strategies to target treatment based on individual needs.

An ambispective, cross-sectional, observational and descriptive study was conducted. The clinical record of 261 pediatric patients diagnosed with obesity in the period from January 2021 to November 2022 in the Child Welfare Unit of the General Hospital of Mexico was evaluated, of which only 80 complied with all the corresponding evaluations. Data were obtained and staging was assigned based on the EOSS-P scale.

In order to make an objective assessment of each of the domains, a general instrument was designed that was built using standardized and validated scales for the pediatric population, which were adapted to the reagents that make up the different domains.

Since the final EOSS-P score is assigned by the highest score obtained in any of the 4 domains, it was evidenced that 5% of the total sample was classified in stage 1, 33.8% in stage 2, and 61.3% in stage 3. Surprisingly, none of our patients were classified as stage 0.

The domains that we found most affected were metabolic and social, since up to 98.7% of patients presented some degree of involvement.

It was found that pediatric patients living with obesity are in advanced stages of severity on the EOSS-P scale, making them susceptible to developing severe comorbidities, from early in life regardless of the degree of obesity.

Achieving the design of a tool that evaluates through validated scales all aspects of each of the domains of the EOSS-P in our population.

This staging can be used in our patients to plan an individualized intervention strategy aimed at their needs, in order to achieve better adherence to treatment and with the aim of improving quality of life in the medium and long term.

P1-265

Evaluation of Clinical and Genetic Characteristics of Non-Syndromic Monogenic Obese Patients

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Keywords: Non-syndromic obesity, single gene disorder, child.

Objective: This study aimed to evaluate the clinical characteristics, molecular genetic analysis results, and obesity-related comorbidities of patients with non-syndromic monogenic obesity

Materials and Methods: The results of a targeted next-generation sequence analysis panel (Clinical Exome Solution v2 - SOPHiA GENETICS) of 73 children and adolescents with non-syndromic obesity, followed up between 2003 and 2022 were analysed. Patients in whom variants were detected and who met at least two of the following criteria were included in the study; diagnosed with obesity at the age of <6 years, body mass index (BMI) SDS >2.5, presence of obesity in one of the parents, or a history of consanguinity between the parents.

The pathogenicity of the variants was determined in accordance with the 2015 “American College of Medical Genetics and Genomics” criteria.

Results: Twenty of the patients had disease-associated variants, MC4R in 11patients, 5 in POMC, 2 in LEPR, 1 in LEP, and 1 in the

CARTPT gene. The median age was 14.5 years (4.5-23.6), the age at presentation was 6.6 years (0-17.5), BMI SDS was 3.25 (1.8-10.1), and BMI according to the 95th percentile was 143.8% (101-311). Family history of obesity was found in 50%, and consanguineous marriage between parents was found in 45% of the patients.

Hepatosteatosis (HS) was found in 8 (40%), hypertension (HT) in 3 (15%), and dyslipidemia in 3 (15%) patients. Patients with MC4R variants had hypothyroidism (primary, central, Hashimoto thyroiditis), tall stature, ectopic neurohypophysis, and psychiatric disorders.

Adrenal insufficiency, central hypothyroidism, cholestasis, epilepsy, and psychiatric disorder were found in patients with POMC deficiency. Hypogonadotropic hypogonadism and subclinical hypothyroidism were found in patients with variants in LEPR. The patient with a variant in the LEP gene had a BMI of 34.4 kg/m2 and a BMI SDS of 4.67 at the age of 6. With metraleptin treatment, BMI decreased to 18.8 kg/m2, and BMI SDS decreased to 0.32 at 10.8 years old.

Conclusions: Elucidation of the causes of obesity due to single gene disorders is important for diagnosing and treating comorbidities such as central adrenal insufficiency, hypothyroidism, and hypogonadotropic hypogonadism. Early genetic evaluation allows for the identification of treatable obesity. Providing timely intervention and implementing personalized management protocols may result in more efficient positive outcomes.

P1-266

Abdominal fat measured with nutritional ultrasound as a risk screening for non-alcoholic hepatic steatosis (NASH) in obese children

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NASH is an increasingly relevant finding in the pediatric population affected by obesity. In adults, its evolution from this steatosis to fibrosis and its correlation with metabolic syndrome is increasingly significant. The existence of a rapid and validated screening tool in consultation would be very useful.

Main Objective: To evaluate if the measurement of intraperitoneal fat measured through nutritional ultrasound, allows the diagnosis of non-fatty hepatic steatosis or metabolic risk in overweight/obese patients. To establish whether there is any type of correlation between the measurements of abdominal fat obtained by nutritional ultrasound and those obtained in routine clinical practice of these patients by means of liver ULTRASOUND if this is performed within routine clinical practice.

Material and Methods: Patients who attend the CCEE of Endocrinology for being overweight. BMI >2 SDS. MINDRAY Z50 ULTRASOUND. (Hamagawa technique) by means of abdominal adipose ULTRASOUND study (superficial subepidermal fat - stored energy, deep and intraperitoneal-risk in adults of NASH)

Results: First national validation study in pediatrics of deep ECOGRAPHY compatible with NASH vs nutritional ECO

Study in 103 patients of deep ECO by radiologist and nutritional ECO. NASH 60/103 (58%). Mild distribution 50/103 (48%), moderate 9/103 (8.9%) and severe 1/103 (1%).

A Mann-Whitney U test was performed. The results showed that the mean intraperitoneal fat (adipose) was statistically significantly higher among the NASH affected groups (z = -7.603, p < 0.01) at a significance level of 0.05.

The cut-off point that presents a positive correlation between NASH YES/NO would be a mean of 0.93 cm CI [0.70-0.94] 95% using the Mann-Whitney U test. Sensitivity 97%. Specificity 95%.

Conclusions: There is a high prevalence of NASH in childhood obesity.

The classical ECO is related by means of a linear and positive correlation with the pre-peritoneal fat mass studied by nutritional ECO.

P1-267

Seven Years Follow Up of a Child with Familial Chylomicronemia Syndrome: Disease Course and Effectiveness of Gemfibrozil Treatment: Case Report and Literature Review

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Keywords: Hypertriglyceridemia; Familial Chylomicronemia Syndrome; Gemfibrozil

Background: Familial chylomicronemia syndrome (FCS) is a rare autosomal recessive disease affecting lipoprotein metabolism. The condition is characterized by hypertriglyceridemia, which may predispose patients to acute pancreatitis. FCS is estimated to occur in 1 in 1 - 2 million individuals [1] and can be diagnosed at any age, affecting all genders, races, and ethnicities equally [2].

Case Presentation: Here, we presented the case of a now seven years old girl with FCS on Gemfibrozil and dietary restrictions. The patient initially presented at 40 days of age with bloody diarrhea. Serum samples showed lipemia with markedly elevated triglyceride levels. She was diagnosed with FCS, confirmed by genetic testing, revealing a homozygous variant c.833C>T(p,Ser278Phe) for the LPL gene. Despite starting a low-fat diet with medium chain triglycerides (MCT) based milk formulas, the patient developed acute pancreatitis two months later, with continued elevated triglyceride levels. She was started on Gemfibrozil and fat-soluble vitamins at two months of age, with marked improvements noted during six years of treatment and follow-up (Table 1). Currently, she is well, with normal growth parameters and no other episodes of acute pancreatitis. Her triglyceride levels have maintained within normal levels (Table 1).

Conclusion: Familial chylomicronemia syndrome is a rare, inherited lipid disorder that often goes underdiagnosed and unmanaged. It is mainly present in childhood but can be seen in infancy, with different manifestations. There are insufficient data regarding its treatment protocol. The mainstay of treatment is a dietary restriction, although some patients may require lipid-lowering agents. It is worth considering the Fibrate derivative (Gemfibrozil) to be one of the lines of management early after diagnosis.

Table 1. Laboratory results of the reported patient since diagnosis

Test / age	normal range	40 days	8 weeks	10 weeks	6 months	1 year	2 years	3 years	4 years	5 years	6 years	6.5 years	7 years
Triglycerids mg/dL (mmol/L)	< 75mg/dl (0.8mmol/) [age 0-9 years]	3221 (36.4)	1009 (11.4)	716 (8.0)	747 (8.44)	965 (10.79)	360 (4.0)	567 (6.4)	406 (4.59)	312 (3.53)	327 (3.7)	304 (3.44)	293 (3.31)
Total cholesterol mg/dL (mmol/L)	< 170mg/dl (4.4mmol/L)	162 (4.2)	80 (2.0)	103 (2.67)	113 (2.9)	-	-	-	-	-	-	-	-
Lipase	13-60 U/L	-	11	272.1	33.3	66.6	56	28.3	-	41	17	26	-
Amylase	28-100 U/L	-	-	13	20	45	61	67	-	58	48	43	-

P1-268

The 2016–2021 Korea National Health and Nutrition Examination Survey for Metabolic Alteration in children and adolescent during the COVID-19 Pandemic

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Purpose: Since the COVID-19 outbreak, the number of obese children and adolescents has increased rapidly. Obesity acts as a gateway to chronic adult diseases, so proper management during childhood and adolescence is essential. We aimed to identify the interannual changes in the prevalence of obesity, diabetes mellitus, dyslipidemia, and hypertension, and to investigate factors contributing to these changes before and during the COVID-19 pandemic.

Methods: This study was conducted using data from the 2016-2021 Korean National Health and Nutrition Examination Survey (KNHANES), which included a total of 3861 children and adolescents aged 10-18 years. The prevalence of obesity and disease was adjusted by age, sex, and income. We also analyzed the socioeconomic, nutritional, and physical activity items of the survey.

Results: During the COVID-19 pandemic, there was a significant increase in the trend of mean body mass index (BMI) (from 21.0 to 21.4 kg/m2, p=0.03) and mean glycated hemoglobin (HbA1c) (from 5.36 to 5.4%, p=0.005). The prevalence of obesity also significantly increased, ranging from 12.55% to 17.29% (p=0.002) among children and adolescents aged 10-18 years. In the obese group, there was an apparent increase in the number of metabolically unhealthy children and adolescents. The prevalence of central obesity showed a significant increasing trend (p=0.016), and the proportion of HbA1c≥5.7% increased from 9.92% to 13.99% (p=0.029). The frequency of parents' central obesity also increased. In terms of central obesity and BMI, children and their parents showed significant linear associations. The intake of food and calorie was significantly reduced in the normal-weight groups but not in the obese groups. The proportion of people who skipped breakfast has increased and eating out has been reduced regardless of obesity status. Health behavior did not show significant changes.

Conclusions: Obesity in children and adolescents is sensitive to the social environment. During COVID-19, the prevalence of metabolically unhealthy obese children has significantly increased, while the proportion of metabolically healthy normal-weight children has decreased. Attention should be paid from the beginning to improve children's health indicators. Age-specific strategies considering growth and development, genetics, and social factors are needed. Additionally, health strategies for the entire family are necessary to develop healthier habits in teenagers.

P1-269

Impact of bariatric surgery on obesity complications in children and adolescents: Evaluation of a large cohort within a specialized French obesity center

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Summary: Severe obesity with various complications is a growing public health problem in childhood. Due to the lack of available hygienic and dietary therapeutic solutions, bariatric surgery has become, in recent years, one of the only effective treatments for severe obesity to induce persistant weight loss and reduce complications.

Material and Method: We analyzed a cohort of 162 patients followed in the specialized obesity center of South Paris between 2012 and 2021.

We retrospectively analyzed anthropometric parameters and obesity complications before and after bariatric surgery (6 and 18 months) in 95 patients.

The primary objective of the study was to assess the effectiveness of the procedure on weight loss and reduction of metabolic, mechanical and psychological complications in non-mature subjects who had completed their growth. We defined minimal, moderate and severe complications in accordance with French recommendations. Psychological complications were monitored

according to a self-reported quality score established in the adolescent department.

The secondary objective of the study was to evaluate the safety of performing this surgery in this population.

Results: We analyzed 95 patients, with a median age of 17 years. Surgery resulted in a decrease in BMI of 10kg/m^2 [24,1-60,7] at 6 months and an additional of 5kg/m^2 [22,5-45,9] at 18 months in the study population. After surgery, complications had regressed in more than half of the patients: 44.2% of patients still had a complication of their obesity, of which 25.2% were minimal complications, 10.5% moderate complications and 8.42% severe complications.

36.84% of patients had no further complications of their obesity, 18 months after surgery.

We observed significant efficacy on mechanical and psychological complications in the population.

We also found the safety of this surgery in adolescents when performed by trained surgeons because only 1 patient out of the 95 operated required a revision surgery.

Conclusion: Bariatric surgery has shown promising results in terms of safety and efficacy on weight loss and reduction of complications for severe juvenile obesity. Our study confirms this efficiency with a significant weight loss at 18 months after surgery. The early realization of this intervention has shown its value on reducing moderate and severe complications for these adolescents who have failed multiple hygienic and dietary measures and develop early metabolic complications.

Meanwhile the proof of effectiveness of pharmacologic therapies in child, bariatric surgery is a safe and effective solution to prevent the development of severe complications of adult obesity for these patients.

P1-270

MC4R deficiency in a portuguese pediatric cohort study

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Background: Melanocortin 4 receptor (MC4R) deficiency is the commonest monogenic form of non-syndromic obesity. MC4R is a seven transmembrane G-protein coupled receptor implicated in central regulation of body weight. The loss-of-function mutations in *MC4R* gene will contribute to early-onset obesity associated with hyperinsulinemia, hyperphagia and "binge eating". We aim to determine the prevalence of *MC4R* variants in a Pediatrics Portuguese cohort with obesity. We present our preliminary results and the clinical description of the identified cases.

Material and Methods: Patients with obesity onset before 10 years and BMI > 95th centile observed at Pediatrics Hospital of Coimbra, without intellectual disability were screened for *MC4R* variants by Sanger sequencing after PCR amplification. Molecular and clinical characterization was performed in cases with identified *MC4R* variants.

Results: A total of 134 patients (mean age was 11 years, 62 boys) were included in the study. It was identified one already described (1/134, 0.75 %) pathogenic heterozygous *MC4R* variant inherited from the mother: c.631_634del (p.Leu211Metfs*6). Additionally, we identified four (4/134, 2.98%) patients with heterozygous variants at *MC4R* classified as unknown significance (VUS) according to ACMG/AMP classification but with *in silico* predictions reporting them as deleterious. All of them were inherited from one progenitor.

Conclusions: Our results point out that *MC4R* deficiency is underdiagnosed in the Portuguese population. The absence of distinctive phenotypic features reinforce the need of screening large cohorts with broad inclusion criteria. This diagnosis will contribute to the follow-up of identified cases, an early diagnosis in other family members and the prospective of using the specific therapies that are under development, partial agonists of the *MC4R*. We will describe the case reports with discussion of reported variants.

P1-271

Investigation of LDL Cholesterol in Children from Seiiku Cohort for Children and Mothers

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Background: LDL cholesterol (LDL-C) levels can be high in familial hypercholesterolemia or other dyslipidemia, and the elevated levels are often found in the pediatric setting.

Objective: To create a pediatric reference using data of a prospective birth cohort study at our hospital (Seiiku Cohort for Children and Mothers) and to examine its association with possible predisposing factors.

Result: LDL-C was measured with direct assay. The mean +/- SD values of LDL-C and numbers of children with high LDL-C (over 140mg/dL) were 107.59 +/- 28.75 mg/dL and 112/894 (12.5%) at the age of 1 year, 93.65 +/- 19.82 mg/dL and 13/715 (1.8%) at the age of 3, 87.79 +/- 19.84 mg/dL and 7/557 (1.3%) at the age of 6, 90.68 +/- 19.94 mg/dL and 4/333 (1.2%) at the age of 7, 94.32 +/- 20.28 mg/dL and 6/251 (2.4%) at the age of 8, and 94.67 +/- 20.68 mg/dL and 8/369 (2.2%) at the age of 9, respectively. There is a positive association between BMI and LDL-C levels at school age. Children who were fed only with breast milk in infancy had relatively higher LDL-C levels at the age of 1 and lower ones after the age of 3, although the multivariate regression analysis did not reveal significant difference in LDL-C levels at the age of 9 between exclusively breast-fed children and the others. Earlier adiposity rebound have positive association with BMI at school age, but no association with LDL-C.

Conclusion: The normal range of LDL-C was higher at the age of 1, but reduced by the age of 3 and remained unchanged in elder children. Breast feeding in infancy may have beneficial effect on LDL-C levels in later life.

P1-272

Various clinical manifestations found in 3 cases with Progeria syndrome

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Background: Progeria syndromes caused by *LMNA* gene variants consist of Hutchinson-Gilford progeria syndrome (HGPS) and Atypical progeroid syndrome (APS). Various phenotypes of APS are previously reported, whereas HGPS shows relatively unique phenotype.

Objective: To investigate the spectrum of clinical manifestations in three cases of Progeria syndrome.

Methods: The history and clinical picture of three cases of Progeria syndrome experienced at our hospital were reviewed retrospectively.

Results: Case 1 was a 22-year-old woman. She was noted to have failure to thrive in infancy, and skin thinning at 1 year of age. Clinical diagnosis was made as Progeria syndrome at 7 years of age based on skin findings and facial appearance. She had decreased early insulin response at 8 years of age and high LDL cholesterol levels at 9 years of age. She had spontaneous menarche at 12 years old with scarce breast fat; the percent whole body fat was 23% at 16 years of age although the fat accumulation was low in the limbs.

Case 2 is a 5-year-old girl. She showed poor weight gain in early infancy and decreased subcutaneous fat at around 2 years of age, suggesting progeria syndrome. Low subcutaneous fat was revealed on MRI before the age of two.

Liver dysfunction, insulin resistance and body fat percentage of 15% was detected at 3 years of age. Progressing hair loss are being observed after 2 years old.

Case 3 is a 2-year-old boy. He had poor weight gain from birth, scleroderma-like skin from 2 months, short stature below -2 SD at 5 months, alopecia, decreased early insulin response and body fat percentage of 20.5% at 1 year of age.

All three cases had *LMNA* gene mutations; in case 1, p.C558R was identified at 18 years of age, in case 2, p.D136Y at 3 years of age and both were novel variants. Case 3 had a point mutation of p.G608G within the *LMNA* gene exon11, which was typical in HGPS.

Discussion: Case 3 had the typical presentation of HGPS. Of the two APS cases, case 2, in which insulin resistance and fatty liver was discovered earlier, had lower body fat percentage, which suggested that the amount of adipose tissue loss might have an influence on the phenotype. Two cases of APS had novel mutations in the *LMNA* gene respectively. Regarding genotype-phenotype association, future follow-up of the clinical picture and accumulation of cases are needed.

P1-273

Congenital Leptin Receptor deficiency: A Novel LEPR gene mutation (LEPR):c.1752G>A (p.Lys584=) in an Indian family producing severe early onset monogenic obesity

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Introduction: Congenital deficiency of the leptin receptor is an extremely rare cause of early-onset monogenic obesity with rapid weight gain and compulsive overeating. LEPR mutations is responsible for extreme form of obesity associated with other endocrine abnormalities and respiratory tract infection. Till date, approximately 50 families have been reported to have mutations in the leptin receptor gene.

Case: 9-year-old girl and her 15-month-old brother born of third-degree consanguineous marriage with Asian ethnicity came for obesity assessment. Their elder sibling with morbid obesity succumbed at 1.5 years. Both children had normal birth weight with rapid weight gain during early infancy. Girl started to put on weight after 3 months of age (weight 10.3 kg; Z score -4.77) rapidly increasing to 19 kg (Z score -6.66) at 11 months. She had undergone bariatric surgery twice first at 11 months of age and later at 7years due to rapid weight gain [weight-49 kg and Z score -3.02] and type 2 DM. Boy also started to put on weight after 4 months with current weight of 18 kgs (Z score: 5.78) and length 80cms (Z score –0.77) with weight for height more than 99th percentile (Z score -6.82). Both had dyslipidaemia and high serum leptin levels.

WES reported novel homozygous mutation synonymous variant NM_002303.6 (LEPR):c.1752G>A (p.Lys584=) on chromosome 1p31, which had not been reported previously. The nucleotide c.1752 in LEPR is predicted conserved by GERP++ and PhyloP across 100 vertebrates. The variant is segregating in two affected siblings whose serum leptin levels were also elevated, parents and an unaffected sibling were heterozygous carriers. For these reasons, this variant was classified as Pathogenic variant in our case. This is only second family in India with LEPR gene mutation and first with novel mutation.

Setmelanotide is a selective melanocortin-4 receptor agonist which has been approved by US FDA in November 2020 for genetically proven obesity with LEPR mutation in children older than 6 years. Currently Setmelanotide is not available in India but could be used in future. Due to non availability of setmelanotide, Younger boy to undergone bariatric surgery

Conclusion: This illustrates importance of early molecular genetic diagnostics in patients with severe, early-onset obesity to avoid lengthy diagnostic and unsuccessful and frustrating therapeutic procedures especially where consanguinity is more common. Improving awareness and availability of genetic testing will help these patients with monogenic obesity to gain access to treatment with recently developed newer drugs.

P1-274

Breakfast skipping is associated with poor diet quality in children with overweight/obesity

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Introduction: Daily breakfast consumption is recommended as part of a healthy lifestyle in children and adolescents. The present study aimed to report the frequency of breakfast consumption and explore the associations between breakfast consumption and diet quality in children with overweight/obesity.

Methods: In total, 1335 children/adolescents 2-18 years old were recruited in a weight-management out-patient clinic in the 'Aghia Sophia' Children's Hospital, Athens, Greece. Participants' body weight and height were recorded by trained researchers, using standard methods and equipment. Family socio-demographic data and data on children's dietary habits (a validated food frequency questionnaire and the frequency of breakfast consumption) were collected via interviews with the parents. Diet quality was assessed using the Diet Quality Index (DQI).

Results: The highest percent of breakfast skipping was identified among children/adolescents 13–18 years old (43.3%, p=0.008) compared to other age groups (2-5 or 6-12 years old). Within this age group, girls were more likely to skip breakfast for at least 1 day per week ("Every day" consumers: Boys Vs Girls: 66.9% Vs 47.3%; p=0.002). In the total study sample, skipping breakfast was significantly associated with poorer diet quality (% percent of children/adolescents having "At least moderate diet quality", i.e., DQI-score: 59.34-90.83, was 77.1% and 50.9% for "Everyday" consumers and "At most 5–6 days/ week" consumers, respectively; p<0.001). The results of the multivariable binary logistic regression showed that daily breakfast consumption compared to skipping breakfast for at least 1 day per week was associated with significantly higher odds of having at least moderate diet quality (OR = 3.25; 95% C.I.= 2.55 – 4.13).

Discussion: The findings of the present study showed that breakfast consumption may contribute to better diet quality in children and adolescents with overweight/obesity. Children/adolescents aged 13-18, especially girls, seem to be at higher risk for skipping breakfast. Future initiatives should focus on the promotion of healthy and balanced breakfast in children and adolescents with overweight/obesity.

P1-275

Child with AR sitosterolemia with no hematological manifestations

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Sitosterolemia is an autosomal recessive disorder affecting lipid metabolism which is characterized by decreased biliary excretion and increased absorption of plant sterols and cholesterol, leading to significantlyelevated serum levels of plant sterols. Approximately 80 homozygous or compound heterozygous variants in adenosine triphosphate-binding cassette subfamily G genes (ABCG5/ABCG8) genes have been described in patients with genetically confirmed sitosterolemia. Clinically, sitosterolemia has been associated with xanthomas, premature atherosclerotic events, and hematologic manifestations. Phenotypic characteristics of sitosterolemia have been described properly in case series or local cohort observations, but identifying this disease in clinically suspected patients can be difficult. It is vital to be able to recognize index cases so that urgent diagnosis and effective management can be provided for family members who might also be affected.

We are presenting a 12 year old boy, medically free, presented to the primary care Clinic with 2 months history of episodic mild chest pain, mainly after exertion, associated with shortness of breath. Investigations were done and he was found to have high serum concentrations of lipids (LDL 6.3, Total Cholesterol 8) and normal levels of triglycerides. On examination, the patient had bilateral single tendon xanthoma over the extensor surfaces of the elbows (Measuring 3x2.5x3 cm). Familial dyslipidemia was suspected, and genetic testing was sent, which came back positive for a homozygous pathogenic variant in the ABCG5 gene, which gives a diagnosis of autosomal recessive sitosterolemia type 2.

Our study findings and clinical manifestations has been consistent with most cases in the literature. However, our case hasn't shown any hematological features, including thrombocytopenia, anemia, or splenomegaly, which are one of the key differentiators between sitosterolemia from familial hypercholesterolemia.

P1-276

A novel mutation in LPL gene in two Brazilian children with familial chylomicronemia syndrome

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Case Report: Patient 1: a 3.6-yr-old girl presented with very severe hypertriglyceridemia (serum triglyceride level >1000mg/dL) in random sampling in the first year of life. She presented with recurring episodes of abdominal pain, and splenomegaly. There is no history of consanguineous marriage. Maternal and paternal family had history of coronary events at an early age. A genetic panel showed homozygous variant chr8:19.953.365 C>T (p.Ala162Val) in the lipoprotein lipase (LPL) gene, of unknown significance. She is currently 4.4-years-old, height 103.4cm (-0.7SDS, WHO), weight 15.3kg (-0.77SDS).

Patient 2: a 2.5-yr-old boy, cousin of patient 1, had history of lipemic serum in blood collected for exams to fever investigation when he was 2-month-old. At 1-year-old, the triglycerides level was 7430mg/dL. A genetic panel showed two heterozygous variants in the LPL gene, a previously described variant of unknown significance and a pathogenic variant, chr8:19.954.222 G>A (p.Gly215Glu). Currently, he is 3.2 years old, height 94.4cm (-1.03SDS), weight 13.4kg (-0.79SDS).

Both families were advised on very-low-fat diet and discontinuation of breastfeeding. Bezafibrate, liposoluble vitamins and medium chain triglycerides (MCT) replacement were initiated for both patients at 2 years. Despite these, patients still presented with severe hypertriglyceridemia. Current fasting triglycerides levels are 4459mg/dL in patient 1 and 4567mg/dL in patient 2.

Discussion: Familial chylomicronemia syndrome is a rare recessive autosomal disease characterized by the abnormal persistence of chylomicrons in blood after 12-14-hours of fasting. It is caused by mutations in genes that code key molecules in the lipolysis cascade. LPL gene mutations are responsible for over 80% of cases, and here, a new unpublished mutation of chr8:19.953.365 C>T (p.Ala162Val) in the LPL gene was described for the first time to our knowledge. It is classified very severe hypertriglyceridemia when fasting triglyceride levels are greater than 1000mg/dL. Patients can present with eruptive xanthoma, lipemia retinalis, hepatosplenomegaly, acute or recurring episodes of abdominal pain and pancreatitis. Management includes restrictive nonfat diet and discontinuation of breastfeeding for infants. There is poor response to traditional hypolipidemic agents such as fibrates. MCTs can be used as a source of fatty acids and allow for adjusting caloric ingestion and dietary macronutrient content. Regular monitoring of liposoluble serum vitamin levels is recommended, with supplementation as required.

Conclusion: A novel mutation in LPL gene was described. Familial chylomicronemia syndrome is a rare, difficult-to-treat disease that responds unsatisfactorily to fibrates. The basis of treatment consists of non-pharmacological measures such as a low-fat diet.

P1-445

Impact of early-life overweight/obesity trajectory on insulin resistance at age 8: a prospective cohort study

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Objective: To investigate whether the early-life overweight/obesity trajectory from ages 2, 4, to 8 affects insulin resistance (IR) in 8-year-old prepubertal children.

Methods: From the Environment and Development of Children (EDC) cohort, 262 prepubertal children (147 boys and 115 girls) who visited Seoul National University Children's Hospital for anthropometric measurements at ages 2, 4 and 8 were included. At age 8, homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as insulin (mIU/ml) × glucose (mg/dl)/405. Normal weight (NW, <85th BMI percentile), overweight (OW, 85–95th BMI percentile), and obese (OB, ≥95th BMI percentile) status from ages 2, 4, to 8 were accessed to define eight OWOB trajectory groups. The relationship of OWOB trajectory groups with glucose and HOMA-IR was analyzed after adjusting for age, sex, prematurity, small for gestational age, parental BMI, and parental education.

Results: NW groups at age 8 were classified into NW at ages 2, 4, and 8 (all-NW, n = 176), OWOB at age 2 and NW at ages 4 and 8 (OWOB-NW-NW, n = 13), NW-OWOB-NW (n = 9), and OWOB-OWOB-NW (n = 5). OWOB groups at age 8 were categorized into NW-NW-OWOB (n = 33), OWOB-NW-OWOB (n = 7), NW-OWOB-OWOB (n = 8), and OWOB at ages 2, 4, and 8 (all-OWOB, n = 11). For glucose levels, all-OWOB group only showed higher fasting glucose than the all-NW group ($p = 0.015$). For HOMA-IR, compared to all-NW group, OWOB at age 8 (all-OWOB, NW-OWOB-OWOB, OWOB-NWOWOB, and NW-NW-OWOB groups) or OWOB at age 4 (OWOB-OWOB-NW, and NW-OWOB-NW groups) showed higher HOMA-IR (all $p<0.05$). However, OWOB at age 2 but NW at age 4 and 8 (OWOB-NW-NW group) showed no difference in HOMA IR compared to all-NW group.

Conclusion: Children who were OWOB at age 8 showed higher insulin resistance than NW children at ages 2, 4, and 8. Children who were OWOB at age 4 had higher insulin resistance than all NW children even if they were NW at age 8.

P1-446

The evolution of diagnosis and care over time in children with Prader-Willi syndrome, born between 2005 and 2021,included in the French database

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Introduction: The French Reference Centre PRADORT set up a national Access® database in 2005 for children diagnosed with Prader-Willi Syndrome (PWS). The medical, socio-demographic and family data of 813 patients were then collected.

Method: We aim to analyse the evolution of diagnosis and care over time, according to the birth year of patients by comparing 3 groups (patients born between 2005 to 2009, 2010 to 2014 and 2015 to 2021).

Results: 403 patients born between 2005 and 2021 were studied: with a median age of 9.85 years and 50.6% boys. The genetic subtypes were specified for 360 patients (89.3%) of which 52.5% paternal deletion, 43.9% maternal uniparental disomy. The median parents' age at birth of children did not change from children born in 2010 (34 years for mother and 38 years for father). Forty percent of parents had a very high education level (BAC+5/8), which is higher from the general population (34%, INSEE 2019). Age at diagnosis decreases over time from 1 month (min 0.1 to max 53) to 0.7 month (min 0 to max 13) for children born in or after 2015. No change was observed in weeks of amenorrhea, weight and length (SD) at birth over time. There was a trend of a lower incidence of caesarean section overtime (66% in [2005-2010] to 57%). The frequency of nasogastric tube feeding did not change (88% of patients at birth) but its duration increased from 30 days to more than 44 days (median at 42 days). This is probably explained by a better identification of choking. Respiratory problems (all causes) were more frequently identified at birth, from 38% to 64%. Concerning growth hormone treatment (GH), 337 patients (93%) are treated with GH at a median age at start of 1.12 years [Min 0.22 to Max 10.15]. The median age at start of GH decreased by birth year of children down to 0.8 years [Min 0.20 to Max 2.4].

Conclusions: The analysis of our database helped us to document the evolution of practices and care, and showed improvements with better identification and management of sucking disorders and respiratory problems at birth. A new tool, the Voozanoo® web application, has been developed for 0-4 years old PWS children to facilitate the inclusion of patients at birth, improve exhaustiveness and data collection by physicians who perform the routine follow-up.

P1-447

A comparison of the usefulness of two indices of insulin resistance: IRIHOMA (calculated from fasting glucose and insulin values) and IRIBelfiore (calculated from OGTT results) in diagnosis of metabolic complications and determining indications for possible dietary or pharmacological treatment in children

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Introduction: The increasing prevalence of obesity in children and adolescents is contributing to the increasing diagnosis of insulin resistance (IR) in these individuals. However, it remains a worldwide problem to establish diagnostic criteria of IR in the developmental-age population. IRIHOMA and the IRIBelfiore are the well-known indices used in clinical practice.

The aim of the study was to compare the usefulness of IRIBelfiore and IRIHOMA in the early diagnosis of IR in children and its metabolic complications.

Patients and Methods: The study group consisted of 553 children aged 2-17.9 years; mean±SD: 12.03±4.2 yr, including 374 girls (67.5%) and 180 boys (32.5%) hospitalized in 2005-2020 at our Department. Based on fasting glucose and insulin - the IRIHOMA, while on results of glucose and insulin during OGTT (0', 60' and 120') - IRIBelfiore were calculated. IRIBelfiore higher than 1.27 was considered as abnormal. IR with respect to IRIHOMA was diagnosed using three criteria: IRIHOMA >2.5 (group A), IRIHOMA >2.67 in prepubertal boys and >2.22 in prepubertal girls and >5.22 and >3.82, respectively, during puberty (group B), and using available centile charts for this index (group C). Next, the IR indices values were compared with clinical data such as TSH, FT4, FT3, ALT, AST, bilirubin and lipids.

Results: In the study group, a normal IRIBelfiore value was found in 184 children (33.2%), while an elevated value was found in 370 children (66.8%). Insulin resistance assessed by IRIHOMA was diagnosed in 40.1% of children in group A, 21.3% in group B and 19.2% in group C. When abnormal IRIHOMA values are found regardless of the criteria used, more than 90% of the participants are also found to have abnormal IRIBelfiore values. Using criteria A and B despite normal IRIHOMA values, insulin resistance can be diagnosed in about 50% based on IRIBelfiore, while according to criterion C in 26.6%. Children with normal IRIHOMA and simultaneously elevated IRIBelfiore had statistically significantly higher levels of triglycerides, HDL-cholesterol, HDL/total cholesterol ratio, AST.

Conclusions: In patients with diagnosed IR based on elevated IRIHOMA, it is not necessary to calculate IRIBelfiore. However, normal IRIHOMA values do not exclude insulin resistance and its associated metabolic complications. It appears that the implementation of adult-accepted IRIHOMA standards (>2.5) may contribute to the overdiagnosis of insulin resistance in pediatric patients.

P1-448

The Association between Vitamin D deficiency and Hepatosteatosis in Obese Children and Adolescents. (Underreview in Hormone Research Journal- HRP-2023-1-19)

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Objective: To compare the serum 25-hydroxy Vitamin D [25(OH)D] concentrations in children and adolescents with obesity with and without hepatosteatosis, and investigate the relationship between serum 25(OH)D concentrations and severity of hepatosteatosis. We also aimed to assess the effect of vitamin D treatment after 6 months on hepatosteatosis and liver biochemistry.

Methods: One hundred thirty-three obese patients with vitamin D deficiency [serum 25(OH)D < 12 ng/ml] and body mass index (BMI) > +2 standard deviations (SD) for their age and gender were recruited. Anthropometric measurements, biochemical parameters [serum calcium, phosphate, alkaline phosphatase, parathyroid hormone, 25(OH)D, glucose and insulin concentrations] and ultrasonographic findings of hepatosteatosis were recorded before and six months after Vitamin D treatment.

Results: Grade 1, 2 and 3 hepatosteatosis at baseline was present in 51 (38.4%), 43 (32.3%) and 10 (7.5%) subjects respectively. Mean (± SD) serum 25(OH)D concentrations were significantly lower in those with hepatosteatosis (8.4 ± 2.4 ng/ml) compared with those without hepatosteatosis (9.9 ± 2.4 ng/ml, $P < 0.005$). Multivariable logistic regression analysis showed serum 25(OH)D concentration was the independent predictor for hepatosteatosis ($P < 0.005$), whereas age, sex, weight SD, BMI SD and HOMA-IR were not ($P > 0.05$) (Table 1). There was no significant difference in BMI SD, HOMA-IR and liver enzymes between subjects with and without hepatosteatosis ($P > 0.05$). Despite improvement in serum 25(OH)D concentrations at 6 months post-treatment (34.7 ± 10.6 ng/ml vs. 8.7 ± 2.4 ng/ml; $p < 0.0001$), there was no significant difference in the proportion of patients with different severity of hepatosteatosis as compared to before treatment ($p = 0.88$).

Variable	Regression Coefficient	95% CI	Significance (P-value)
Age	-0.045	-0.298 to 0.198	0.721
Sex	-0.017	-1.086 to 1.075	0.975
Weight SDS	-0.338	-2.051 to 1.159	0.678
Height SDS	0.157	-0.605 to 0.992	0.698
BMI SDS	0.836	-1.152 to 3.177	0.443
25 (OH) Vitamin D	-0.377	-0.657 to -0.146	<0.005
HOMA-IR	0.988	-0.381 to 2.649	0.182
Glucose	-0.026	-0.125 to 0.045	0.508
Insulin	-0.247	-0.624 to 0.071	0.146

Conclusion: Serum 25(OH)D concentrations were lower in obese children and adolescents with hepatic steatosis as compared to those without hepatic steatosis, with an inverse association between the severity of hepatosteatosis and serum 25(OH)D concentrations. Vitamin D treatment in obese children and adults with hypovitaminosis D did not improve severity of hepatic steatosis on ultrasonography at 6 months.

P1-449

Body composition following initiation of daily glucocorticoid in Duchenne Muscular Dystrophy: Identifying the timing of increase of fat mass to introduce intensive weight management strategies

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Background: Glucocorticoid (GC) therapy is standard of care of management of Duchenne Muscular Dystrophy (DMD) but its use is associated with a range of side-effects. Weight gain leading to significant obesity is common in GC treated boys. There are limited studies evaluating body composition in DMD following initiation of GC, and the timing of increase in fat mass is not known.

Aim(s): To evaluate changes in growth parameters: height-SDS, weight-SDS, body mass index(BMI)-SDS, lean mass index(LMI)-SDS and fat mass index(FMI)-SDS following initiation of daily GC in DMD.

Methods: Between 2013-2017, 24 boys with DMD were commenced on daily GC. 18 boys who had DXA for assessment of bone health at baseline(prior to initiation of GC but no more than after 3 months), 1-year, 2-year and 3-year were included. Height-SDS, weight-SDS, BMI-SDS and DXA measured body composition: LMI and FMI-SDS were compared between time-points. Data were expressed as mean(SEM). p<0.05 was accepted as statistical significance.

Results: Mean age prior to initiation of GC was 5.2(0.36) years. Mean GC dose was 0.6(0.01) mg/kg/day in Prednisolone equivalent and remained stable throughout the follow-up. Mean height-SDS continued to decline following initiation of GC with significant differences between 3-year of GC and baseline with difference of means -0.99 [95% CI: -1.89 to -0.09; p=0.03]. There were no significant mean differences in weight-SDS, BMI-SDS and LMI-SDS between time-points. Mean FMI-SDS began to rise after one year of GC exposure. Mean FMI-SDS after 3-year of GC was significantly different from baseline (difference of means +0.71 [95% CI: +0.20 to 1.22; p=0.003]) and 1-year of GC (difference of means = +0.85 (95% CI: 0.34 to 1.36; p<0.0001]). After 3-years of GC therapy(mean age 8.6 years, 11/18(61%) were categorised overweight, obese or severely obese, whereas this was noted in 9/18(50%) at 2-year of GC; 5/18(28%) at 1-year of GC and baseline.

Conclusion: Substantial increase in fat mass occurs early after the first year of initiation of daily GC in young boys with DMD. Routine structured nutritional input for all boys with DMD should be part of clinical care following initiation of GC. Current management strategies of childhood obesity and its complication may not be not suitable for boys with DMD(eg exercise and use of statins contraindicated). Clinical pathways of evaluation and management of obesity-metabolic complications in DMD should now be developed.

P1-450

Longitudinal analysis of *CCDC3* methylation in placenta and peripheral blood in school-age children: association with gestational obesity and childhood obesity

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Introduction: The *CCDC3* gene encodes for a protein expressed in endothelial cells and adipose tissue. Insulin increases its expression and, in turn, *CCDC3* positively regulates adipogenesis and lipid accumulation. *CCDC3* expression is increased in visceral adipose tissue from subjects with obesity. Gestational obesity can modify the metabolic programming in the offspring through epigenetic mechanisms. However, it is unknown whether the methylation of the *CCDC3* gene can explain the relationship between gestational obesity and childhood obesity.

Objective: To study the methylation of *CCDC3* in the placenta and peripheral blood in school-age children, analyze the associations with obesity and insulin resistance parameters in children and study whether maternal obesity can modulate these associations.

Methods: The study population consisted of a prenatal cohort of pregnant women and their newborns (n=125) who were followed from birth to school age (mean age 6.1 ± 0.9 years). Children were classified into two subgroups according to their mother's gestational weight gain [normal pregnancy weight gain (n=72) and gestational obesity (n=53)]. The methylation of two cytosine guanine dinucleotide sites (CpGs) of the *CCDC3* gene was studied using pyrosequencing in placental and peripheral blood samples in the children. The correlation of *CCDC3* methylation with parameters of obesity [weight, height, BMI, fat mass, visceral fat and serum lipids] and insulin resistance [glucose, insulin and HOMA-IR] was assessed.

Results: The methylation of *CCDC3* (mean methylation of the studied CpGs) in peripheral blood was positively associated with obesity and insulin resistance parameters in school-age children: fat mass (r=0.200; p=0.013), visceral fat (r=0.193; p=0.034), glucose (r=0.285; p=0.010) and HOMA-IR (r=0.192; p=0.032). These associations were more evident in children born to mothers with gestational obesity (r between 0.277 and 0.300), in whom a negative correlation with HDL cholesterol was also evident (r=-0.344; p=0.014). In addition, in this group, peripheral blood methylation of *CCDC3* was correlated with placental methylation of *CCDC3* (r=0.348; p=0.022). All these associations were independent from children's sex, age and BMI in multivariate analyses (β between -0.325 and 0.340).

Conclusions: Our results show that *CCDC3* methylation is associated with obesity and insulin resistance parameters in school-age children and is modulated by maternal gestational obesity. In addition, methylation of *CCDC3* persists over time from birth (placenta) to school age (peripheral blood). We suggest that epigenetic alterations in *CCDC3* can condition the development of childhood obesity and that maternal gestational obesity can aggravate such metabolic programming.

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Diagnostic Journey with an 80-gene Panel in Non-syndromic Early-Onset Severe Obesity: Association of Outcomes with Metabolic Status and Hyperphagia

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Background: Monogenic defects are among the significant causes of early-onset non-syndromic severe obesity in childhood. Identifying the genetic cause of obesity can guide for treatment. The aim of our study is to investigate the clinical and biochemical features of patients with early-onset severe obesity and evaluate the underlying molecular diagnosis.

Materials and Methods: A total of 39 patients (M/F: 22/17) with non-syndromic, early-onset (<5 years) and morbid obesity (body mass index (BMI)/95th percentile BMI ratio >120%) were included in the study. Demographic data, clinical findings, and biochemical results of the cases were recorded. Hyperphagia was evaluated using the Dykens hyperphagia questionnaire. Genetic analyses were conducted within the ROAD (Rare Obesity Advanced Diagnosis) project. 80 genes were examined using the next-generation sequencing method.

Results: The median age of the cases was 12.1 (2.1-20.1) years. The consanguinity rate was 30.8%, while the obesity rate among first-degree relatives was 66.7%. Based on birth weight according to gestational week; 2.9% were SGA, 22.9% were LGA. Bariatric surgery was performed on 7.7% of patients (n=3), and 17.9% (n=7) had a family history of bariatric surgery. The mean height SDS was 1.2±1.4; BMI SDS was 3.4±0.7; the ratio of BMI value to the 95th percentile BMI value was 146±27, the rate of acanthosis nigricans was 30.8%, the prepubertal patient rate was 33.3%. Except for one patient diagnosed with type 2 diabetes mellitus, 32% of 25 patients who underwent OGTT (n=8) had impaired glucose tolerance and hyperinsulinemia, and 48% (n=12) had hyperinsulinemia. Dyslipidemia was present in 35.9% of patients, and hepatosteatosis was present in 60.7%. The frequency of metabolic syndrome in patients >10 years (n=23) was 39.1%. In 30.8% of patients (n=12), at least one variant was detected in obesity-related genes. Homozygous variants were detected in 3 patients in the LEPR gene, and heterozygous variants were detected in 4 in PCSK1, 2 in MC4R, 2 in UCP3, 1 in NTRK2, 1 in PPARG, and 1 in DYRK1B. There was no difference in metabolic parameters, hyperphagia score, severity, and onset of hyperphagia between those with and without documented monogenic obesity (p>0.05). The median age at onset of hyperphagia was 4(0.3-15) years.

Conclusion: The genetic cause of early-onset non-syndromic severe obesity can be determined with extensive gene panels, thus enabling a rapid and cost-effective diagnosis and offering treatment options. If the cause can be identified, genetic counseling can be provided to the patient.

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Single center experience on using Liraglutide in adolescents with obesity +/- Type 2 diabetes

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Background: Childhood obesity is recognized as a chronic illness with limited therapeutic options. Addressing this condition through lifestyle interventions has proven to be challenging, particularly for adolescents, with only minimal outcomes observed. The use of GLP-1 agonists (such as Liraglutide) for reducing body weight in pediatric patients has yielded conflicting results. To date, no studies conducted in the Middle East have reported on the outcomes of GLP-1 receptor agonists in the treatment of obesity, both with and without diabetes, in children and adolescents. Our study represents the first investigation of Liraglutide utilization for weight reduction in this population within the region.

Methods: The study included 22 obese participants with or without type II diabetes, ages 12-19 years, who attended endocrine clinics between 2020-2022—inclusion criteria of Z score +2, free of chronic diseases. The study consisted of 18 months of liraglutide treatment period, with follow-up appointments at 6 months intervals. The primary outcome was changes in weight and BMI at 18 months compared to baseline. Biochemical markers were taken at baseline, 6 months, 12 months, and 18 months to monitor HbA1c changes and detect possible adverse effects on the liver enzymes, pancreas, and kidney function test.

Results: Of the 22 patients, 12 continued till 18 months, and 10 did not comply with the treatment or stopped the medications early due to side effects. 6 out of 12 patients who completed the entire duration were Type 2 Diabetic. At baseline, the weight, weight SDS, BMI, and BMI SD were 113.9kg, 2.9, 40.9 kg/m^2, 2.6 respectively. At the 18-month follow-up, the weight, SDS, BMI, and BMI SD were 117.8kg, 2.6, 39kg/m^2, and 2.5, respectively. Thus no statistically significant change in the weight parameters were evident at the 18-months compared to baseline. Dropout from the study and poor compliance was high (10 out of 22 patients) due to side effects, mainly gastrointestinal (nausea, abdominal pain, diarrhea, and vomiting). No statistically significant differences were observed between obese vs. obese with type 2 diabetes. No significant change in HbA1c between the baseline and the treatment follow-up in the diabetes patients. No adverse effects (in terms of impairment of liver and kidney function or pancreatitis) were observed.

Conclusions: Real-life experience in clinical practice can vary significantly from clinical trials. In our study participants experienced significant gastrointestinal adverse events effecting their mood, productivity, and lifestyle. Also the time interval between the follow up periods affected the motivational levels of participants. Obese patients being treated with Liraglutide need a multidisciplinary team approach to tackle all aspects of their treatment.

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Echocardiographic assessment of periaortic fat thickness and its relationship to cardiovascular risk factors in children with simple obesity

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Keywords: Childhood, Obesity, Periaortic fat thickness, Echocardiography, Cardiovascular risk.

Aim: To assess the periaortic fat thickness (PAFT) by echocardiograpy in a cohort of children with simple obesity and to evaluate its relationship to clinical and metabolic cardiovascular risk factors.

Methods: Fifty children and adolescents with simple obesity and 25 healthy sex and age matched controls were enrolled in the study. Periaortic fat thickness (PAFT) was measured by conventional echocardiography. Anthropometric measurements, and assessment of blood pressure status were performed. All participants were subjected to basal evaluation of plasma insulin, glucose, and lipid profile and underwent oral glucose tolerance test (OGTT).

Results: PAFT (axial, sagittal) were significantly higher among obese group (2.41+0.51mm), (2.08+0.51) than controls (1.76+0.34), (1.57+ 0.35) (p values<0.001). In children with obesity, PAFT was significantly correlated with diastolic blood pressure, systolic blood pressure, body mass index (BMI), waist circumference (WC), cholesterol levels, fasting plasma glucose, 2-hours postprandial glucose, fasting insulin, and Homeostatic model assessment insulin resistance (HOMA-IR). There was significant increase in septal wall thickness, left ventricular end diastolic diameter (LVEDD), and left atrial diameter among obese children than the controls (p values 0.001,0.003, 0.003) respectively.

Conclusion: Conventional echocardiography is a useful method for early detection of subclinical cardiovascular morbidities in pediatric obesity. The measurement of PAFT by conventional echocardiography is easy and convenient method for early prediction of atherosclerotic changes among obese children.

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Identification of Distinct Metabolic Profiles in Childhood Hypercholesterolemia Using Metabolomics Analysis

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Background: Despite the importance of hypercholesterolemia in children, it is overlooked, and there are currently few metabolomics-based approaches available to understand its molecular mechanisms.

Methods: Children from a birth cohort had their cholesterol levels measured with the aim of identifying the metabolites for the molecular biological pathways of childhood hypercholesterolemia. One hundred and twenty-five children were enrolled and stratified into three groups according to cholesterol levels (acceptable, <170 mg/dL, n = 42; borderline, 170–200 mg/dL, n = 52; and high, >200 mg/dL, n = 31). Plasma metabolomic profiles were obtained by using 1H-nuclear magnetic resonance (NMR) spectroscopy, and partial least squares-discriminant analysis (PLS-DA) was applied using the MetaboAnalyst 5.0 platform. Metabolites significantly associated with different cholesterol statuses were identified, and random forest classifier models were used to rank the importance of these metabolites. Their associations with serum lipid profile and functional metabolic pathways related to hypercholesterolemia were also assessed.

Results: Cholesterol level was significantly positively correlated with LDL-C and Apo-B level, as well as HDL-C and Apo-A1 level separately, whereas HDL-C was negatively correlated with triglyceride level ($p < 0.01$). Eight metabolites including tyrosine, glutamic acid, ornithine, lysine, alanine, creatinine, oxoglutaric acid, and creatine were significantly associated with the different statuses of cholesterol level. Among them, glutamic acid and tyrosine had the highest importance for different cholesterol statuses using random forest regression models. Carbohydrate and amino acid metabolisms were significantly associated with different cholesterol statuses, with glutamic acid being involved in all amino acid metabolic pathways (FDR-adjusted $p < 0.01$).

Conclusion: Hypercholesterolemia is a significant health concern among children, with up to 25% having high cholesterol levels. Glutamic acid and tyrosine are crucial amino acids in lipid metabolism, with glutamic-acid-related amino acid metabolism playing a significant role in regulating cholesterol levels.

P1-455

Non-Syndromic Monogenic Obesity and Psychiatric Disorders

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Introduction: Childhood obesity has been associated with many physical and mental health problems. A significant relationship has been reported between psychiatric disorders, especially attention deficit hyperactivity disorder(ADHD) in obese patients due to the melanocortin 4 receptor(MC4R) gene variant, and it has been claimed that these two conditions may share common molecular pathways. However, studies on this subject are quite insufficient.

Purpose: To determine the frequency of psychiatric disorders in non-syndromic monogenic obese patients,the distribution of diagnosis,and their difference from exogenous obesity.

Method: Nineteen non-syndromic monogenic obese(group 1) and18 exogenous obese(group 2) patients were included in the study. Demographic data and anthropometric measurements were recorded from patient files.

All cases were evaluated in the Child and Adolescent Psychiatry outpatient clinic according to the "Semi-Stuctured Schedule for Affective Disorders","Schizophrenia forSchool-Age Children - Present and Lifetime Version-Turkish Adaptation","Depression Scale for Children for Depression Screening and Grading"and "Childhood Anxiety Disorders Self-Report Scale (CAD-SR)" was used to screen,rate and categorize anxiety and worry levels. For parents, "Conners' Parent Rating Scale-Revised Long Form",which was validated and reliable between the ages of 3-18 to evaluate attention deficit and hyperactivity findings,"Social Responsiveness Scale" for screening autistic features,and "Child Sleeping Habits Questionnaire" for assessing sleep habits was applied.

Results: Group1 had lower mean age, weight standard deviation score,body mass index (BMI) SDS, while AST, ALT, and thyroid stimulating hormone was statistically significantly higher.

At least one psychiatric disorder was detected in89.5% of group1 and77.8% of group2. Exogenous obese subjects had a higher assessment of the "Conners Parent Rating Scale's" psychosomatic sub-dimension(p:0.017) and "CAD-SR" social anxiety sub-dimension(p:0.027). In addition,the sub-dimensions of BMISDS were positively correlated with "Child Sleep Habits Questionnaire" sleep distress(r:0.344,p:0.049), daytime sleepiness (r:0.473, p:0.005) and sleep scale total score (r:0.39,p:0.025).

Itwas observed that the exogenous obese group had higher scores inthe psychosomatic sub-dimension of"Conner's Parent Scale" and "CAD-SR" social anxiety. The high level of psychosomatic sub-dimension in the exogenous obesity group continued to be significant when the monogenic obese groups were divided into MC4R and others(p:0.038).

Conclusion: There was no difference between the obese groups devided into non-syndromic monogenic obesity and exogenous obesity,in terms of having a psychiatric disorder. At least one psychiatric disorder was detected with a very high frequency in both non-syndromic monogenic obese and exogenous obese patients. Therefore,routine psychiatric consultation may be required for these patients, regardless of the etiology of obesity.

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Higher levels of liver enzymes are associated with increased left ventricular mass in apparently healthy children. Potential role of HMW-adiponectin and epicardial fat

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Introduction: An increase in liver enzymes predicts cardiac hypertrophy secondary to increased left ventricular mass in patients with cardiovascular disease. The mechanisms involved include decreased adiponectin concentration and increased epicardial fat in these subjects. We hypothesized that associations between these parameters would also be readily apparent in otherwise healthy children.

Objectives: Our objective was to study the associations between the liver enzymes alanine transaminase (ALT) and gamma-glutamyl transferase (GGT), left ventricular mass, high molecular weight adiponectin (HMW) and epicardial fat in apparently healthy children.

Subjects and Methods: A total of 174 apparently healthy children (98 boys and 76 girls; age 9.4 ± 1.8 years) were recruited from primary health care centers in Girona (Northeastern Spain). Anthropometric parameters were measured: body mass, height and body mass index (BMI), and fasting venous blood was sampled to quantify ALT, GGT, and HMW-adiponectin serum levels. To assess epicardial fat, cardiac ultrasonography was performed following the recommendations of the American Society of Echocardiography. Left ventricular mass was derived from the following ultrasound parameters: interventricular septal thickness, left ventricular posterior wall thickness and the internal diameter of the left ventricle (Devereaux's formula).

Results: Liver enzymes were positively associated with left ventricular mass in these children: ALT ($r=0.297$, $p<0.0001$) and GGT ($r=0.297$, $p<0.0001$). In turn, HMW adiponectin was negatively associated with both GGT ($r=-0.215$, $p=0.007$) and left ventricular mass ($r=-0.285$, $p<0.001$), while epicardial fat was positively associated with both liver enzymes [ALT ($r=0.169$, $p=0.027$) and GGT ($r=0.327$, $p<0.0001$)] and left ventricular mass ($r=0.357$, $p<0.00001$). All these associations were independent from potential confounding variables in multiple linear regression analyses.

Conclusions: Higher liver enzyme values are associated with increased left ventricular mass in apparently healthy children. Lower HMW-adiponectin concentration and higher epicardial fat in these children may contribute to explain these associations. These results justify the need for longitudinal studies in children to prevent the increased risk for cardiovascular disease associated with liver dysfunction.

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PCSK1 Heterozygous Gene Polymorphisms are Associated with Early Onset Morbid Childhood Class III Obesity Across Diverse Ethnic Groups

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Aim of the Study: Correlate genetic data of patients heterozygous of PCSK1 gene variations with the clinical phenotype.

Introduction: Heterozygous variants of the PCSK1 gene have been described in cases of early onset of morbid obesity in childhood. This gene encodes prohormone convertase 1/3 enzyme, a serine endoprotease expressed in neuroendocrine cells that converts inactive prohormones into functional hormones important in regulation of energy metabolism.

Methods: 293 cases of morbid obesity underwent genetic testing at Prevention Genetics after obtaining consent.

Results: All cases presented with early weight gain from 3-5 years of age, hyperphagia, acanthosis nigricans. 35 (12 %) cases had heterozygous PCSK1 gene variations. 22 were females and 13 males: 15 Caucasian, 9 Hispanic, 6 Asian, and 5 African American. The age at diagnosis was 16.7 ± 9.4 (from 3 to 42 yrs.), BMI was extremely high 40.7 ± 4.6 kg/m2.

24 cases of 35 (68.5 %) carried the heterozygous polymorphism c.661A>G, which is predicted to result in an amino acid substitution p.Asn221Asp (rs6232). In other cases different PCSK1 variants were found: 2 cases c.818_820del, p.Asp273del; 2 cases c.1381G>A, p.Val461Met; 2 cases c.1918A>G, p.Thr640Ala; 2 cases c.28T>G, p.Cys10Gly; 1 case c.2099_2101del, p.Phe700del; 1 case c.1387G>A, p.Glu463Lys; 1 case c.760A>G, p.Ile254Val.

11 cases were only heterozygous for one PCSK1 gene variant, 14 cases in a combination of PCSK1 and one additional gene, 3 cases in combination with 2 additional genes, 5 cases in combination with 3 additional genes, 1 case each of 4 and 5 additional genes.

There were no cases of diabetes type 2. Intellectual development was normal in all patients, no evidence of autism, learning disability or mental retardation.

Only 2 patients had fatty liver, 2 had hypertension and another 2 had borderline elevated HbA1c of 5.9 and 6.2%. As a group the average Insulin was 24.91± 16.82 mcIU/mL; TG of 133.3 ± 53.6 mg/dl, HDL of 43.5 ± 7.6 mg/dl. They had low-normal Leptin levels of 25.73± 14.5 ng/mL.

Conclusion: Genetic screening of early onset of obesity can identify patients with PCSK1 heterozygous gene polymorphisms. PCSK1 rs6232 is a frequent gene polymorphism associated with morbid obesity. Insulin resistance was not severe as expected for the degree of morbid obesity and leptin levels were relatively low. This information can help in the understanding of the natural history of PCSK1 gene carriers in diverse ethnic groups.

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Dietary and physical activity habits in children and adolescents in Greece

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Introduction: Obesity in childhood and adolescence is a major problem with many adverse consequences in public health due to its increasing prevalence, as well as the burden on the health system. Recently, the need to find effective intervention and prevention strategies for the management of obesity has led to the development of e-health technologies, which record behavioral data objectively and correlate them with factors that increase body mass index (BMI).

Objective: To determine the dietary and exercise habits of children and adolescents at the beginning of their participation in the study 'BigO: Big Data against Childhood Obesity' (http://bigoprogram.eu, Horizon2020, No. 727688).

Methods: Nine hundred (n=900) children and adolescents aged 8-18 years who attended the Out-patient Clinic for the Prevention and Management of Overweight and Obesity in Childhood and Adolescence participated in this cross-sectional study. Medical history and anthropometric measurements were obtained by a single trained observer and participants were clinically evaluated by a multidisciplinary management team. The data collection system included the BigO technology platform, which interfaces with a Smartphone and Smartwatch, and records data on diet, sleep and exercise objectively for each patient. Children's caregivers were asked to complete the self-administered food frequency questionnaire for children "ToyBox" and a physical activity questionnaire. The statistical analysis was carried out by the Statistical Package for Social Sciences (SPSS) software program.

Results: The study sample consisted of 900 children and adolescents of which 73,1% were obese, 24,7% overweight and 2,2% had normal BMI. A higher number of boys had obesity (76,3%/69,7%, p-value:0.031), while a higher number of girls were overweight (28.5%/21.1%, p-value:0.031). According to the descriptive data, the consumption of cereal without sugar and no added sugar was higher in all BMI categories than those with addition of sugar (p-value:0.025), although children with obesity tended to consume higher proportions of cereal than those with overweight and normal BMI (p-value: 0.041). In all BMI categories, participants had large proportions of meat and poultry (p-value:0.031) while the consumption of potatoes was more frequent in obese than overweight children (p-value:0.029). Boys, consumed larger amount of water, light beverages, vegetables, meat, fried potatoes and chocolate spread than girls (p-value:<0,05). In both sexes, participants who never watched television during meals were more than those who watched (p-value:<0.05).

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Conclusion: Monitoring the nutrition and physical activity in childhood and adolescence may lead to the development of evidence-based guidelines for the prevention and treatment of childhood obesity.

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Digestive manifestations are frequent in iPPSD/ Pseudohypoparathyroidism

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Introduction: Pseudohypoparathyroidism (hereafter named iPPSD for inactivating PTH/PTHrP Disorder) is a rare disease characterized by hormonal resistance including PTH, subcutaneous ossifications, short stature, brachymetacarpy and early onset obesity. iPPSD type 2 and 3 are caused by genetic or epigenetic variations in the GNAS gene or its promoters. Although uncommon features have been identified such as severe asthma or sleep apnea, digestive manifestations have been poorly addressed in the literature. However, in the clinical practice for the follow-up of a large cohort iPPSD at the French reference center for rare diseases of calcium and phosphate metabolism (CRMR CaP), relatives of children and affected children frequently reported digestive manifestations and especially severe constipation.

Objective: To precise the incidence and characteristics of digestive manifestations in children with iPPSD2 or iPPSD3.

Material and Method: We included 36 patients aged between 2 and 18 years with iPPSD (iPPSD2 n=32; iPPSD3 n=4) followed at the CRMR CaP. Each family filled in a specific questionnaire to assess the presence of digestive symptoms in their children including constipation, feeding difficulties or vomiting. The Bristol visual scale was used to confirm the existence of constipation.

Results: Constipation was the most frequently reported feature, present in more than 60% of the children (n=22/36 children). More than 80% of these 22 children had a Bristol score between 1 and 2, confirming constipation. Specific treatment had had been already administered in 55% of them but only 3 families (14%) considered this treatment effective. Neonatal vomiting and eating disorders, such as lack of satiety or food selectivity, were also observed in 50% of patients, as well as gastroesophageal reflux in the neonatal period in 40% of children. No significant difference was found according to the type of iPPSD or the age of the patients.

Conclusion: We report for the first time the high incidence of digestive manifestations and especially constipation in children with iPPSD. This is significantly higher than in healthy children where constipation is found in 10% of children. This suggests the potential dysfunction of GNAS and the G protein coupled receptors expressed in the digestive tract. Early adapted management of digestive manifestations and specifically constipation is essential to improve the quality of life for children with iPPSD, even if these data should be confirmed with a larger cohort.

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Improvement of Depressive and Anxiety Symptoms in Children and Adolescents with Overweight and Obesity Following Implementation of a Comprehensive, Multidisciplinary, Personalized, Lifestyle Intervention Program

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Introduction: Childhood obesity is one of the most challenging contemporary public health problems. Children and adolescents with obesity experience multiple psychosocial difficulties, such as low self-esteem, depression, anxiety, and behavioral problems. Psychosocial problems noted in youngsters with excess adiposity persist for a long time. The aim of our study was to assess mental health symptoms in overweight and obese children and adolescents before and after the implementation of a personalized obesity lifestyle intervention program.

Methods: Six hundred and eleven (315 female-296 male, mean age± SD: 10.39 ± 0.10 years, 326 prepubertal-285 pubertal) children and adolescents, aged 6-18 years, were studied prospectively and classified as obese (50.2%), overweight (33.5%), and normal BMI (16.2%), according to IOTF criteria. All participants entered a 12-month lifestyle intervention program that provided personalized guidance on healthy diet and physical activity to patients and their families. A multidisciplinary team evaluated all subjects at baseline and at frequent intervals thereafter. Laboratory investigations were obtained at the beginning and the end of the study. All participants completed two psychometric questionnaires, the Children's Depression Inventory (C.D.I) and the Screen for Child Anxiety Related Disorders (S.C.A.R.E.D), aiming to evaluate depressive and anxiety symptomatology respectively.

Results: At baseline, subjects with obesity, overweight, normal BMI and the total sample scored in the psychometric questionnaires as follows: 7.89 ± 0.33, 7.49 ± 0.39, 6.84 ± 0.56 and 7.59 ± 0.23 respectively in C.D.I, 1.65 ± 0.09, 1.59 ± 0.11, 1.49 ± 0.15 and 1.60 ± 0.06 respectively in S.C.A.R.E.D for parents and 2.14 ± 0.10, 2.05 ± 0.11, 1.97 ± 0.16 and 2.08 ± 0.07 respectively in S.C.A.R.E.D for children. After the completion of the study, a significant decrease in the score of S.C.A.R.E.D was noted in participants with obesity based on children's opinion (p<0.001), as well as in all subjects independently of BMI based on parent's opinion (p<0.003). Furthermore, significant reduction in C.D.I. scores (p=0.03) was recorded in participants with obesity. When subjects were categorized based on the questionnaires threshold to detect pathology, depressive symptomatology was found in 12.1% of participants and anxiety symptomatology in 35.3% based on children's perspective and in 23.5% based on parent's opinion. These percentages significantly decreased following the intervention (p<0.001).

Conclusions: The implementation of multidisciplinary, personalized lifestyle interventions in the management of obesity in childhood and adolescence is associated with a significant improvement of anxiety and depressive symptomatology. Further studies are required to clarify the underlying pathophysiologic mechanisms.

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Study on the correlation of metabolic syndrome with sex hormone binding protein and testosterone in obese boys

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Objective: To explore the correlation of sex hormone-binding globulin (SHBG) and Total Testosterone (TT) with the development of Metabolic syndrome (MetS) in obese boys. To explore the relationship between components of MetS and TT levels in boys.

Methods: A total of 439 boys aged 6-18 years old from April 2020 to February 2023, include boys who visited the Department of Endocrinology, Genetics and Metabolism in Jiangxi Province Children's Hospital and healthy boys who underwent physical examination in our hospital were collected. According to the diagnostic guidelines for metabolic syndrome, dividing those boys into Control (CON) group (76); obesity (OB) group (249); MetS group (114). Collecting data and using spss26.0 software to analyze and compare the differences of metabolic indices and TT level between three groups. And analyzing the relationship of TT level among those group.

Eight boys randomly from each three group were selected as subjects for targeted proteomic analysis, screening differential protein for functional analysis and protein interaction network analysis.

Result:

1. Clinical data analysis:

The CON group, OB group and MetS group were pairwise compared, and age, puberty and HbA1c were no statistically significant differences (P > 0.05) in three pairwise comparisons, respectively. Compared with CON and OB groups, BMI, SBP, DBP, LDL-C, non-HDL-C, TG, TC, FBG, FINS, HOMA-IR, ALT and AST levels were higher in MetS group, and HDL-C, FAA and TT levels were lower(P < 0.05).

Analyzing the correlation between TT and other variables in the sample showed that TT level was independently correlated with puberty, TC and age (P<0.05).

After adjusting for confounding factors of puberty, TC and age, Compared with CON and OB groups, TT levels were lower in MetS group, OR values and 95%CI were 1.012 (1.005-1.020) and 1.009 (1.003-1.016).

2. Proteomic analysis:

The CON group, OB group and MetS group were pairwise compared all showed SHBG is significantly down-regulated differential proteins;proteins associated with SHBG are IGF1, IGFBP1 and CRP.

Conclusion:

1. BMI, SBP, DBP, LDL-C, non-HDL-C, TG, TC, FBG, FINS, HOMA-IR, ALT and AST of MetS boys were higher than those of healthy boys and obese boys; HDL-C, FAA and TT were lower than healthy boys and obese boys.

2. TT level was independently correlated with puberty, TC and age; Low TT can be an independent risk factor for the development of metabolic syndrome in boys.

3. Decreased SHBG level is an independent risk factor for MetS in boys.

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Determinants of reduced insulin sensitivity in young adults born from preeclamptic pregnancies

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Background: Maternal preeclampsia has been associated with increased risk for later metabolic disturbances in the offspring.

Objective: We investigated whether maternal preeclampsia influences insulin sensitivity (IS) and low-grade inflammation in young adulthood and whether unfavourable metabolic features in childhood predict low IS at 20 years of age.

Methods: Forty-seven 20-year-old subjects (25 women) born from preeclamptic pregnancies (PRE) and 55 controls born from non-preeclamptic pregnancies (non-PRE, 36 women) were studied. Previously, 38 of these PREs and 46 of the non-PREs had been studied at the age of 12 years. Body mass index (BMI), BMI adjusted for sex and adult height (BMIadj) (at age 12 years), and waist-to-height-ratio (WHtR) were calculated. Fasting serum insulin, IGFBP-2, high-molecular-weight adiponectin (HMW-adipo), triglycerides, HDL cholesterol, high-sensitivity CRP (hs-CRP), interleukin-1 receptor antagonist (IL-1Ra) and blood glucose were measured. IS was estimated by Quantitative Insulin Sensitivity Check Index (QUICKI).

Results: The PRE subjects had lower HMW-adipo (1.69 vs. 2.24 ug/ml, P=0.027) and HDL cholesterol (1.42 vs. 1.56 mmol/l, P=0.024) concentrations than the controls at 20 years of age. The means of other measured parameters had no difference between the PRE and non-PRE groups (P>0.05 for all). The PREs in the lowest QUICKI tertile (n=16) had lower IGFBP-2 (124.9 vs. 255.1 ng/ml, P<0.001), higher hs-CRP (3.82 vs. 1.71 mg/l, P=0.004) and

IL-1Ra (544.7 vs. 250.3 pg/ml, P<0.001) concentrations and WHtR (0.52 vs. 0.46, P=0.014) than the PREs with higher IS (n=31). In the non-PREs, those in the lowest QUICKI tertile (n=18) had higher BMI (26.7 vs. 22.4 kg/m^2, P=0.011) than those with higher IS (n=37), otherwise the differences between the two QUICKI groups in the corresponding parameters were similar as in the PREs. In the controls, the difference in IGFBP-2 and hs-CRP concentrations was dependent on BMI. In the whole study population and in the non-PREs, higher BMIadj at 12 years predicted low QUICKI at 20 years (n=84, β=-0.374, P=0.025 and n=46, β=-0.750, P=0.003, respectively). In the PREs, none of the parameters measured at 12 years predicted low QUICKI at 20 years of age.

Conclusion: Young adults born from preeclamptic pregnancies did not have reduced IS compared with controls. At 20 years of age, those with lowest IS had higher low-grade inflammation markers and lower IGFBP-2 concentrations; in the PRE group all differences were BMI-independent. In those exposed to maternal preeclampsia, other factors than childhood BMI may affect reduced IS in young adulthood.

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Association between lean mass and metabolic syndrome risk in Korean children and adolescents

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Introduction: Skeletal muscle plays a crucial role in glucose disposal, and studies have shown a positive relationship between muscle mass and insulin sensitivity. However, an elevated lean mass has also been associated with metabolically adverse outcomes. This study aimed to evaluate the association between the risk of metabolic syndrome (MetS) and lean mass using dual-energy X-ray absorptiometry (DXA) in a nationally representative sample from the Korea National Health and Nutrition Examination Survey.

Methods: DXA was used to measure total body lean mass (LM) and fat mass (FM), as well as trunk LM and FM. Fat mass index (FMI) and lean mass index (LMI) were calculated using the following equations: FMI = (total FM in kg) ÷ (height in m)2, LMI = (total LM in kg) ÷ (height in m)2. The standard deviation score (SDS) for FMI and LMI was determined using age- and sex-specific LMS reference values.

Results: The prevalence of MetS was 5% in the study population, with a significantly higher prevalence in boys than in girls (6.5% vs. 3.0%). LMI was significantly associated with an increased odds of MetS. Odds ratios (OR) of LMI were statistically significant with waist circumference (OR; 3.0, 95% CI; 2.5-3.5), elevated triglyceride concentration (OR; 1.3, 95% CI; 1.2-1.4), and decreased HDL-C (OR; 1.4, 95% CI; 1.3-1.5) among the MetS components. The odds of MetS were greatest with FMI SDS (OR; 4.9, 95% CI; 3.5-6.7). The odds of LMI were 1.8, the best among the crude values (BMI, total mass index, FMI, and LMI itself), and had the best sensitivity. BMI showed the lowest odds ratio but had the best performance.

Conclusions: This study suggests that lean mass is positively associated with MetS, particularly with lipid metabolism. A parameter that reflects both muscle content and fat component may enhance the prediction of metabolic risk in children and adolescents.

P1-464

Occurrence of cardiovascular risk factors in Polish children and adolescents with severe obesity. Preliminary results of the Polish-German study project on severe early-onset obesity

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It is estimated that 1-5% of children and adolescents in Europe suffer from severe obesity (corresponding to an adult BMI > 40 kg/m^2). However, in risk stratification, the occurrence of metabolic complications is more important than BMI itself. The study aimed to assess the occurrence of cardiovascular risk factors in a cohort of children and adolescents with severe obesity.

Patients and Methods: The analysis included 140 patients (75 female) with severe obesity at the mean age of 14 (range 10-18) years (all recruited in 4 regional reference centers in Poland). Severe obesity was defined as BMI>35 kg/m2 (children in the age 6-14 years) and BMI>40 kg/m2 (in older). Cardiovascular risk factors – high blood pressure (>90percentile), dyslipidemia (HDL cholesterol <1.03 mmol/L, triglycerides ≥1.7 mmol/L), and glucose metabolism disorders (fasting and 120 min. after OGTT; > 5.5 mmol/L and > 7.8 mmol/L respectively were assessed in all patients.

Results: 89% (n= 124) patients had elevated blood pressure, 83% (n=117) with abnormal lipid profile (16 % with isolated low HDL, 23% isolated high TG, and 44% with both disorders), 19% (n=26) with the hyperglycemic state (3% impaired fasting glucose, 14% impaired glucose tolerance, 2% diabetes mellitus). Only

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1.4% (n=2) was free of cardiometabolic risk factors. A single cardiometabolic risk factor was noticed in 24% (n=33) participants, two were present in 61% (n=85), and three in 7% (n=10) participants. Female patients presented with significantly lower BMI z-score (3.5 vs. 3.8, p <0.001), but higher fat mass percent (48.3 vs. 44.6, p<0.001). They had also lower mean fasting glucose levels (4.8 vs. 5.0 mmol/L, p<0.008) and higher mean HDL cholesterol levels (43.7 vs. 40.1 mg/dL, p=0.01) compared to male patients.

Conclusions: The most common cardiovascular risk factor in children and adolescents with severe obesity was elevated blood pressure. More than 60% of patients had more than one cardiovascular risk factor. This calls for an early intervention in severe obesity.

P1-465

When a pandemic hits another pandemic: the rising overweight and obesity in children in North Macedonia

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Childhood obesity is a growing concern and a worldwide pandemic. North Macedonia, a small middle-income country with a population of around 2 million, is among the top 10 countries in Europe with a high prevalence of overweight and obesity.

The aim of this study is to observe how the COVID-19 pandemic has affected children's BMI compared to an earlier study conducted just before the pandemic, between 2019 and 2020.

Between February and April 2022, we conducted a prospective cross-sectional study in 1004 children aged 6-13, from four different ethnicities. We measured their weight, and height, calculated their BMI percentile and z score, and compared them with CDC 2000 for weight by gender and age classification.

Results: The analysis of the prevalence of classified BMI for the entire sample of school children indicated that the restrictive measures of isolation and social distancing during the COVID-19 pandemic decreased the prevalence of malnutrition from 10.1% in 2019 to 5.9% in 2022. However, it increased the prevalence of overnutrition from 13.5% in 2019 to 15.9% in 2022 and obesity from 19.6% in 2019 to 21.9% in 2022. Overall, overweight and obesity increased from 33% to 37.4% during the COVID-19 pandemic. A significant association was established with an increased prevalence of overweight and obesity in 2022 (Pearson Chi-Square test: X2=13.813; df=3; p<0.003).

In addition, a general decrease in undernutrition was observed in 2022 compared to 2019 for each of the analyzed ages (6-13 years). For p<0.05, there was a significantly lower proportion of undernourished in 2022 compared to 2019 for boys aged 6+ (p=0.008), as well as a significantly lower proportion of undernourished overall for boys in 2022 compared to 2019 (p=0.017). Boys in 2022 had a significantly higher prevalence of overweight and obesity at 41.6% compared to girls at 32.9%.

In conclusion, according to the World Obesity Federation, North Macedonia has a 7 out of 11 risk score, and if we don't implement effective strategies to prevent and manage childhood obesity, we may experience a prevalence increase of 52.4% of overweight and obese children by 2030, meaning 1 out of 2 children would be affected.

P1-466

The effect of lifestyle intervention on glycaemic variation, quality of life and satiety levels in children and young people with obesity

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Introduction: Childhood obesity is associated with pre-diabetes and type 2 diabetes mellitus. The gold standard investigation for these is an oral glucose tolerance test (OGTT). The aim of our study is to investigate glycaemic dysregulation in children and young people (CYP) with obesity using continuous glucose monitoring (CGM) and evaluate the effect of intense lifestyle intervention on various complications.

Methods: 34 patients were recruited onto a single-arm study that investigated glycaemic variation using CGM along with anthropometric measurements. These measurements were taken at baseline and at 3-months post-lifestyle intervention (fortnightly telephone reviews by a clinician). PedsQL 4.0 Generic Score questionnaires were used to assess quality of life (QoL) and three-factor eating questionnaire was used for satiety levels.

Results: 23 patients completed the 3-months intervention. Mean age was 13.9 years (range: 10.1-16.7) and 52.2% (12/23) were female. The average BMI (39.1±7.1kg/m^2 vs 39.5±7.3kg/m^2) and BMI SDS (3.5±0.4 vs 3.5±0.5) were similar pre- and post-intervention. There was no significant change in body fat percentage (49.9% vs 49.6%).

On CGM, the average glucose at baseline was 6.4mmol/L (±0.8SD) with a mean coefficient of variation of 15.9% (±2.4SD). Percentage time in range (3.9-7.8mmol/L) reduced from 85.7% to 83.1% during the study period. The percentage time over 10mmol/L increased from 0.7% to 1.0%. All patients, except for one post-intervention, had normal OGTT results, despite evidence of glycaemic dysregulation on CGM. HbA1c levels remained stable (33.4 vs 33.8mmol/L).

The fasting lipid profile and C-reactive protein improved over 3-months. Alanine transaminases and aspartate transferase levels reduced, with the latter being statistically significant (-1.57iu/L;95%CI 0.10-3.03;p<0.05).

QoL improved in both child and parent-reported questionnaires with an increase in the mean psychosocial summary score (child:55.4 vs 60.2/100; parent:50.3 vs 50.5/100) and overall total score (child:58.4 vs 61.5/100; parent:52.3 vs 52.6/100). Better satiety levels were noted with a reduction in uncontrolled eating (40.5 vs 36.3/100) and emotional eating scores (39.9 vs 35.3/100), and an increase in cognitive restraint (38.5 vs 39.7/100).

Conclusion: The results of this study show that intense lifestyle advice and regular contact over 3-months can improve liver function, lipid profiles and inflammation, as well as increasing QoL and satiety in CYP with obesity. The use of CGM has revealed evidence of glycaemic dysregulation, despite normal OGTT and HbA1c levels, demonstrating the ability to identify early abnormalities. Lifestyle intervention was not beneficial in improving glycaemic status highlighting the potential need for considering pharmacotherapy in high risk CYP with obesity.

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Evaluation of concentrations of homocysteine in obese and overweight adolescents and its correlation with lipid and carbohydrate parameters

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Background: Metabolic and hemodynamic obesity-related disorders are a major risk factor for cardiovascular disease in children with excess body fat mass. Studies in adults suggest that serum homocysteine is a marker of atherosclerosis and is associated with vascular dysfunction. Studies in children are inconclusive.

The aim of the study was to evaluate the association between homocysteine concentrations and lipid and carbohydrate metabolism parameters in obese and overweight adolescents.

Material and Methods: The study involved 42 obese, 14 overweight and 25 normal weight participants aged 10.0 to 17.6 years. Anthropometric measurements were performed in each patient. Overweight and obesity were defined according to the value of z-score BMI for age and sex: z-score BMI ≥ 1 was considered overweight, z-score BMI ≥ 2 was classified as obesity. Serum homocysteine, fasting glucose, fasting insulin, uric acid and lipid profile parameters were assessed. Additionally, oral glucose tolerance test (OGTT) was performed in obese and overweight children. Following atherogenic and insulin resistance indices were calculated: Matsuda Index, Quantitative Insulin Sensitivity Check Index (QUICKI), Homeostasis Model Assessment-Insulin Resistance (HOMA-IR), triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) ratio. The concentration of non-HDL was also evaluated.

Results: Serum homocysteine concentrations were comparable in the groups of children with obesity, overweight and normal body weight [median: 11.08 (9.04-12.81) vs. 10.71 (9.79-1350) vs 12.45 (10.88-14.44), respectively] and did not differ after taking gender into account. Homocysteine concentrations correlated with age (R = 0.47, p = 0.017) in normal weight children and with waist circumference (R = 0.85, p = 0.001) in overweight children. We did not find any associations in obese children. Homocysteine was not associated with anthropometric parameters, lipid profile, or atherogenic and insulin resistance indices in any of the study groups.

Conclusion: We did not find any statistical differences in homocysteine concentrations in children with excess body fat mass compared to normal weight peers. Cardiovascular obesity-related risk factors did not correlate with homocysteine levels.

We may assume, that changes in homocysteine concentrations may appear later in adulthood.

P1-468

Efficacy of zinc and myo-inositol on weight loss and metabolic features in a pediatric population with obesity

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Pediatric obesity is constantly increasing and exposes to serious cardiovascular and metabolic risks. The first treatment against obesity is lifestyle change. Actually, any intervention seems to be effective on the evolution of this condition, especially in the long term. For this reason, the interest in non-pharmaceutical compounds is growing.

Several studies mentioned the use of zinc and inositol as compounds acting on weight loss and insulin resistance. The aim of this study is to investigate the benefits of combined administration of Zinc and Myo-inositol in children and adolescents with obesity, assessing the improvement in clinical parameters, such as insulin resistance index (HOMA-IR), the lipid panel and glucose and insulin levels during oral glucose tolerance test.

For that, 56 patients with obesity and insulin resistance have been enrolled. The age was between 10.7 and 17.7 years, with an average BMI of 33.3 ± 4.5 Kg/m^2. Subjects were randomly assigned to two homogeneous groups: treatment group has received 5 mg of Zinc, 2000 mg of Myo-inositol and 1000 mg of galactooligosaccharides from Pisum sativum, while the placebo group received 1000mg of galactooligosaccharides from Pisum sativum. The treatment lasted 3 months and all patients enrolled were subjected to an isocaloric diet consisting of 55% carbohydrates, 30-35% fat and 15% protein. Clinical auxological investigations and biochemical evaluations were carried out for the determination of lipid profile, liver function and glucose-insulin metabolism. In both groups, a statistically significant reduction of BMI and BMI Z-score has been observed. An improvement of fasting insulin and fasting glucose, HOMA-IR, ISI and QUICKI (insulin-sensitivity indices) has occurred in both groups.

Also, the treatment group showed a reduction in triglycerides and LDL cholesterol and an increase in HDL cholesterol, with a statistically significant variation between the two groups ($p< 0.02$).

In conclusion Zinc and Myo-inositol seem to have a positive role on lipid profile and the association with an isocaloric diet leads to a reduction in body weight and insulin resistance. To strengthen the effects of lifestyle changes, supplementation with Zinc and Myo-inositol could be used as a non-pharmacological agent for the control of complications related to obesity. However, further investigations are still needed to define the physiological effects and therapeutic treatments related to their administration using a larger sample and a longer follow-up duration.

P1-469

Compound heterozygous SLC5A2-Mutation leading to familial renal glucosuria in an 11-year-old boy

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Background: The SGLT2 (Sodium-Glucose Cotransporter 2) protein is responsible for the majority of glucose reabsorption in the proximal tubule. Mutations in SLC5A2, encoding SGLT2, have been first described in 2002, leading to familial renal glucosuria (FRG). Herein we describe the clinical course of an 11-year-old boy in whom a compound heterozygous SLC5A2-mutation was detected, who presented with glucosuria and vomiting with a suspected diagnosis of diabetes.

Case Report: An 11-year-old boy with hitherto unexplained glucosuria (300 - 1.000 mg/dl), known since 5 years, presented with recurrent early morning nausea and vomiting since 3 months. Liquid uptake and urinary output were normal, no weight loss, HbA1c 30 mmol/mol. He was otherwise healthy with normal growth and BMI. Oral glucose tolerance test (oGTT) was pathological (1h blood glucose (BG) 203 mg/dl; 2h BG 160 mg/dl) in the presence of normal fasting BG (89 mg/dl), insulin levels, electrolytes and negative islet cell antibodies (GAD, IAA, IA2). Apart from decreased glucose reabsorption, urine tests were normal. Hyperthyroidism, hypercorticism, growth hormone excess and pheochromocytoma could be ruled out. Brain MRI and abdominal ultrasound were normal. Genetic analysis revealed a compound heterozygous SLC5A2 mutation, inherited from both asymptomatic parents (c.885+5G>A/known; c.1409T>C/novel), the latter leading to a single base pair substitution with very low allele frequency and disrupted SGLT2 function predicted by bioinformatic tools. Oesophagogastroscopy revealed reflux oesophagitis that resolved with PPI treatment.

At oGTT reevaluation 6 months later, 2h BG was borderline normal (141 mg/dl) in the presence of normal fasting (89 mg/dl) and 1h BG (135 mg/dl). Renin levels increased significantly after 2h (from 32.5 to 56.1 µU/ml) without change of sodium levels, illustrating activation of the renin-angiotensin-aldosterone system by volume contraction after glucose challenge.

Conclusions: SGLT2-associated FGD represents a perhaps underdiagnosed benign condition. We hypothesize that the unexpected first pathological oGTT result was probably due to significant stress caused by the investigation procedure leading to delayed gastric emptying and/or intestinal absorption, which was further aggravated by reflux oesophagitis.

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Evaluation of the Frequency and Time Course of Side Effects Asscociated With Metformin Use In Obese Adolescents As Related to Weight Loss: A Prospective Single-Centre Observational Study

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Background: Metformin is a well-known biguanide approved for treatment of Type2 Diabetes. Metformin is not considered as an anti-obesity drug despite its common off-label use. Currently, there are no data regarding the profile of metformin related gastrointestinal side effects (MRGSE) in obese adolescents.

Aim: To identify the frequency and time course of MRGSE in obese adolescents and assess the presence of any association of side effects with change in BMI standard deviation (ΔBMI-SD).

Design-Setting: 6-month prospective, observational study in a tertiary-care center

Patients and Methods: 200 consecutive treatment-naïve adolescents with exogenous obesity aged 10-17yr were enrolled. Metformin was given (maximum dose: 2g/d) to 100 obese patients with glucose intolerance and/or insulin resistance(IR) in addition to standard dietary and life style related recommendations. Standard clinical and biomedical evaluations were performed. MRGSE profile;i.e.nausea, vomiting, diarrhea, abdominal pain and the severity of these side effects was recorded and evaluated with a validated likert scale questionnaire on a monthly basis. Associations between metformin dose, severity of side effects and ΔBMI-SD were investigated.

Results: 173 patients (103females) with the median age of 13.5 yr completed the study. The median BMI-SD at presentation was 2.3 (range:1.8-3.8). Compared to patients in the untreated group, patients in the metformin treated group (MTG)(n=98) had similar BMI-SD (p=0.09) and higher HOMA-IR (p=0.02); as expected. ΔBMI-SD was higher in the MTG than in the untreated group at the sixth month when compared to baseline BMI-SD, but not significantly (p=0.074). In the MTG; severe, moderate and mild MRGSE were noted in 13(13.7%), 14(14.7%), 9(9.5%) patients; respectively at the first month of follow-up. The majority of MRGSE diminished significantly at the fourth month (p=0.007). At the sixth month,13(14%) patients had MRGSE with varying degrees of severity. The presence of MRGSE was unrelated to gender, BMI and HOMA-IR (p> 0.05;for all). In the MTG, the decrease in BMI-SD was greater at the first and second months of follow-up in the patients with MRGSE than those without (p=0.036 and p=0.048; respectively). These significant differences in ΔBMI-SD owing to MRGSE did not persist on further follow-up.

Conclusions: The frequency of MRGSE was variable in our cohort with the majority subsiding at the fourth month. The initial mild decrease in BMI-SD during metformin treatment owing to MRGSE disappeared on follow up, thereby confirming the absence of a direct association of metformin use with weight loss in parallel to the decline in IR.

P1-471

Life-saving management and therapy in a growth-hormone naive superobese adolescent with Prader-Willi Syndrome: Very low energy diet, GLP-1 analog and nasal oxytocin

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Introduction: Prader-Willi Syndrome (PWS) is characterized by severe neonatal hypotonia and feeding difficulty with subsequent hyperphagia, hypogonadism, and short stature. PWS has a prevalence of 1 in 10,000-30,000. Obesity-related complications occur from early childhood onwards. Liraglutide is a glucagon-like peptide-1 (GLP-1) analog that reduces appetite and body weight and improves glycemic control. Scarcity of oxytocin-producing neurons in the hypothalamic paraventricular nucleus in PWS has been associated with hyperphagia and obesity.

We report the effectiveness very low energy diet (VLED), and treatment with GLP-1 agonist and nasal oxytocin in an immobilized PWS patient with supermorbid-obesity and respiratory failure.

Case Report: A 17-year-old male who had never been treated with growth hormone presented with severe dyspnea and cyanosis. He had chronic obstructive sleep apnea and was receiving home CPAP treatment. At presentation his height, weight, and BMI were 150.3cm (-3.86SDS), 196kg (6.01SDS) and 87.1 kg/m^2 (4.96SDS), respectively. His heart-rate was 115 beats/minute, breathing-rate was 48 breaths/minute and body temperature was 36°C. He had limited mobility due to super-obesity. Blood gas was compatible with respiratory acidosis (ph:7,14 CO2:109), fasting blood glucose 110mg/dL, insulin 18mU/L, HbA1c 6.2%, but acute marked elevation of aminotransferases (AST 2357U/L, ALT 2439U/L) were suggestive of hypoxic hepatitis. Due to respiratory failure he received one week of ventilation support in ICU and was then transferred the pediatric ward. He was started on VLED (850 kcal/day, gradually reduced to 650 kcal) with appropriate vitamin and essential nutrient support. Liraglutide therapy was started at a dose of 0,6mg/day, following which aminotransferases reduced to less than five times upper normal limit. On a liraglutide dose of 1,2mg/day his weight decreased to 170 kg(5.3SDS) after two months, BMI reduced to 75.5 kg/m2(4.75SDS) and his mobility increased. Hypoxic hepatitis resolved (AST 50U/L,ALT 29U/L) although hepatosteatosis persisted on ultrasonography. Fasting blood glucose was 79 mg/dL with insulin 27.5 mU/L and HbA1c 4.8%. Nasal oxytocin treatment was added to the combination of VLED and GLP-1 analog treatment for its suggested hyperphagia-reducing effect.

Conclusion: The main treatment approach for PWS in childhood should aim to control obesity and its complications. There are no published definitive recommendations regarding anti-obesity drugs, bariatric surgery is controversial and carries risks in cases with such severe obesity. The appetite of this hyperphagic patient was controlled with Liraglutide and nasal oxytocin, and BMI decreased with VLED. With these interventions, he recovered greater mobility and improved respiratory function.

P1-472

First Case of Familial Partial Lipodystrophy Type 2 (FPLD2) from Kazakhstan Presenting with Life Threatening Arrhythmias and Dilated Cardiomyopathy

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Background: Familial partial lipodystrophy type 2 (FPLD2) is a heterogeneous rare disease characterized by selective fat loss, mainly affecting the limbs. It is attributed to *LMNA* gene, which encodes lamins A and C, structural proteins components of the nuclear lamina. LMNA variants have been previously described with cardiac abnormalities with and without lipodystrophy in FPLD2.

Case Description: We describe a 17-year-old girl who is followed in the Endocrine clinic for evaluation of significant acanthosis nigricans on abdominal wall, neck, axillary and inguinal areas; muscular extremities, hirsutism, decreased fat on face, abdomen and extremities. Her BMI was low at 17 kg/m2. BP was elevated. She initially presented at 15 years of age with right ovarian cyst for which she underwent laparoscopic surgery. She had menarche at 11 years, the menses were irregular. Endocrine profile showed normal ACTH, prolactin, LH, FSH, 17 OHP, testosterone levels and thyroid function. Fatty infiltration of the liver was noticed on the sonogram and CT of the abdomen. Elevated ALT 104 U/L (nl < 35), AST 69.8 U/L (nl < 35), consistent with fatty liver. Elevated insulin levels of 218 mcIU/ml, TG levels of 1.56 mmol/L (0.44-1.4) and HbA1c 6.2 %, consistent with prediabetes and insulin resistance. C-peptide was normal at 3.54 ng/ml (1.1-4.4). LDL was low 0.67 mmol/L (0.91-1.91). At 16 yrs. she had ischemic stroke in the left frontal area, confirmed by brain MRI. Thrombotic work up was normal. At 17 yrs. she presented with syncope episode, hypertension, arrhythmias with alternating tachycardia during daytime with severe bradycardia at night. Echocardiogram revealed dilatation of the left ventricle, mitral valve insufficiency. She was diagnosed with dilated cardiomyopathy and conduction defects. A Cardioverter-defibrillator was implanted. She was diagnosed with partial lipodystrophy and treatment with Metreleptin is currently being planned.

Results: She was tested for mutational analysis of the *LMNA* gene, which causes autosomal dominantly inherited FPLD2. She was found to have a heterozygous pathogenic c.1488+1G>A mutation in the *LMNA* gene. This variant is listed as "pathogenic" in HGMD mutation database (CS094346) (PubMed ID:20848652,34240052) and ClinVar mutation database.

Conclusion: It is important to evaluate cardiac function in patients with FPLD type 2. This mutation has been reported previously in patients with various lipomusculodystrophies, cardiomyopathies and channelopathies with fatal outcomes. It is imperative for a Paediatric Endocrinologist to recognize that early detection of the cardiac phenotype in FPLD2 can prevent stroke and life-threatening arrhythmias in such cases.

P1-473

Metabolic Profile of Obese North Macedonian children and adolescents

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Introduction: Obesity in children and adolescents is increasing, and represents a global concern regarding future health related consequences. It has been classified as a disease that affects a large number of individuals.

Materials and Methods: We have recruited 119 obese children and adolescents from our outpatient Pediatric Endocrine Clinic for metabolic evaluation between the year 2018-2022. There was a 2year discontinuation of the study period due to Covid-19 pandemic. Physical examination was performed along with measurement of arterial blood pressure, weight and height with body mass index (BMI) calculation. Blood samples were collected for cholesterol, lipoproteins, triglycerids, insulin and thyroid function. An OGTT was performed for each patient.

Preliminary Results: The mean age of patients was 11,2 years, with mean BMI of 31,7. Hypertension was found in 36 children (30%), mean age 12,6 years (BMI 34,4), dyslipidemia in 34 children (28,5%) BMI 32, mean age 11 years, subclinical hypothyroidism in 27 (22,6%), with a mean age of 10,4 years and BMI of 33,2. Hyperinsulinaemia in 46 children (38,6%) and mean age of 10,9 years BMI 32,3. Impaired glucose tolerance was found in 9 children (7,5%) with a BMI of 32, prediabetes in 1(0,8%) and diabetes type 2 in 4 (3,3%) patients. Metabolic syndrome had 2 patients, 1,6% age 13 and 14 years, BMI 36 and 34. Only 11 subjects (7,4%) were metabolically healthy, mean age 10,6 years and BMI 31,4.

Conclusion: Our results raise concern regarding the long term outcome of examined subjects. Only 7,4% of the patients were metabolically healthy. Before this time period, type 2 diabetes was not diagnosed in children. The growing incidence of obesity in our country requires the need for medical intervention, multidisciplinary approach and wide spread preventive education.

P1-474

Identifying MAFLD and its metabolic risk factors in Polish children and adolescents with severe obesity. Preliminary results of the Polish-German study project on severe early-onset obesity

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Background: Fatty liver disease in children and adolescents is the most common cause of chronic liver disease in many countries. Criteria for a diagnosis of pediatric metabolic associated fatty liver disease (MAFLD) are based on hepatic steatosis in ultrasound, blood biomarkers or liver biopsy in association with one of the three criteria: excess adiposity (overweight, obesity or abdominal obesity), prediabetes or type 2 diabetes, or evidence of metabolic dysregulation.

The study aim is to investigate characteristic features of MAFLD in children and adolescents with severe obesity.

Methods: The study group included 113 individuals with severe obesity (52 males) with the BMI z-score 2.5-9.2 (3.9±0.9aged 1.0-18.8years (13.3±3.1years) enrolled in the Polish-German Study Project on Severe Early-Onset Obesity (SEOO) in four Polish Medical Centers. In all subjects physical examination with anthropometric measurement was performed. Lipids, carbohydrates parameters and liver enzymes were assessed in the fasting state. MAFLD diagnosis was established in all patients with hepatic steatosis detected by the liver ultrasound.

Results: Liver steatosis on US was foundin 65 (57%) children (male 53.8%) and was significantly related to male sex (p=0.009). GGT activity was significantly higher in MAFLD than non-MAFLD group (30.2±19.0 vs. 19.0±7.4µU/ml, p=0.03). Elevated ALT was present in 43 children (66.1%) with MAFLD but the difference between MAFLD and non-MAFLD group did not reach statistical significance (p=0.055). Patients with MAFLD had higher waist circumference than non-MAFLD patients (116.0±12.9 vs. 109.4±15.9cm, p=0.02). Moreover, compared to non-MAFLD group, children with MAFLD showed higher fasting and 120'glucose level in OGTT(90.0±9.7 vs. 84.8±7.8mg/dl, p=0.02; 126.1±30.7 vs. 102.6±32.6mg/dl, p<0.001, respectively), insulin resistance indexes [triglyceride-glucose index (TyG): 8.7±0.5 vs. 8.5±0.4, p=0.008; HOMA-IR: 6.9±4.1 vs. 4.5±3.0,p<0.001)] and lower QUICKI (0.36±0.06 vs. 0.4±0.07, p=0.008). We found positive correlations between the presence of liver steatosis and BMI z-score (p=0.02), waist circumference (p=0.003), fasting and 120'OGTT glucose (p=0.002; p<0.001), fasting and 120'OGTT insulin (p=0.004; p=0.002), HOMA-IR (p<0.001) and TyG (p=0.01) as well as negative correlation with QUICKY (p<0.001) and HDL-cholesterol (p=0.02). There was no correlation between MAFLD and the age of children or obesity duration.

Conclusion: In more than the half of children and adolescents with severe obesity hepatosteatosisis present in abdominal ultrasound. The correlation of MAFLD with abdominal obesity and insulin resistance indexes shows that these factors could be indicators of hepatosteatosis in children and adolescents with severe obesity.

P1-475

A girl with ROHHAD syndrome – a rare cause of rapid-onset obesity and hypothalamic dysfunction

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Background: The rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation (ROHHAD) is a long-known rare condition with a high morbidity and mortality rate, and still unknown etiology.

Objective: We aim to present the clinical findings and treatment in a patient with ROHHAD syndrome.

Case Presentation: A 4-year-old girl had normal development until March 2022 when rapidly progressing weight gain of 13 kilograms in less than 8 months began due to hyperphagia. The parents also noticed behavioral changes in the child including irritability and aggression, loss of acquired motor skills, fatigue with significant daytime sleepiness, hypodipsia and oliguria. In December 2022 the girl was hospitalized due to continuous central hyperthermia up to 42 °C lasting for more than 2 weeks prior to admission, without elevated inflammatory markers and with a normal brain CT scan. The patient was referred to our paediatric endocrine center for further investigations. At the admission she was severely obese, tachypneic and tachycardic, without cyanosis or signs of sleep apnea, showing deterioration in the expressive speech and gait disturbance with instability. She was continuously febrile and the laboratory investigations showed anemia, hypoxemia and compensated respiratory acidosis, central hypothyroidism and hyperprolactinemia, sodium dysregulation and low-normal IGF-1. The imaging findings (abdominal and heart US, brain MRI) were insignificant. Karyotype was normal, and there were no pathological findings in MLPA and single WES. The combination of rapid-onset obesity, hypothalamic dysfunction and autonomic dysregulation was compatible with the ROHHAD(NET) syndrome. After a CPMS Endo-ERN consultation of the patient we performed a whole-body DOTA-NOC PET-scan in order to screen her for neural crest tumors but the imaging test was negative for solid tumors or lymphadenopathy. We initiated treatment with oxygen, Levothyroxine, Bromocriptine, dietary regimen and intravenous infusion of electrolytes. Lumber puncture for additional investigation could not be performed, and 33 days after the admission the patient was transferred to the PICU for mechanical ventilation and parenteral infusions with Rituximab as the fever was constantly above 39.8°C. However, one week later the girl had consecutive episodes of cardiorespiratory arrest leading to fatal outcome.

Conclusion: ROHHAD/NET syndrome is a complex condition with unspecific diagnostic tests and yet to be revealed etiology. A high suspicion is warranted in patients with rapid early-onset obesity and hypothalamic dysfunction without structural pituitary abnormality. The possibility to receive medical support and guidance through the CPMS tool of the European Rare Diseases Networks is a practice-changing opportunity.

P1-476

Complications of excess weight (CEW) seen in tier-3 paediatric weight management services: A two-centre experience

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Background: Children and young people living with severe obesity experience a range of complications of excess weight (CEW), however the prevalence of complications is not well defined. We have evaluated baseline clinical characteristics and CEW of patients seen in two multi-disciplinary tier-3 paediatric weight management services in different regions of the UK.

Methods: All new patients (n=185) aged 2-17 years seen in a 12-month period from March 2022 to February 2023 were included. Baseline demographic data was collected, and patients were screened for a range of CEW. PedsQL-4.0 Generic Core Scales questionnaire was used to assess quality of life (QoL).

Results: The mean age was 13.04 years (range 3.33-17.95) and 50.8% (94/185) were female. The majority of patients were white British (73.8%) and a significant excess living in the most deprived decile (41.4%). The mean BMI was 36.47kg/m^2 (±8.37 SD) and BMI SDS was +3.54 (±0.70 SD). Mean body fat (n=77) was 48.6% (±8.44 SD). A combination of ASD, ADHD and learning difficulties were vastly over-represented in this cohort.

Dyslipidaemia (as defined by total cholesterol >5.17mmol/l, LDL > 3.36 mmol/l, HDL < 1.02mmol/l or triglycerides >1.5mmol/l) was the most common (51.6%) complication identified, followed by hypertension (29.7%), evidence of non-alcoholic fatty liver disease [NAFLD] on ultrasound imaging (17.8%), obstructive sleep apnoea [OSA] (9.0%) and idiopathic intracranial hypertension [IIH] (4.9%) (Table 1). Mean HbA1c was 39.0 mmol/mol (±15.18 SD; NR <42). Sixteen (8.6%) patients had type 2 diabetes mellitus (T2DM), with two cases diagnosed through screening in the CEW clinics.

QoL scores were low with a mean child-reported questionnaire (n=82) total score of 49.51/100 (±19.19 SD) and a mean parent-reported questionnaire (n=87) total score of 45.81/100 (±19.35 SD). Mean scores from a healthy UK paediatric reference population were 82.25 and 81.12 respectively. Mental health problems were common, with 26.2% and 7.7% having diagnoses of anxiety and depression respectively.

Conclusion: The results from this study have demonstrated the significant and profound pathology resulting from severe obesity, highlighting the clinical necessity of CEW MDT clinics. A rigorous approach to identify and manage these physical and mental health complications at an early stage is essential to improve long-term health outcomes.

Table 1. CEW

Complication	Percentage of patients (number with complication/ number screened)
Dyslipidaemia	51.6 (65/126)
Hypertension	29.7 (43/145)
NAFLD on ultrasound	17.8 (33/185)
OSA	9.0 (16/177)
OSA requiring respiratory support	3.4 (6/177)
IIH	4.9 (9/185)
T2DM	8.6 (16/185)

Fetal, neonatal endocrinology and metabolism (to include hypoglycaemia)

P1-84

Impact of bariatric surgery on newborn growth parameters

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Keywords: Bariatric surgery, Pregnancy, Maternal obesity, Small for gestational age, fetal growth, Nutritional deficiencies.

Background: Maternal obesity is known to have many detrimental effects on pregnancy. Bariatric surgery represents the most efficient therapy for severe obesity. Although it is known to positively impact many pregnancy outcomes, bariatric surgery can disturb fetal growth due to nutritional deficiencies.

Objective: Our study aims to examine the repercussions of bariatric surgeries on fetal growth, and to evaluate the risk of delivering a small for gestational age (SGA) newborn while taking into consideration the type of bariatric surgery performed.

Methods: This is a single center retrospective study. Data was collected from the medical archive of Notre Dame Des Secours University Medical Center (NDS-UMC), Byblos, Lebanon between January 2013 and September 2021. In an effort to examine the effects of bariatric procedures on offspring growth, a study group(n=36) containing pregnant women who underwent bariatric surgeries, was compared with a control group of women who did not do a bariatric procedure(n=98). Then the study group was divided into purely restrictive bariatric procedures and mixed procedures.

Results: Pregnancy after bariatric surgery was associated with a reduction in mean birth weight (2885.97 versus 3244.69; P<0.001); mean birth length (48.13 versus 48.93; P<0.019), mean head circumference (33.91 versus 34.59;P=0.017) and risk of large for gestational age (0% versus 7.1%; P<0.001). However it was linked with an increased risk of small for gestational age (SGA) infants (13.9% versus 0% ; P<0.001). When comparing bariatric surgery types, a higher mean birth length was linked with purely restrictive surgeries compared with gastric bypass procedures with this association tending to significance (47.39 ± 2.03 versus 48.43 ± 1.30;P=0.052).

Conclusion: Bariatric surgery was associated with an increased risk of small for gestational age (SGA). Women of child bearing age should do a nutritional follow-up after bariatric surgery and decide carefully whether benefits outweigh adverse outcomes.

P1-85

Associations of eating behavior and metabolic status in young children and variants of energy metabolism genes

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Objectives: The aim of the study was to evaluate the associations of metabolic status and eating behavior (EB) in young children and variants of energy metabolism genes.

Materials and Methods: A longitudinal study of 106 children in the dynamics of the first 2 years of life was carried out. Groups of children were identified taking into account BW at birth (large-weight by gestation (n=50), underweight by gestation (n=31) and corresponding to the term (n=25)) and during questioning (with excess (n=37) and normal weight (n=69)). Variants of the genes for leptin (LEP), leptin receptor (LEPR), adiponectin (ADIPOQ), insulin (INS), peroxisome proliferator-activated receptor gamma (PPAR-γ), lipoprotein lipase (LPL) and interleukin-6 (IL-6). Parents were surveyed using the CEBQ questionnaire (Wardle, 2001) to study PP in young children. When analyzing the results of answers to 35 questions. The calculation and evaluation of indicators of physical development were carried out using the WHO Anthro program. Additionally, body mass index, fasting glucose and serum leptin were determined at birth and at 2 years of age.

Results: Associations with MT at birth were established for the GG genotype of the IL-6 gene in the groups of small and normal weight by gestational age (p=0.050 and p=0.039). Analysis of the scales of the eating behavior questionnaire showed significant differences in indicators that contribute to the development of obesity. Carriers of the AA genotype of the INS gene had higher scores on the "desire to drink" criterion (p=0.033). The "feeling of satiety" parameter in children with the GC genotype of the IL-6 gene was 3 (3–4) points, GG 3 (3–4), CC 4 (3–4) points (p=0.046). The "emotional malnutrition" indicator in IL-6 gene GC genotype owners was 3 (2–4), GG 3 (3–4), CC 4 (3–4) points (p=0.007). Significant differences were established by the criterion of "emotional overeating", the level of glucose and leptin for the LEPR gene (p=0.045, p=0.024, p=0.041 respectively). Cord blood leptin was not associated with EB at 2 years of age. An analysis of the distribution of gene variants in 37 overweight children and 69 infants of the comparison group revealed an association with overweight of the rs2167270 variant of the LEP gene (p=0.022), serum leptin levels at 2 years of age (p=0.034).

Conclusion: The results obtained indicate the importance of hereditary factors in the anthropometric and metabolic status and the formation of eating behavior in young children.

P1-86

Measurements of Growth Hormone using dried blood spots in preterm neonates: reference values and longitudinal evaluation

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Background and Aim: Congenital growth hormone deficiency (cGHD) is a rare but life-threatening condition whose diagnosis is challenging in the absence of reliable reference values, both in healthy neonates and in preterm ones. We recently estimated GH reference interval in 1036 healthy, at-term newborns (HN) form dried blood spot samples using a previously validated analytical method.

Aim of this study is to provide values for random GH in preterm newborns (PN).

Methods: GH was evaluated in 78 PN (M:F 51:49%) attending the Neonatal Intensive Care Unit of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan. GH measurement was performed as above described at 48 hours after birth (GH1). In 41 out of 78 PN a second GH determination (GH2, at 15 days after birth) was also available.

Results: Median (IQR) GH1 values were 14.9 µg/L (9.8-21.1). No gender differences were found (p=0.089). The percentile 5th (3.4 µg/L) calculated in PN was lower than the lower limit of reference interval estimated in HN (reference limit at percentile 5.0th: 7.0 µg/L, 90%CI 6.7-7.3). In PN, decreasing GH levels were associated with increasing invasiveness of ventilation (no ventilation: 20.1, CPAP/biphasic: 15.1, high flows ventilation: 12.4, invasive ventilation: 5.4; overall KW p=0.026). Indeed, GH was significantly lower in PN needing invasive ventilation than not ventilated ones (Bonferoni's correction p=0.048). A low-to-moderate, although significant, correlation (rho=0.295, p=0.009), was found between GH levels and gestational age (GA). No association was, instead, found with maternal age (p=0.072), smoke (p=0.138), parity (p=0.520) or other neonatal variables, including jaundice (p=0.276) and auxological parameters (all p>0.05). Considering PN with both GH determinations (n=41), GH1 levels were significantly higher than GH2 (14.4 vs 9.8 µg/L, respectively, p=0.018). GH decreased in most neonates (26/41=63%), as expected after the first week of life. Interestingly, in PN with GH increase (GH2>GH1), GA was significantly lower than in those with GH decrease (GH1>GH2), with a median 30 vs 33 weeks (p=0.024).

Conclusions: Our data show for the first time that PN have lower median GH levels than HN. GH in PN is associated with ventilation and GA. The latter finding, along with the association between lower GA and increase in GH2 levels could be explained by an incomplete maturity at birth of the somatotropic axis in very PN, with the subsequent GH increase reflecting an extra-uterine maturation of the axis itself.

P1-87

A novel *CACNA1D* mutation leading to severe diazoxide unresponsive CHI

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Introduction: Approximately 25% of congenital hyperinsulinism (CHI) patients are unresponsive to medical therapy. These cases are usually associated with inactivating *ABCC8/KCNJ11* genes mutations or rarely with dominant *GCK* variants. Activating dominant mutations in the *CACNA1D* gene were recently found to cause mild form of CHI, muscle hypotonia and autistic features.

Objectives: Herein we describe a clinical case of a patient with severe medically unresponsive CHI and global developmental delay due a novel *CACNA1D* mutation.

Results: A female baby from nonconsanguineous healthy parents was born large for gestational age at 34 weeks with low Apgar score. Persistent hypoglycaemia (0.7-1.9 mmol/l) was noticed with glucose requirement rate (GRR) of 18.3 mg/kg/min. Due to pulmonary hypertension, the patient was treated with IV Ca channel blockers. CHI was diagnosed at day 7 of life. Diazoxide and Octreotide treatment were ineffective. NGS panel for known CHI genes did not reveal mutations. Subtotal pancreatectomy was performed at the age of 2 months. Histological examination confirmed diffuse CHI. Hypoglycaemia persisted postoperatively. Octreotide was restarted with partial effect. Follow-up examination at 9 months revealed excessive weight gain, severe developmental delay and muscle hypotonia. Diazoxide and Chlorothiazide were restarted with partial effect and led to progressive weight loss. At 24 months, the patient was diagnosed with bilateral congenital glaucoma. At 30 months, investigations showed persistence of hyperinsulinaemic hypoglycaemia. There were no progression in patient's psycho-motor development despite regular rehabilitation and absence of typical hypoglycaemic brain injury picture on MRI. The whole exome sequencing revealed a novel de novo variant (p.Phe767del) in the *CACNA1D* gene. The girl was started on Ca channel blockers therapy. After 6 months of treatment, there was no improvement neither in patient's glucose control, nor in her mental and motor development.

Conclusions: Mutations in the *CACNA1D* gene were previously reported to cause mild CHI, muscle hypotonia and autistic features. We reported a case of severe Diazoxide-unresponsive CHI and global developmental delay due to a novel *CACNA1D* mutation, indicating the clinical variability of Cav1.3 defect associated CHI.

P1-88

The variable outcome of childhood growth in congenital hyperinsulinism

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Background: There is limited knowledge about the natural history of growth in patients with congenital hyperinsulinism (CHI). The disease itself, as well as its treatment methods with common long-term sequalae in terms of pancreatic endocrine and exocrine dysfunction have the potential to affect growth. We investigated longitudinal height growth of CHI patients in a large Finnish cohort.

Materials and Methods: In this cross-sectional study, comprehensive auxological and clinical data of 93 eligible patients from the nationwide cohort of 106 patients with persistent CHI (born 1972-2015) were collected from medical records and examined from birth until 6.5 years of age. Growth parameters and outcome measures of height were statistically compared to the national growth references, parental heights, and between different treatment subgroups. Growth failure was defined as end-height below 10th percentile (<-1.3 SD).

Results: The median follow-up time of the 93 patients (53% male, 66% with identified genetic etiology, 33% surgically treated, 77% in clinical remission without medication for hyperinsulinism) was 5.0 (IQR 2.4 – 6.1) years. The patients reached mean end-height of -0.22 SD (95% CI -0.48 – 0.04), corresponding to mean of -0.19 SD (95% CI -0.36 – -0.02) compared to their target height SD. Growth failure was found in 43% of the patients treated with octreotide, 26% of those with near-total pancreatectomy (nt-Px), 13% of patients treated with diazoxide, and in 9% of patients who had lesionectomy for focal CHI. Patients treated with octreotide (n=7) showed markedly lower meandian end-heights of -1.27 SD (95% CI -2.35 – -0.19) compared to standard references, corresponding -0.72 SD (95% CI -1.51 – 0.08) difference compared to their target height. The patients with nt-Px reached lower meandian end-height of -0.26 SD (95% CI -0.99 – 0.46, n=19) compared to their target height, with a statistical difference compared to 0.88 SD (95% CI -0.41 – 2.18, n=12) of the patients with pancreatic lesionectomy (p=0.04) and a non-significant tendency of higher proportion of clinical exocrine pancreatic insufficiency in nt-Px group (25% vs 58%, p=0.092).

Conclusions: The overall prognosis of childhood growth is favorable in CHI but varies between patients treated with different treatment methods. Especially the patients with diazoxide-unresponsive CHI form treated with octreotide are at significant risk of childhood growth failure.

P1-89

Maternal, placental and fetal IGF-1/IGFBP in Diabetic pregnancies and their effect on fetal/infantile growth

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Introduction: In diabetic pregnancies, data about the interaction between maternal, placental, and fetal IGF1/IGFBP in relation to newborn size is not clear,

Aim: To review research papers published in Pubmed, Google scholar, Research gate, and Scopus in the past 20 years on the relation between placental IGF1/IGFBP-1 and fetal/infantile/childhood growth in pregnancies associated with maternal diabetes.

Results: 28 research papers were selected and reviewed.

In 527 GDM patients and 527 healthy pregnant women, the GDM group had higher BMI, fasting blood glucose, blood glucose level at 1 h, 2 h after the meal, and AUCG than the NGT group. IGF-1 and Growth/differentiation factor 15 (GDF-15) levels (a member of the transforming growth factor (TGF)-beta family, is released as a response to oxidative stress and inflammation) of the GDM group were higher than those of the NGT group. IGF-1 levels were positively correlated with maternal FBG. In 30 women with GDM and their 30 macrosomic babies, the serum concentrations of IGF-I and IGF-BP3 were higher in GDM women and their macrosomic babies compared to controls (n = 30). Maternal IGF-1 levels were positively correlated with the birth weight of GDM newborns. In 27 with GDM, and 277 women maternal and fetal IGF-I levels were significantly higher in GDM than in nondiabetic pregnancies and were associated with larger birth weights. In 157 mothers maternal IGF1 level was significantly correlated with the length and ponderal index of their newborns. In 157 healthy newborns, newborn IGF-1 was positively correlated with placental weight, birth weight, and ponderal index. A positive relationship was detected between maternal IGF-1, fetal IGF1, and birth weight in 339 healthy women.

In 50 women with GDM, birth weights were positively correlated to maternal IGF-1. The mRNA expression of three growth factor receptors, (IGF-IR, EGFR, and PDGFR-beta) was upregulated in the placenta of GDM women. The activity of placental IGF-I and mTOR signaling were positively correlated to birth weight. In the placental tissue from T1DM mothers (n = 20), the IGF-1R phosphorylation was significantly increased compared to the NGT women. Increased maternal blood glucose level during pregnancy was associated with an increased IGF-1R phosphorylation in the placenta (promotes excessive growth).

Conclusion: Higher maternal IGF1 in diabetic mothers can increase the size of the placenta, and stimulate mTOR signaling which stimulates protein synthesis, and nutrient transport which contributes to fetal overgrowth.

P1-90

Low-Dose Diazoxide Therapy in Hyperinsulinaemic Hypoglycaemia

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Background: Diazoxide therapy is used as first line treatment in hyperinsulinaemic hypoglycaemia (HH). Apart from a single study reporting efficacy of low dose diazoxide in small for gestational age (SGA) infants, diazoxide has been reported to be used in doses of 5-20 mg/kg/day [1].

Objective: To report the outcomes of infants with HH responsive to low dose diazoxide (≤5mg/kg/day).

Methods: Retrospective analysis of 34 patients with biochemically confirmed HH that were treated with low-dose diazoxide at two Tertiary Children Hospitals in London from April 2020 to March 2023. Patient characteristics and treatment details were collected from electronic patient records. SGA was defined as birth weight <10th centile.

Results: Of the 34 patients, 15 were SGA. The patient characteristics and details of diazoxide treatment are summarised in Table 1. All infants underwent an age appropriate controlled fast successfully prior to discharge from the hospital. During follow-up, 6 (17.6%) babies required minimal increase in the dose of diazoxide for borderline blood glucose concentrations, with the total daily dosage still remaining ≤5mg/kg/day. 5 (14.7%) patients were identified to have minimal fluid retention during follow-up which resolved on increasing the dose of diuretics. 2 patients had a genetic confirmation of *HNF4A* mutation, done in view of the strong family history of diabetes. No significant neurodevelopmental concerns have been identified on follow-up so far.

Conclusion: Low-dose diazoxide is effective treatment for babies with HH, independent of birth weight. Certain genetic forms of HH may also be suitable for treatment with low dose diazoxide. Hence, lower doses of diazoxide should be considered in infants with HH prior to using traditionally published doses (>5 mg/kg/day). Although generally well-tolerated, fluid retention can develop in a minority of patients, confirming a need for regular follow-ups and vigilance even at lower doses.

Reference

1. Chandran S et al. Safety and efficacy of low-dose diazoxide in small-for-gestational-age infants with hyperinsulinaemic hypoglycaemia. Arch Dis Child Fetal Neonatal Ed. 2022 Jul;107(4):359-363. doi:10.1136/archdischild-2021-322845.

Table 1: Patient characteristics and outcomes

	SGA (n=15)		**Non-SGA (n=19)**	
	Preterm	**Term**	**Preterm**	**Term**
Median birth weight (g)	1810	2385	2680	3150
Median birth weight standard deviation score	-3.20	-2.02	-0.0515	-0.0410
Gestational age range (weeks)	33-36+6	37-41	24-36+6	38-41+6
Median dose of diazoxide on discharge from hospital (mg/kg/day)	3.00	2.74	2.48	3.00
Median starting age of diazoxide (days)	17	12	19	15
Median age of stopping diazoxide (months)	5.5	4	4	4

P1-91

Short- and Long-term Outcomes of Diazoxide Unresponsive Infants with Diffuse Hyperinsulinism

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Background: Severe diazoxide unresponsive hyperinsulinism (DUHI) is most often caused by autosomal recessive variants in the KATP channel genes. Because of the limited medical treatments available, many patients are treated with 98% pancreatectomy. This results in a high rate of diabetes by the age of 15 years. Many centers now try to avoid surgery to prevent the inevitable transition to post-surgical diabetes.

Objectives: To report our single center experience of the treatment of DUHI and to determine if there are clinical differences between those treated with surgery versus high intensity medical treatment.

Methods: We performed a retrospective review of children treated for hyperinsulinism at our Congenital Hyperinsulinism Center between January 2014 and March 2023. We compared those with DUHI treated by 98% pancreatectomy versus medical therapy. We evaluated the long term glycemic outcome, length of stay, and …. Data is stored in our IRB approved Hyperinsulinism Registry.

Results: There were 95 patients treated over the study period. 27 (28%) were diazoxide responsive and 68 (72%) DU. Off these 41 (60%) had Focal HI and 27 (40%) had diffuse HI. Of those 27, 8 (30%) were managed medically and 19 (70%) had 98% pancreatectomy. Of the 8 who had no surgery 3 were treated in the Dasiglucagon study, and the remaining 5 were treated with octreotide plus continuous night feeds. Following a lengthy trial of medical therapy 5 of the 8 (63%%) families returned for surgery because medical management was too difficult to continue. Baseline data are shown in Table 1. Of the 19 surgeries, 5 (26%) have diabetes at last follow up, 5 (26%) hypoglycemia and 9 (48%) eat normally for age without hypoglycemia. Age of last follow up is 3 years

Conclusions: Long term medical therapy was attempted in 30% of our DUHI diffuse patients. Only 38% of them were able to continue to manage long term medical therapy and 62% opted to have a 98% pancreatectomy because they were unwilling to continue intensive therapy and felt diabetes was an "easier" path.

	n	**Age of Hypoglycemia Diagnosis**	**Age of HI Diagnosis**	**Age at Admission**	**Age at Discharge**	**Length of Stay**
Medical Treatment	3	0 (0-4)	14 (13-17)	35 (16-43)	47 (44-58)	15 (12-28)
Surgery	19	0 (0-5,123)	7 (0-41,130)	18 (0-39, 148)	46 (33-93,163)	26 (13-58)
Returned for Surgery	5	3 (0-6)	19 (2-242)	356 (154-874)	375 (161-919)	19 (9-45)

P1-92

Relationship between birth body weight<10.th centile (sga) and insulin-like growth factor binding protein-3: relevance of birth chest circumference / birth body weight ratio independently of birth gestational age, insulin-like growth factor binding protein-1 and -2 in the not-life threatened newborn

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Birth chest circumference(CC) shows often, like birth gestational age(GA), tight direct relations to birth body weight(BW). However distinct connections of hypoxia/undernutrition with different body structures might be suspected based on brain-, heart- and adrenal-sparing following intrauterine growth restriction and, postnatally, on higher chest size for body mass observed at high altitude. Growth retarded fetuses gestated by hypoxic pregnant animals may present increments of blood serum Insulin-like Growth Factor Binding Protein(IB)1 (IB1) and IB2, but not of IB3. An evaluation of the relevance of human newborn(NWB) CC/BW ratio(i.e., CC through BW, CC/BWR) to relationships between BW<=10.th centile for GA(SGA) and IB3 was conducted by multiple linear regression(MLR). NWBs with any among total parenteral nutrition, parenteral nutrition other than dextrose, blood component transfusion, postnatal corticosteroid-, catecholamine- or methylxantine-based treatments, life-threatening disease, diabetes mellitus(DM) or other endocrine diagnosis, malformation, and mother with DM were excluded. 78 included NWBs, all studied before covid-19 pandemic and from conception to study end near sea-level, had complete data for 1) same-day records at one of the first 5 postnatal days(x), 5 days after x(y) and 10 days after x(z) of postnatal age(PNA, unit:day), IB1, IB2 and IB3 radioimmunoassay(unit=uM/dl), and for 2) gender(SEX), GA(unit: complete week; extremes=28–42), GA<=36 present(PTB, n=46), CC(25th-75th centiles=27-32cm), BW(25th-75th centiles=1926-2942g), and SGA(n=20)(computations; male SEX(n=43), SGA; condition absent=0, condition present=1). SPSS-28 software was used to generate GA-unrelated CC/BWR standardized residuals(CC/BWRsr)(i.e., Linear regression procedure-Save pushbutton/ Standardized residual checkbox-Continue pushbutton/ regress CC/BWR on only GA). IB1, IB2 and IB3 averages were calculated at x-y-z time-points (i.e., (x+y+z)/3; resp. IB1M, IB2M and IB3M). IB3RM normal score according to Van der Waerden(IB3M-NS) was normally distributed. Spearman rank correlations between the following variable pairs are reported(Rho; significance): CC/BWRsr vs IB3M(-.304; p=.007), IB1M vs IB3M(-.251: p=.027), IB2M vs IB3M(-.257; p=.015). SGA partial correlation(pc) coefficient(pcc) with outcome IB3M-NS in MLR was significant 1) with SEX-GA-SGA-PNAx-IB1M-IB2M as predictors (SGA vs IB3M-NS; t=-3.526, p=.0007, pcc=-.386), but non-significant 2) with SEX-GA-SGA-CC/BWRsr-PNAx-IB1-IB2 as predictors(MLR R2, .501 / .568, always significant). CC/BWRsr could be involved in inverse relationships between SGA and IB3M-NS after controls including GA, IB1M and IB2M in not-life-threatened NWBs.

P1-93

Incidence and etiology of congenital hyperinsulinism in Slovakia

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Background: Congenital hyperinsulinism (CHI) is the most common cause of the persistent hypoglycemia in children and occurs in approximately 1 in 50,000 live births. Genetic testing provides information on the pancreatic histological subtype (i.e. focal vs diffuse) and determines further management and prognosis of the patients. At least 11 known monogenic forms and several syndromes have been associated with CHI. Mutations in ABCC8 and KCNJ11 genes coding potassium channel subunits in pancreatic beta cells are the most common cause of CHI and are responsible for the majority of diazoxide-resistant cases.

Aims and Objectives: The aim of this study was to evaluate incidence and genetic causes of permanent forms of CHI in Slovakia.

Patients and Methods: Based on the data from the nationwide database of children with persistent hyperinsulinemic hypoglycemia, 28 children were diagnosed with CHI in the period of recent 18 years (2005-2022). In all of them was performed DNA analysis of the most common CHI genes. Incidence of CHI in was calculated using the Slovak demographic data.

Results: Incidence of CHI in Slovakia is 1 in 39 217 live births. Genetic cause of CHI was identified in 12 children (42%). The most common were mutations in ABCC8 (n=7) gene, followed by KCNJ11 (n=2) and HNF4A (n=2) mutations. Five of six patients with a diazoxide-resistant form of CHI had an ABCC8 or KCNJ11 mutation. Three of these patients had focal form of CHI based on the paternally inherited recessive mutation. One patient was identified with Beckwith-Wiedemann syndrome.

Conclusions: CHI is a rare disease with nation-wide incidence in Slovakia of 1:39 217 over the last 18 years. Genetic cause was identified in 42% of the patients; mutations in ABCC8 gene were the most prevalent. The type of mutation determinates the most appropriate management strategy of these patients including pancreatic surgery.

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P1-94

Thyroid function in small for gestational age and appropriate for gestational age preterm infants admited to the NICU at Notre Dame Des Secours - University Medical Center

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Keywords: Preterm newborn, Small for gestational age, Thyroid hormones, Thyroid-stimulating hormone, Thyroid dysfunctions, Thyroid function tests.

Background: A common cause of neurodevelopmental impairment in children is congenital hypothyroidism, but can be preventable with adequate screening and proper management. Preterm newborns are more likely to have thyroid dysfunction, with small for gestational age (SGA) being an additional risk factor. However, only few studies addressed the altered thyroid hormone concentrations in the first few weeks of life concluding that TSH levels are higher in SGA newborns. As a result, we conducted a study to compare thyroid hormone levels and the incidence of thyroid dysfunction between SGA and appropriate for gestational age (AGA) infants.

Methods and Materials: This is a cross-sectional retrospective single-centered study conducted at Notre Dame Des Secours University Medical Center (NDS-UMC), Byblos, Lebanon, between January 1, 2016 and November 31, 2020. The medical records including thyroid function test results, socio-demographic characteristics and clinical conditions of 260 preterm infants admitted to the NICU, were reviewed then divided into 2 groups: preterm SGA and preterm AGA newborns.

Results: A significantly higher percentage of preterm newborns who were SGA had abnormal thyroid function in general (31.8% versus 14.4%, p=0.002), and hyperthyrotropinemia in particular (18.2% versus 6.2%, p=0.004) compared to preterm AGA newborns. Moreover, preterm who were SGA had significantly higher mean TSH levels compared to those who were AGA (6.86 ± 4.31* versus 4.55 ± 3.22*, p <0.001).

Conclusion: Preterm SGA neonates had higher TSH levels and an increased incidence of thyroid dysfunction. Therefore, close follow up with periodic thyroid function testing, endocrine and cognitive assessment is of significant importance in SGA infants presenting these features. A small dose of L-thyroxin should be discussed for these preterm SGA newborns.

P1-277

Severe neonatal hypoglycemia ≤30 mg/dl is associated with adverse neurodevelopment in mid-childhood

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Introduction: Neonatal hypoglycemia (NH) affects about 15% of all neonates and about 50% of neonates born with risk factors, including maternal diabetes, large- or small for gestational age, or prematurity. Although it is known that hypoglycemia in congenital hyperinsulinism can lead to brain injury, it is still not clear to what extent transitional NH is tolerated during the first days of life without brain damage. Thus, treatment thresholds and management strategies are controversially discussed. Aim of this study was to obtain evidence on whether episodes of severe transitional NH with blood glucose ≤30 mg/dl are a risk factor for mild brain damage.

Material and Methods: Between 04/2022 - 02/2023, neurocognitive outcomes were examined in a total number of 140 healthy children aged 7-11 years with a history of severe NH ≤30 mg/dl (n=70) or mild NH >30 mg/dl / without NH (n=70) using standardized tests for cognitive, motor, and visual-motor functions (WISC-V, MABC-2, DTVP) as well as standardized questionnaires to assess executive functions and behavior (BRIEF, CBCL). Groups were matched for gender, birth weight, gestational age, parental socioeconomic status, and primary risk factors for NH. Statistical analysis included student's t-test, Mann-Whitney-U test, Pearson's chi-squared test and Fisher's Exact test where applicable.

Results: The groups did not differ with respect to any potential confounders of the neurodevelopmental outcomes assessed. Children with at least one episode of NH ≤30 mg/dl had significantly lower mean total IQ scores of 5 points (p = .037) with significantly lower scores on the subscales 'verbal comprehension' (p = .045) and 'processing speed' (p = .026). They had significantly lower scores for total motor function (p = .013), mainly due to poorer fine motor skills (p = .007) and for general visual perception (p = .009), driven by a decrease in visual-motor integration (p <.001). In the questionnaires, parents of children with NH ≤30 mg/dl reported that they showed poorer working memory performance (BRIEF, p = .032) and increased attention problems (CBCL, p = .006) compared to the control group.

Conclusion: In this study, severe NH ≤30 mg/dl was associated with poorer total IQ scores, fine motor function, and visual-motor integration in mid-childhood compared to a control group. In addition, children with severe NH may be more prone to attention problems and ADHD. Treatment thresholds should therefore be set high enough to avoid any episodes of NH ≤30 mg/dl.

P1-278

Exploration of O-link protein biomarkers in children born after IUGR and early impaired developmental changes in heart function

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We recently assessed systolic heart function in children from IUGR and normal control pregnancies and reported early developmental impairment of left ventricular longitudinal strain – a sensitive echocardiographic measure – during the first 3 months of life in IUGR children. In accordance with previous studies, this suggest that the increased cardiovascular risk later in life imposed by IUGR/SGA may, at least to some extent, be primary and not entirely secondary to hormonal and metabolic programming including early insulin resistance.

We investigated 192 cardiovascular protein biomarkers in cord serum in children from IUGR and normal control pregnancies (N=48) using linear regression models to explore their association with birth weight SDS.

In our primary analysis we demonstrated that 7 cardiovascular protein biomarkers were associated with birth weight SDS. Two hormonal markers related to insulin resistance were among the top 4 associated and included Leptin, an adipokine signaling fat content in adipocytes and IGFBP-1, a liver derived and insulin suppressible regulator of IGF-I bioactivity. Of these, Leptin association with birth weight SDS was enriched in premature children while maternal BMI and diastolic blood pressure did not impact the association with birth weight SDS in secondary analysis. Other cardiovascular protein biomarkers known to affect birth size and metabolism such as PAPPA, FGF-23, FGF-21, IL-6 did not correlate with birth weight SDS (in some cases due to undetectable values in this setting).

In conclusion, cardiovascular protein biomarkers that are associated with later metabolic phenotype in accordance with Barkers hypothesis of early in life programming of metabolism were demonstrated to be associated with birth weight SDS. Since we have previously reported impact of birth weight directly on developmental left ventricular function, these may be parallel phenomenon or there may be early cross-talk between metabolic and cardiovascular function.

P1-279

A Year-Long, National Trial of Prospective CGM Use in Families with Hyperinsulinism

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INTRO: Congenital hyperinsulinism (CHI) is the commonest cause of severe hypoglycaemia in early childhood but glycaemic characterisation remains scarce. Continuous glucose monitoring (CGM) offers a deep understanding of glycaemic control to understand disease burden, individualise patient care and inform therapeutic trials in CHI.

Preliminary studies suggest inadequate accuracy and no efficacy of standalone CGM to reduce hypoglycaemia. Provision is historically restricted to those with severe disease; thus performance of CGM and family experiences have only been described in a limited and biased cohort.

Methods: We aimed to report CGM data in an unbiased cohort of British patients during a year-long prospective study. Primary objectives were:

1. Determine baseline glycaemic characteristics
2. Evaluate hypoglycaemia trends and patterns
3. Understand families' experiences and opinions of CGM

Eligible patients had a diagnosis of CHI and were cared for at a specialist centre. Dexcom G6™ CGM consumables were provided for 12 months. Self-monitoring blood glucose (SMBG) with a Contour Next One™ glucometer was done at least twice a day and to confirm CGM hypoglycaemia. Ten months from study start, all patients were sent a questionnaire to report their experiences of CGM.

Results: Of the 49 patients recruited, 45 used CGM (35 CGM naïve). Mean (range) age was 6 years (2 months – 17 years) and 24 patients (53%) had a genetic diagnosis of CHI. The accumulated 2.7million CGM data points confirmed an increased hypoglycaemia risk in the early morning (0300–070H) with no longitudinal reduction in hypoglycaemia over 12 months. When paired with 17,500 SMBG values, CGM accuracy was poor; values differed by a mean of 25% (1mmol/L) from SMBG.

Dissatisfaction with long-term CGM use was high, with 50% of patients discontinuing use. Questionnaires received from 43/46 parents and 9/9 patients identified pain and accuracy as primary reasons for discontinuation. CGM use reduced anxiety scores of parents but increased those of patients. In response to questionnaires, 80% of parents reported gaining understanding of hypoglycaemia patterns and trends from their CGM, suggesting CGM may inform changes in behaviour and routine with continued use.

CONCLUSIONS Our large, prospective dataset of unblinded CGM in an unbiased selection of British CHI patients confirmed earlier findings of early-morning hypoglycaemia risk. CGM without interpretive support failed to reduce hypoglycaemia over an extended period, with dissatisfaction leading to significant discontinuation from long-term use. Future CGM use in CHI should focus on short-term provision to selected groups, accompanied by structured CGM education.

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P1-280

The Metabolism of 11-Oxy Androgens by Fetal CYP3A7 and CYP3A4 is Less Efficient Compared to Classical Androgens

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Steroidogenic enzyme expression in the fetal adrenal and the placenta hints at the production and metabolism of adrenal-derived 11-oxy androgens (11OxyAs) in the fetal-placental unit. Thus, 11OxyAs are present in placental tissue, fetal cord blood and neonatal serum, and could have a particular role during fetal development. The metabolism of the 11OxyAs in the fetal unit, therefore, presents as a focal point of investigation.

Adrenal androgens are primarily metabolized by the fetal liver cytochrome P450 3A7 (CYP3A7) producing metabolites that circulate to the placenta, evident in the conversion of dehydroepiandrosterone/-sulfate (DHEA/-S) to 16α-hydroxy-DHEA/-S in the liver and the production of estriol in the placenta. Notably, CYP3A7 expression decreases after birth, with a concomitant increase in the expression of CYP3A4. To date, the catalytic activities of these CYP3A isoforms towards the 11OxyAs have not been studied and the role of CYP3A7 in this biological route from the adrenal to the liver to the placenta is of interest, as it would regulate the biological activity of the 11OxyAs, especially in clinical conditions characterized by adrenal androgen excess.

This study aimed to investigate the conversion of the 11OxyAs (11β-hydroxyandrostenedione [11OHA4], 11β-hydroxytestosterone [11OHT], 11keto-androstenedione [11KA4], 11keto-testosterone [11KT]) and the classical androgens (androstenedione, testosterone, and DHEA) by CYP3A7 and CYP3A4. Using recombinant proteins and transiently transfected HEK293 cells, together with liquid- and gas-chromatography mass spectrometry (LC-/GC-MS), steroid conversions and steroid products were investigated.

The conversions of 11OHA4, 11KA4 and 11KT were catalyzed comparably by recombinant CYP3A7, while the conversion of 11OHT was doubled compared to the other 11OxyAs. Most interestingly, the 11OxyAs were converted 2.5-fold ($p<0.01$) and 4-fold ($p<0.001$) less compared to testosterone and androstenedione, respectively, and DHEA (90% metabolized) was the control for the reaction. CYP3A4 metabolized both testosterone and DHEA, 95%, compared to androstenedione, 75%, and again the 11OxyAs were not as efficiently metabolized compared to the classical androgens (3.5-fold less). In support of these results, our cell system also showed less efficient conversion of the 11OxyAs compared to androstenedione and testosterone. Moreover, unique GC-MS spectral patterns identify the novel CYP3A metabolites of the 11OxyAs as C6-hydroxylated 11OxyAs.

To summarize, our data show the metabolism of 11OxyAs by CYP3As is less efficient compared to classical androgens. Therefore, if overproduced, 11OxyAs would not be efficiently metabolized by CYP3A7 in the fetal stage nor by CYP3A4 in the neonatal stage, underscoring the bioavailability of the 11OxyAs in hyperandrogenic endocrine disorders.

P1-281

Steroid secretion and morphological aspects of fetal adrenal before/after freezing/thawing and 14 days in organotypic culture

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Introduction: The human fetal adrenals (HFA) produce high levels of steroids. The gland is distinguishable from the 7th gestational week and can be separated in two zones: the fetal zone in the center which correspond of 80 % of the gland and the definitive zone in the periphery. At this time of the development, neural crest cells are reaching the adrenal primordium, producing catecholamines. A third zone, the transitional zone appears later in the early 2nd trimester.

The objective of our study is to evaluate the functionality of adrenals after freezing, thawing and cultured in "hanging drops" for 14 days.

Tissues and Methods: Adrenal tissues from surgical elective abortions at 9-13 weeks of gestation was cut in several fragments of 1mm3 and cultured in "hanging drops" either straight after dissection or after vitrification or slow freezing and thawing in a drop of 40 µl of media containing ACTH 1ng/ml or not. Twelve steroids were measured by LC-MS/MS in medium recovered all along the culture and the expression of CYP17 was explored by immuno-histo-chemistry (IHC) after 2 weeks of 3D culture. Histology was compared between fresh tissue, cultured tissue for 14 days after vitrification, slow freezing or without cryopreservation.

Results: Four fetuses have been used for adrenal vitrification and slow freezing. Steroidogenesis is persistent after 2 weeks in organotypic culture and ACTH stimulate cortisol and corticosterone secretion. After vitrification or slow freezing procedure, steroid secretion was similar. Analysis is in progress to compare the IHC results between the first and the second week of culture and between the tissues that have been frozen and those that have not. The histological architecture is similar after 14 days of culture between the different techniques and is similar to those cultured without cryopreservation. Nevertheless, we observe an alteration of the tissues in comparison with the fresh tissues.

Conclusion: We showed that 1er trimester fetal adrenals can maintain functional activities and produce steroids comparable to fresh tissue after vitrification or slow freezing and 2 weeks in organotypic culture. Adrenals, as gonads, derivate from the mesoderm. Indeed, the optimization of these techniques could help us to enhance the freezing/thawing protocols of immature testicular tissue in the context of fertility preservation of prepubescent youth.

P1-282

Measurement of fetal subcutaneous fat in the diagnosis of fetal macrosomia in pregnancies with diabetes mellitus

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Background and Aim: Pregnancy with diabetes mellitus is associated with obstetric and neonatal complications, including the development of fetal macrosomia. Fetal macrosomia of diabetic origin is characterized by a disproportionate distribution of subcutaneous fat with predominant localization in the upper half of the fetus body. The cause of excess fetal growth is maternal hyperglycemia, regardless of the type of diabetes in the mother. The aim of study was to assess the possibility of diagnosing disproportionate development of a newborn according to antenatal measurements of fetal subcutaneous fat.

Material and Methods: A study included 76 pregnant women with diabetes mellitus. The inclusion criteria were as follows: singleton pregnancy, gestational age > 37weeks; the exclusion criteria: in vitro fertilization, fetal malformations, hemolytic disease and non-immune fetal hydrops. To assess the excess accumulation of fat mass in newborns, the anthropometric ratio (weight/length ratio (WLR)) was calculated and assessed by sex and gestational age (calculator for WLR INTERGROWTH-21st). Groups were formed: WLR by sex and gestational age less than 90 centile - group 1 (n=46), WLR by sex and gestational age equal to 90 centile and more - group 2 (n=30).

Results: Fetuses from mothers with diabetes mellitus are characterized by a more significant accumulation of subcutaneous fat in the upper half of the body, which correlates with the WLR by gestational age and sex: fetal sub-scapular fat mass and WLR rs=0.76, p<0.001, fetal abdominal fat mass and WLR rs=0.85, p<0.001, fetal mid-thigh fat mass and WLR rs=0.77, p<0.001. The calculated cut-off values of fetal subcutaneous fat (fetal sub-scapular fat mass 5.8 mm or more (AUC 0.93 (0.86-0.99), p<0.001), fetal abdominal fat 5.8 mm or more (AUC 0.97 (0.93-1.00), p<0.001), fetal mid-thigh fat mass 4.4 mm or more (AUC 0.94 (0.87-0.99), p<0.001) with high specificity (95.7%, 91.3% and 87.0%) and sensitivity (73.3%, 93.3% and 93.3%) allow antenatal diagnosis of disproportionate fetal development in women with diabetes mellitus.

Conclusion: The study of fetal subcutaneous fat is an important step in the diagnosis of fetal macrosomia.

P1-283

Developing a Collaborative Research Network to Accelerate the Understanding and Treatment of the Rare Disease Congenital Hyperinsulinism

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Background: Congenital Hyperinsulinism International (CHI) is an international non-profit organization focused on improving the lives of patients and families living with hyperinsulinism (HI). Despite many advances in the care of patients with HI, long term neurologic outcomes have not significantly improved, highlighting the need for CHI's goals for robust and rapidly translatable research. We describe the development of a collaborative research network (CRN) of HI experts and patients to drive sustainable research excellence that leads to faster and more accurate diagnosis, drives new evidence-based treatments and cures, standardizes clinical guidelines, and facilitates increased and improved access to care.

Objective: To report on the formation of the HI CRN, to present our prioritized research agenda, and to report on progress.

Methods: CHI applied for and received funding to launch an HI CRN from the Chan Zuckerberg Initiative in 2020. A total of 60 academic and industry researchers, clinicians, and expert patient advocates from 19 countries were invited to join the CRN. Clinical expertise included endocrinology, genetics, radiology, nursing, and other related disciplines. Participants worked in groups over two years in virtual meetings to identify gaps in knowledge and resources in 7 key areas: genetics, diagnostics, glucose monitoring, medication and surgical management, care-guidelines and centers of excellence, nomenclature, and clinical trials/industry engagement.

Results: The HI CRN outlined and defined >360 individual deficits in information in various aspects of HI. Through deliberation of current evidence and patient needs, a prioritized research agenda was identified in five key areas: (1) investigation of the natural history of HI, (2) development/adoption of a newborn HI screening approach, (3) investigation of specific causes of hypoglycemia related neurological injury, (4) development of continually evolving global care guidelines, and (5) development of an expert group advising on clinical trials for regulatory approval of novel and repurposed therapeutic options for HI. The summated and synthesized interactions within sub-groups and whole group in the CRN has led to strategic workplans for five key working groups, an in-person meeting of participants in these groups, and inspired peer-reviewed publications.

Conclusion: The HI CRN has identified key areas of information deficit by successfully integrating clinicians, industry partners, and patient representatives to enhance research perspectives and lay the foundations for sustainable HI research tailored for patient need. The HI CRN will continue to develop and refine research and advocacy strategies to improve understanding and treatment of HI through meaningful ongoing international collaboration.

P1-284

Neonatal hypoglycemia at one and four hours of life: incidence and associated factors

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Keywords: neonates, hypoglycemia, size for gestational age, gender, mode of delivery.

Introduction: Neonatal hypoglycemia is one of the most common treatable metabolic disorders. Universal newborn screening for hypoglycemia is primordial in detecting persistent hypoglycemia and asymptomatic episodes in order to save neonates from adverse neurological outcomes and brain injury.

Objectives: To assess the incidence of neonatal hypoglycemia and to correlate it at one and four hours of life with size for gestational age, gender and obstetric mode of delivery. To prove the importance of hypoglycemia screening and monitoring.

Methods and Materials: This is a longitudinal prospective study conducted at Notre Dame Des Secours University Medical Center (NDS-UMC), Byblos, Lebanon, involving 300 asymptomatic healthy newborns with no known neonatal hypoglycemia risk factors and small for gestational age (SGA) newborns, who were admitted to the maternity ward. Glycemia was measured by a glucometer using reagent strips at one and four hours of life.

Results: The incidence of neonatal hypoglycemia in our population was 30% at one hour of life and 18.7% at four hours of life. At one hour of life, there was only a significant relationship between the mode of delivery and neonatal hypoglycemia, whereas a higher percentage of neonates born from vaginal birth had a normal hemoglucotest. At four hours of life, no statistical significance was found between the studied variables and hypoglycemia, whether the newborns were normoglycemic or hypoglycemic at one hour of life.

Conclusion: Vaginal birth was found to be a protective factor associated with neonatal normoglycemia after delivery. There was no gender predilection. Universal neonatal hypoglycemia screening in all newborns is necessary in order to prevent recurrent hypoglycemia and to detect asymptomatic episodes.

P1-285

Severe Neonatal Donohue Syndrome: Extreme Hyperinsulinemia, Progressive Hypertrophic Cardiomyopathy (HCM) and Failure to Thrive

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Introduction: Donohue syndrome (DS) is presenting as the most severe form of insulin resistance. Most of the patients are dying within the first two years of life. As potential treatment has been described the administration of rhIGF1 (Mecasermin) to stimulate the pathway of insulin-like action. An improved metabolic control was reported with continuous subcutaneous administration of rhIGF1 instead of twice daily injections [Plamper 2018].

Case Report: At birth our female patient (38^{+2} weeks of gestation) presented the following clinical features: large ears, thick lips, acanthosis nigricans, hyperplasia of nipples, decreased subcutaneous fat mass, small toenails, abdominal distension and clitoris hypertrophy.

The girl was small for gestational age (1,820g birth weight) and appeared in the first days with hypoglycemia (min. 37 mg/dl). A first episode of hyperglycemia (343 mg/dl) was seen on 13th day of life. We noticed the absence of ketoacidosis. The patient received treatment with i.v. insulin, max. at 0.6 IE/kg/h. Laboratory showed an extremely elevated c-peptide (>30.0 µg/l) and insulin levels (max. 2,640 mU/l).

Further signs of the patient were hypertrophic cardiomyopathy, extremely enlarged polycystic ovaries and renal tubular dysfunction with nephrocalcinosis grade III. Due to the suspicion of an insulin resistance syndrome we started a modified ketogenic diet to achieve sufficient energy gain in the event of insufficient glucose metabolism. It was possible to establish reliable continuous blood glucose measurement with a Dexcom® sensor despite the very small subcutaneous fat tissue.

Genetic testing confirmed DS (compound heterozygous mutation of the INSR gene: c.1610+1G>A paternal and c.32_52del (Ala11_Ala17del) maternal).

Our primary treatment approach was a significant reduction in hyperinsulinemia to reduce the life-limiting factor of progressive hypertrophic cardiomyopathy (HCM). Therefore, we started administration of diazoxide, which did not significantly improve hyperinsulinemia and severe HCM. After switching to subcutaneous administration of octreotide HCM improved rapidly and insulin level fell down (min. 15 mU/l).

Our current goal is sufficient thriving of the patient which is challenging. At the age of one month we started continuous subcutaneous administration of rhIGF1. We also gradually modified the ketogenic diet to avoid hypoglycemic events and to improve the disturbed enteral absorption of food.

Conclusion: Severe neonatal DS is challenging. One main goal seems to be to reduce the massive hyperinsulinemia causing life-limiting hypertrophic cardiomyopathy.

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P1-286

Aetiology and Outcome of Hypoglycaemia in Young Children

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Background: Hypoglycaemia is one of the most common presenting complaints at paediatric emergency department. There are many distinct causes of hypoglycaemia, ranging from nutritional insufficiency, infectious origins, to metabolic disorders. A thorough investigation can help differentiate the cause of hypoglycaemia, with subsequent tailored management. All patients with hypoglycaemia should have a full clinical assessment and together with a hypoglycaemia screen if appropriate.

Aim: This clinical review aims to determine investigation of hypoglycaemia in young children (≤ 6 years), and whether these patients received a subsequent diagnosis and adequate follow-up plan.

Methods: The local biochemistry laboratory information management system (LIMS) was searched for all children from 0 to 6 years-old, with hypoglycaemia defined as < 3.0 mmol/L from 2013-2021 at the Royal Hospital of Children, Glasgow. All cases were reviewed for the biochemistry investigations to determine if they had a full or partial hypoglycaemia screening requested and/or performed, the presenting complaint, clinical diagnosis, and subsequent follow-up arrangements.

Results: 501 children were identified with hypoglycaemia (< 3.0 mmol/L) over the nine-year period. Of these patients, around 28% (142/501) of patients had a full hypoglycaemia screen, 38% had a partial screen, and 34% (166/501) had no blood tests related to hypoglycaemia screening. The cause of hypoglycaemia was identified in 15 % (77/ 501) with gastroenteritis being the most common cause. Of those who were hypoglycaemic, 48 % had ongoing follow-up. Those with severe hypoglycaemia (≤ 1.5 mmol/L) (86/501), causes were identified in 72% (62/86) of the total hypoglycaemia incidence and 63 % (54/86) were followed up after first presentation.

Conclusions: Screening is not performed in all patients presenting with hypoglycaemia. A great portion of patients are not fully investigated and not followed up, including those with severe hypoglycaemia which can have long-term consequences and need to be managed appropriately.

P1-287

Mutations in exon 28 of ABCC8 gene in Egyptian patients with congenital hyperinsulinism

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Background: Congenital hyperinsulinism in infancy (CHI) is the most frequent cause of persistent hypoglycemia in infants. The most common and severe form of monogenic CHI is caused by inactivating mutations in ABCC8 and KCNJ11 genes located on chromosome 11p15.1. On the ABCC8 gene; previous studies have shown that mutations were reported to be mostly localized in exon 28. There is no sufficient research in Egyptian population about different mutations in congenital hyperinsulinism (CHI). The aim of this work was to study the prevalence as well as clinical associations of mutations in exon 28 of ABCC8 gene in a sample of Egyptian children with CHI.

Methods: A cross-sectional study was conducted on 13 patients diagnosed with CHI. Hyperinsulinism was diagnosed in cases with persistent and recurrent hypoglycemia, in the presence of an intravenous glucose infusion rate of > 8 mg/kg/min, detectable insulin, elevated C-peptide ≥ 0.5 ng/ml and suppressed ß-hydroxybutyrate <1.8mM during spontaneous or induced hypoglycemia.

Clinical, biochemical, phenotypic characteristics, clinical outcomes as well as genetic testing by DNA sequencing were studied in children with CHI who were following at Diabetes, Endocrine and Metabolism Pediatric Unit, Children's hospital, Cairo University.

Results: The mean age of patients was (13.9±13.3) months ranging from 17 days to 38 months, the majority were males (61.5%). Hypoglycemic seizures were the presenting feature in 84.6% of cases, lethargy in 61.5% of cases, poor feeding in 38.5%, and apnea in 15.4% of patients. 61.5% of patients presented by symptoms in first week of life, 15.4% presented in first 6 months, the rest presented later. Abnormal motor development was found in 46.2% of cases, abnormal mental development in 7.7%, delayed speech in 38.5%, while abnormal vision in 7.7%.

Results of DNA sequencing showed that only one patient had intronic homozygous variant on intron 28 (rs1954399854), where there was G to A nucleotide substitution at nucleotide position 77550 Seventy % of patients were treated with octreotide, 15% with diazoxide (drug less available) and 15% with combination of both drugs. On treatment, 30% of cases had recurrent admission, 69.2% recurrent hypoglycemia, while 46.2% had recurrent convulsions.

Conclusion: Molecular studies for patients with CHI are important as it may provide important information regarding the histology of the disease, and the recurrence risk in future generations. It should be routinely carried out in those patients to correlate the type of mutation and specific management and prediction of remission.

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P1-477

Newborn screening for Congenital adrenal hyperplasia in Pakistan; Pioneering the way forward

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Objective: This study aims to evaluate the effectiveness and efficiency of weight-based threshold levels for 17-hydroxyprogesterone (17-OHP) in screening newborns for 21 hydroxylases deficiency-congenital adrenal hyperplasia (CAH)

Design: In April 2021 CAH screening was incorporated into the ongoing newborn screening program at aga khan university Hospital Karachi Pakistan,17OHp was assayed through Spectro fluorometry of Dried blood spots obtained via heel prick. The cutoff levels of 17OHP were determined based on the birth weight and age of the sampling.

Results: From April 2021-March 2023, 9837 newborns were screened for CAH out of a total of 10821 births, only one CAH patient was detected, and therapy was started at a median age of 7 days. A recall for suspected CAH was performed in 124 cases with a mean coverage of 90.9%. 'The overall prevalence was 1:9837. The specificity was 98.8%. The positive and negative predictive value was 81.0% and 100%, respectively. To date, no false-negative cases have been detected.

Conclusion: Employing weight-based standards to assess 17-OHP levels during the screening process for 21-OH-D-CAH has been found to significantly lower the number of false-positive outcomes. The effectiveness and efficiency of utilizing this method for screening newborns for 21-OH-D-CAH will be determined through extended follow-up of the screened population.

P1-478

Whole-exome sequencing results in patients with congenital hyperinsulinism

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Background: Congenital hyperinsulinism (CHI) is a heterogeneous group of disorders, characterized by hypoglycemia due to inappropriate insulin secretion. Despite huge progress in understanding the pathophysiology of CHI, its etiology remains unknown in about 30% of cases.

Aim: To perform whole-exome sequencing in patients with CHI.

Results: A total of 314 patients with congenital hyperinsulinism underwent genetic testing using NGS panel (*GLUD1, HNF1A, GCK, ABCC8, HNF4A, INSR, KCNJ11, SLC16A1, HADH, KDM6A, KMT2D*). Additional tests for syndromic CHI forms included chromosome 11 methylation analysis (n=28), karyotype (n=9), transferrin isoelectric focusing (n=13) and Chromosome microarray (n=5). Pathogenic variants were found in 187 (59.5%) cases: *KCNJ11/ABCC8* (n=138); *GLUD1* (n=18), *GCK* (n=6), *HNF4A* (n=6), *HADH* (n=2), *INSR* (n=2), *HNF1A* (n=1), *SLC16A1* (n=1), Beckwith-Wiedemann syndrome (n=8), Kabuki (n=3), Turner (n=2).

94.6% of the cases with negative genetics were diazoxide (Dzx) responsive. Whole exome sequencing was performed in 17 patients with either Dzx unresponsive CHI (n=4) or those having unusual clinical phenotype (n=13). Mutations in various genes were found in 3/4 and 6/13 patients with Dzx-unresponsive and Dzx-responsive CHI resp (Table 1). Some of these genes are well-known to cause CHI whereas others are not clearly established. Two patients with medically resistant CHI required subtotal pancreatectomy and conservative treatment after the surgery (somatostatin analogues, Dzx, insulin receptor antibody).

Conclusions: Whole exome sequencing is helpful to diagnose rare syndromic forms of CHI. Studies on bigger cohorts will allow to estimate significance of the candidate genes and to modify CHI gene panel.

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Table 1. Clinical characteristics of patients and genetic results of the whole-exome sequencing.

Case	Gene	Variant	Inheritance	Age at onset	Phenotype
1*	*CACNA1D*	p.Phe767del	Denovo	1 d	Profound developmental delay, muscle hypotonia, subclinical hyperaldosteronism, congenital glaucoma
2*	*NOTCH2***	p.S2427T, heteroz	Denovo	8 m	UR
3*	*ABCC5***	c.129G>A: p.P43P, heteroz	Denovo	3 y	UR
4	*EIF2S3*	c.671T>G, heteroz	Maternal	21 m	Obesity, dysmorphism, mental delay
5	*EP300*	c.3163C>T, p.R1055X. heteroz	Denovo	1 d	IUGR, short stature, facial dysmorphism,
6	*CREBBP*	c.4270C>T, p.Pro1424Ser, heteroz	ND	3 w	Developmental delay, facial dysmorphism, epilepsy, cerebral palsy, corpus collosum hypoplasia
7	*KCNH6*	c.1136G>A, p.Arg379Gln, heteroz	ND	3 d	Facial hemi hyperplasia, flat nasal bridge.
8	*MAFA***	p.Hiz208del, heteroz	Denovo	3 m	Muscle hypotonia, cerebral palsy
9	*DNAJC3*	p.Arg393Ter/p.Arg346Ter	ND	6 m	hypothyroidism, short stature, dysmorphic features

*Dzx unresponsive
**genes not previously described in CHI
d- days, m – months, w – weeks, y – years, UR - unremarkable

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Early-life exposure to phthalates and minipuberty: is there any relationship?

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Background: Nowadays, the role of minipuberty in influencing pubertal development is well documented. Phthalates are ubiquitous environmental contaminants and endocrine-disrupting chemicals (EDCs) with reproductive toxic effect. Aim of this study is to assess phthalate exposure within the first months of life in a cohort of healthy term infants and their mothers and the possible relationship with minipuberty.

Methods: Single-center, prospective birth-cohort study, assessing phthalate exposure in urine samples collected from mothers after the delivery and in their infants at birth(T0), 3(T3) and 6(T6) months. Phthalate-free containers were used. After solid-phase extraction, samples were analysed by triple Quad LC/MS Mass Spectrometry. Eight major phthalate metabolites (MMP, MEP, MnBP, MBzP, SDHEP, MCOP) of 6 of the most used phthalates were assessed. Urinary hormonal pattern (uLH, uFSH, testosterone–uT, oestradiol-uE) at T0,T3,T6 was performed. Ano-penile distance(AGD-AP), ano-scrotal distance(AGD-AS) and penile length(PL) for male, ano-fourchette distance(AGD-AF) and ano-clitoris (AGD-AC) for female, were collected at each timepoint.

Results: 188 mother-infant pairs were enrolled. In female, at T0 a positive association was detected for uE and MnBP, MBzP, SDEHP and MCOP. At T3 and T6, significant positive associations between phthalates exposure and uE and uFSH were found for all the metabolites but MCOP. Maternal concentrations of MMP were negatively associated to AGD-AC at T0 and positively associated to AGD-AF at T3. Maternal and neonatal MEP were positively associated to AGD-AF at T6. Neonatal MnBP and MCOP were respectively related to AGD-AF and AGD-AC at T3. In male positive associations at T0, T3 and T6 were detected within MnBP and uFSH and uT. At T0 a positive association was found between MbzP, SDEHP and uT; while negative association was found within MCOP and uLH and uFSH. At T3, uFSH was related to MMP, MBzP and DEHP while uLH was associated to MMP and uT to MCOP, this last was also negatively related to AGD-AP at T3. A negative association was found within MEP at T3 and uFSH at T6 and MBzP at T3 and uLH at T6. At T6, uT and uFSH were positively related to: MEP, MBzP, SDEHP while uLH was negatively related to MCOP.

Conclusions: Associations within phthalates and hormonal pattern were detected during the first six months of life. Effects of these relations are not clear, but exposure to EDCs may influence minipubery and longitudinal studies are needed to estimate the possible impact on puberty and fertility.

P1-480

Grb10a Knockdown in Early Life Permanently Alters Growth, Cardiometabolic Phenotype, and the Co-ordination of the Whole Transcriptome in Zebrafish

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The ‘Developmental Origins of Health and Disease’ (DOHaD) hypothesis encapsulates the relationship between pre- and perinatal exposures causing altered growth and the development of later life disease. Mediators of this relationship have not been fully defined. We have used zebrafish [ZF] (Danio rerio) as a potential model for DOHaD, modifying expression of *grb10a*, an adapter protein that interacts with the insulin and IGF receptors, to act as a negative regulator of fetal and postnatal growth.

We have characterised growth, cardiometabolic status, and the impact on co-ordination of gene expression following morpholino-induced embryonic knockdown (KD) of *grb10a* expression. This led to a decrease in *grb10a* expression in the embryo with increased levels of phosphorylated AKT and S6, indicative of increased insulin and IGF-I signalling. *Grb10a* mRNA levels returned to those seen in control ~10 days post fertilisation (pf).

Between 24- and 120-hours pf, KD ZF showed increased growth in body length (+7%), increased glucose uptake (+25%) and decreased heart rate (-50%) compared to control-injected embryos.

The transcriptome was assessed between 5- and 30-days pf, coinciding with major changes in ZF maturation and development. The expression of age-related genes in the control fish was characterised by three clusters, while this pattern was markedly disrupted in the KDs. We also modelled transcriptomic networks using hypergraphs and quantified changes to the network structure over time by measuring entropy, a marker of cellular differentiation potential. Entropy of biological pathways differed significantly between the two groups. Thus, *grb10a* KD results in major functional and organisational changes to the transcriptome.

The ZF were followed to 18 months. KD ZF had greater body length and mass than controls. Ventricular muscle in the heart was thicker and the cross-sectional area of muscle fibres was increased in KD. Basal metabolic rate (MR), defined by oxygen consumption, was comparable between KD and control ZF, but maximum MR was higher in KD, resulting in greater aerobic scope. Fasting glucose was higher in KD, while both groups showed a similar glucose response to insulin.

This study demonstrates that knockdown of a single gene, *grb10a*, in ZF embryos results in changes in growth and metabolic phenotype from early life through to 30 days, coincident with major transcriptomic remodelling. In addition, alterations in growth and cardiometabolic function persist in adult KD ZF. Embryonic disruption of gene expression in zebrafish could be a valuable model to identify pathways associated with long-term disruption to health.

P1-481

Treatment of Transient Hypothyroxinaemia Of Prematurity may improve premature newborns' neurodevelopment. NEOTHYR, a multicentered retrospective cohort study about 373 subjects

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Background: Transient hypothyroxinaemia of prematurity (THOP), defined as low levels of FT4 without the expected TSH surge, may concern up to 50% of infants born <30 weeks' gestational age. Most studies showed a link between THOP and impaired neurodevelopment, as shown in the review of Eerdekens. Data about the benefit of supplementation are scarce, with few randomised trials and inconclusive results. To date, there are no clear recommendations regarding screening, diagnosis criteria and treatment of THOP.

Aim: To compare neurodevelopment at two years of corrected age between newborns with treated and untreated THOP.

Materials and Methods: This study was a multicentered, retrospective cohort study, based on prospectively collected data in 4 neonatal ICU, during years 2009 to 2020. Newborns were included if they were born before 32 weeks of gestation (GW) and underwent a thyroid function test. They were divided into 3 groups: noTHOP, treated THOP and untreated THOP. Primary outcome was neurodevelopment at two years of corrected age, evaluated by the child's paediatrician as normal or not. Secondary outcomes were revised Brunet Lezine score at 2 years, ASQ-3 scores.

Results: 601 newborns met inclusion criteria, 373 were included. Compared to noTHOP group, subjects with THOP had lower gestational age, lower birth weight and younger age at first thyroid evaluation (20 days versus 25 days). Subjects from the treated group had lower FT4 than untreated ones (8.4 pmol/L versus 9.4 pmol/L). In the treated group, L-thyroxine was started at median age of 22 days at mean dose of 7.5 µg/kg/j and continued until 39 GW.

266 subjects were analysed. There was no statistically significant difference in neurodevelopment at two years of corrected age between the 3 groups. We showed a tendency for better neurodevelopment in noTHOP group as compared with THOP group (OR 1.37 [0.8-2.3]) and worse neurodevelopment in untreated group as compared with treated group (OR 0.8 [0.3-1.9]). Results remained the same after adjusting for confounding factors. There were no statistically significant differences on secondary outcomes.

Conclusion: Premature newborns who received LT4 for THOP may have a better neurodevelopment than untreated infants. Our results are not statistically significant but relied on an observational study with inherent bias (the biggest being the absence of randomisation for treatment allocation). The absence of statistically significant difference does not mean the absence of effect. Randomised controlled trials should follow this study to improve our knowledge on this subject.

P1-482

Human milk short-chain fatty acids promote early myelination in a 2D human co-culture of oligodendrocytes and cortical neurons

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Background: Human milk is considered the most advantageous source of nourishment for infants. Although there is a growing body of evidence showing that human milk feeding fosters

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early neurodevelopment, the underlying process is still not completely known. Indeed, clinical and animal research has linked human milk to enhanced myelination in the infant's central nervous system, however, access to human oligodendrocytes and neurons in the early stages of development has been limited, making it difficult to comprehend the potential effects of human milk components on myelination.

Aims: To test if physiological concentrations of short-chain fatty acids (butyrate, propionate, acetate) could promote early myelination in a human co-culture of oligodendrocytes and cortical neurons.

Methods: Neonatal oligodendrocytes as well as cortical neurons were generated by direct differentiation using human induced pluripotent stem cells (iPSC). Each cell line was validated separately at different time points. Specific cell lineage markers expression was analyzed by immunofluorescence, qRT-PCR, and western blot. Cortical neurons (day 37) and oligodendrocyte progenitor cells (day 67) were then combined into a co-culture and grown together for additional 28 days. Markers of myelination (oligodendrocyte transcription factor (Olig2), myelin basic protein (MBP), and O4) were probed following treatment of the co-culture with several concentrations of butyrate, propionate, and acetate.

Results: Short-chain fatty acids, particularly butyrate, significantly promoted oligodendrocyte differentiation. The co-culture resulted in almost 60% of O4+ promyelinating cells being further differentiated into Olig2+ and MBP+ mature oligodendrocytes within 10 days of treatment.

Conclusion: In summary, we established a 2D human co-culture model containing 50% of oligodendrocytes and 50% cortical neurons. Short-chain fatty acids treatment of the co-culture resulted in a significant increase in myelination markers within 10 days.

P1-483

Incidence of Perinatal Stress Hyperinsulinism Requiring Diazoxide Treatment in Newborn Infants

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Background: The incidence of perinatal stress hyperinsulinism (PSHI) requiring diazoxide treatment is estimated to be 1:12,000 (Hoe et al., 2006). Diazoxide is used to treat PSHI, but it has been shown to have adverse effects including pulmonary hypertension. Gray et al, reported that of 1.25 million infants admitted to NICUs for hypoglycemia over a period of 18 years, only 1066 received diazoxide suggesting 1:1172 babies had HI however 92% of them were off diazoxide by the time of discharge and there was no diagnostic data given.

Objectives: 1) Determine the precise incidence rate of PSHI requiring diazoxide therapy in our service area.

Methods: We reviewed the charts of patients born in our service area who required diazoxide treatment of their PSHI (DrxPSHI). In our service area, all patients requiring diazoxide were referred to our institution during the study time frame of 2012 to 2019. We used public health records to determine the annual number of births and calculated the incidence. Outcome data was tracked in our IRB approved Congenital Hyperinsulinism Center REDCap registry.

Results: Forty-eight patients met our inclusion criteria (60% male, 67% Caucasian, 31% Hispanic). From 2012 to 2019, there were an average of 2.15 infants who had DrxPSHI per 10,000 live births (1/4652). The annual incidence of Infants with DrxPSHI ranged from a low of 1.41/10000 (1/7093) in 2015 to a high of 2.58/10000 (1/3880) in 2019. Of the 48 infants with DrxPSHI treated at our institution during this time, the average gestational age was 35.9 weeks and size was appropriate for gestational age for 48% (42% small for gestational age). Ninety (90) percent presented with hypoglycemia at birth (range 0 – 86 days) and were diagnosed with PSHI at 20 days on average (median: 10, range: 1-88, 384*).

Conclusions: We have shown the incidence of DrxPSHI is 1:4652. This contrasts to previous data showing 1/12000 (Hoe et al., 2006). Recent data suggesting the overall incidence of PSHI being around 1/1200-1700 suggests that 1:3-4 patients with PHSI need prolonged diazoxide therapy.

Table 1. Incidence rate of Perinatal Stress Hyperinsulinism by Year.

Year	Tarrant County Birth Rate	New PSHI Cases	Per 10,000 Births	Incidence Rate
2012	27684	7	2.53	1/3955
2013	27839	7	2.51	1/3977
2014	28420	5	1.76	1/5684
2015	28370	4	1.41	1/7093
2016	28745	5	1.74	1/5749
2017	27820	6	2.16	1:4637
2018	27280	7	2.57	1:3897
2019	27161	7	2.58	1:3880
2012–2019	223319	48	2.15	1:4652

P1-484

Relationships between birth body weight <10.th centile (SGA) and insulin-like growth factor-ii / insulin-like growth factor binding protein-3 ratio in the not-life threatened newborn: relevance of birth chest circumference / birth body weight ratio and oxygen supplementation

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Direct relationships of estimated birth brain weight(BRW) to birth body weight (BW) ratios (BBR) and of BW<=10.th centile for GA(SGA) with blood serum Insulin-like Growth Factor-II(IG2) to blood serum Insulin-like Growth Factor Binding Protein-3 (IB3) ratios (IG2/IB3R), and inverse relations between BW-SDS and birth chest circumference(CC) / BW ratio (i.e., CC through BW; CC/BWR) have been detected by our group in the human newborn(NWB). We evaluated the possibility that CC/BWR could be involved in NWB BBR-IG2/IB3R relationships. NWBs with any among total parenteral nutrition, parenteral nutrition other than dextrose, blood component transfusion, postnatal corticosteroid-, catecholamine- or methylxantine-based treatments, life-threatening disease, diabetes mellitus(DM) or other endocrine diagnosis, malformation, and mother with DM were excluded. 78 included NWBs, all studied before covid-19 pandemic and from conception to study end near sea-level, had complete data for 1) same-day records at one of the first 5 postnatal days(x), 5 days after x(y) and 10 days after x(z) of postnatal age(PNA, unit:day), %O2 in respiratory gases(FiO2; range, x=21-80, y=21-30, z=21-26) and IG2 and IB3 radioimmunoassay(unit=uM/dl), and for 2) gender (SEX), GA(unit:complete week; extremes=28–42), GA<=36 present(PTB, n=46), CC(25th-75th centiles=27-32cm), BW(unit=g; 25th-75th centiles=1926-2942g), and SGA(n=20) (computations; male SEX(n=43), SGA; condition absent=0, condition present=1). BRW (unit=g; 0.037 × head circumference (cm)2.57) and BBR(100 x (BRW/BW)) were calculated according to Lindley - McLennan. SPSS-28 software was used to generate GA-unrelated BBR and CC/BWR standardized residuals(resp. BBRsr and CC/BWRsr)(i.e., Linear regression procedure-Save pushbutton/ Standardized residual checkbox-Continue pushbutton/ regress either BBRsr or CC/BWR on only GA). IG2/IB3R at x-y-z time-points was averaged (i.e., (x+y+z)/3; IG2/IB3RM). IG2/IB3RM normal score according to Van der Waerden(IG2/IB3RM-NS) resulted normally distributed. Spearman rank correlations between the following variable pairs are reported(Rho; significance): BBRsr vs CC/BWRsr(.738; p<.000001), CC/BWR vs IG2/IB3RM(,564; p<.000001), CC/BWR vs FiO2x(.401, p=.0003), FiO2x vs IG2/IB3RM(.451, p<.00005). Partial correlation(pc) coefficient(pcc) of BBRsr pc with outcome IG2/IB3RM-NS in Multiple linear regression (MLR) was significant(t=4.287, p<.00005, pcc=.451) with SEX-GA-BBRsr -FiO2x-PNAx-FiO2x as predictors, but was non-significant with SEX-GA-BBRsr-CC/BWRsr-FiO2x-PNAx-FiO2x as predictors (MLR R2, .332 / .440, always significant). CC/BWRsr could be involved in direct relationships between BBRsr and IG2/IB3RM-NS independently of GA and FiO2x in not-life-threatened NWBs.

P1-485

A case of a newborn diagnosed with CMAMMA suspected of primary immunodeficiency

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Background: Combined malonic and methylmalonic aciduria (CMAMMA) is a rare genetic disorder that affects the body's ability to break down certain proteins and fats. It is caused by mutations in the ACSF3 gene, which provides instructions for making an enzyme involved in the metabolism of fatty acids. As a result of the enzyme deficiency, individuals with CMAMMA experience an accumulation of malonic and methylmalonic acids in their blood and urine.

Case: At 2 days old, a baby born at 36+5 weeks with a weight of 2.02kg was brought to the emergency room due to apnea. Initial laboratory testing revealed an elevated C-reactive protein level of 2.31 mg/dL (reference range, 0-0.3 mg/dL) and cerebrospinal fluid analysis showed an increased white blood cell count of 48 cells/mm^3, raising concern for meningitis. Despite negative culture results for viral and bacterial pathogens, the infant was treated with antibiotics and discharged without complications. At approximately 1 month of age, the infant presented with a fever of 38.2°C and physical examination revealed a left inguinal mass, ultimately diagnosed as necrotizing lymphadenitis after imaging studies. The infant underwent incision and drainage by a surgeon, and cultures were positive for methicillin-resistant Staphylococcus aureus. At 7 months of age, the infant was readmitted for a 1-2cm abscess in the perianal region that spontaneously drained during hospitalization and was treated with intravenous antibiotics.

Result: The infant underwent immunological tests including lymphocyte subset analysis and primary immunodeficiency next-generation sequencing panel analysis, which revealed the presence of the ACSF3, c.[689G>A];[1240-3C>G](p.[Trp230Ter];[?]). These findings led to a diagnosis of CMAMMA, which was confirmed to be inherited from both parents through family testing. Although newborn screening via dried blood spot was negative for this condition, metabolic disease testing was initiated following diagnosis. Serum amino acid testing did not reveal any significant findings, but urine organic acid testing demonstrated elevated levels of malonic acid (MA) at 49.2 (reference range, < 0 mmol/mol of creatinine) and methylmalonic acid (MMA) levels at 332.1 (reference range, <32.9 mmol/mol of creatinine), resulting in an MMA/MA ratio of 6.75.

Conclusion: The infant has been doing well without any significant complications following the diagnosis, despite experiencing more frequent cold symptoms. It is believed that the patient has a high likelihood of having a benign course. This is the first reported case of an ACSF3 mutation in Korea.

P1-486

Severe hypercalcemia due to subcutaneous fat necrosis despite minimal skin lesions in a newborn: a case report

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Introduction: Subcutaneous fat necrosis of the newborn (SCFN) is a self-limiting panniculitis which can develop in the first weeks of life. The disorder is characterized by firm, red or purple subcutaneous nodules and plaques on the trunk, buttocks, cheeks, and extremities and is associated with perinatal stress. SCFN may lead to hypoglycemia, anemia, thrombocytopenia, hypertriglyceridemia and hypercalcemia. The proposed mechanism for the hypercalcemia is extrarenal 1,25-di-OH-vitamine D formation due to expression of 1α-hydroxylase in the inflammatory infiltrate of the subcutaneous adipose tissue.

Case Description: We present a female neonate who suffered from perinatal asphyxia due to a complicated delivery. She quickly recovered and was dismissed after one week. She was re-admitted to the neonatology department after another week with poor feeding, weight loss and lethargy. Clinical examination showed no abnormalities except for a subtle slightly firm swelling (2x2cm) on the back without discoloration of the skin. Laboratory evaluation showed an elevated calcium ion [2.34 mmol/l (ref. 1.15-1.33)], and 1,25-di-OH-vitamin D3 [586 pmol/L (ref. 59-159)] level. Parathyroid hormone level was suppressed, phosphate and 25-OH-vitamin D values were normal. Electrocardiogram was normal. Ultrasound of the kidneys showed nefrocalcinosis. Ultrasound of the skin revealed subcutaneous fat necrosis. The diagnosis of subcutaneous fat necrosis with hypercalcemia was made. Initial treatment with hyperhydration, low-calcium diet for the mother and discontinuation of vitamin D suppletion did not decrease the calcium ion level. A gift of pamidronate i.v. was given for the long-term lowering of calcium ion levels which resulted in hypomagnesemia, hypokalemia, and hypophosphatemia. Also hypertriglyceridemia, hypoalbuminemia and an increased lactate level were present. For acute lowering of the calcium ion level a gift of furosemide i.v. and calcitonin s.c. were given. On the third day breast milk was replaced with low-calcium formula. A week after presentation more subtle skin lesions appeared. In total, 2 gifts of pamidronate and 9 gifts of calcitonin in a period of 14 days were necessary to decrease and maintain the calcium ion level within normal values.

Discussion: Despite only very subtle skin lesions severe hypercalcemia developed in our patient with SCFN after mild perinatal asphyxia. The tachyphylaxis which is observed by others after 24-48 hours of successive doses of calcitonin did not occur in our patient. This case report adds to the relatively scarce available literature on the metabolic changes which can occur in patients with SCFN and the effective treatment of the associated hypercalcemia.

P1-487

The Association of Maternal Pre-pregnancy BMI and Gestational Weight Gain on the Course of Pregnancy and Some Neonatal Parameters

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Keywords: Pre-pregnancy BMI, gestational weight gain, pregnancy outcomes, neonatal outcomes.

Background: Overweight and obesity epidemic is still expanding, and it is affecting women of childbearing age. Multiple studies have shown unmatched results concerning the effect of Body Mass Index (BMI) besides gestational weight gain (GWG) on pregnancy and neonatal outcomes.

Objectives: This study aims to determine the effect of each of the two anthropometric indicators: pre-gestational BMI and gestational weight gain on the course of pregnancy and neonatal outcomes.

Material and Methods: A retrospective study was conducted at Notre Dame de Secours University Medical Center (NDS-UMC), Byblos, Lebanon. The data was collected from the NDS-UMC archive. Out of 804 deliveries during the year 2020, 583 women were included after choosing their files randomly and after eliminating those with the exclusion criteria or incomplete data.

Results: Underweight/healthy BMI mothers had a higher chance of having low GWG (45.5%), vaginal delivery (51.3%), and a baby of appropriate size (78.6%) or small size for gestational age (10.4%). Obese women had a higher risk of excessive GWG (49.3%), delivery via C-section (69.3%), and large for gestational age babies (26.7%).

Mothers who had low GWG were at a higher risk of having babies of appropriate size (80.1%) or small size for gestational age (13.1%). Mothers who had high GWG had a higher risk of having baby boys (58.9%), large for their gestational age (26.1%), with hypoglycemia at birth (20.6%).

Conclusion: Both extremes of BMI and GWG are linked to adverse neonatal outcomes. This highlights the importance of weight monitoring even during pregnancy to prevent its negative impact on neonates.

P1-488

Characteristics of the neonatal period in children with Prader-Willi syndrome

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Background and Aim: Prader-Willi Syndrome (PWS) is a rare disease with various clinical signs in different age periods. Early diagnosis has a proven benefit in PWS, allows for timely diet therapy and prevention of obesity, early administration of growth hormone. The purpose of the study is to analyze the features of neonatal adaptation in children with PWS, to evaluate the diagnostic efficacy in the dynamics of the analyzed period.

Material/Methods: The study included 48 patients (23 boys, 25 girls) with PWS diagnosed in the republic from 01/2012 to 02/2023. Perinatal and neonatal manifestations, anthropometric status were analyzed. INTERGROWTH-21st was used to calculate percentiles and SDS birth weight. Paternal deletion of 15q11.2-q13 was confirmed in 38 (79%) patients (Group 1, Gr1): 27 by FISH, 11 by molecular genetic methods. Maternal uniparental disomy (UPD) was found in 4 (8%) cases (Gr2). Aberrant methylation was found in 6 (12%) patients (Gr3).

Results: Median age at established genetic diagnosis was 3.0 [0.5; 6.0] years, varied from 5 days to 16 years and had no differences among the groups (H=4.26, p=0.119). During the study period, the age of PWS genetic typing decreased; during the first year of life, the diagnosis was confirmed in 4 (17.4%) patients in 2012-2017 versus 14 (56.0%) in 2018-2023 (p<0.01). For boys the median age at diagnosis was 2.0 [0.5; 4.0], for girls – 4.0 [1.0; 9.0] years, U=185.5, p=0.034. The rate of preterm birth (25.0%) was higher than the national rate of 4.5%. Small for gestational age - 16.7%. 85.4% of newborns had hypotonia. In every second child a feeding tube was used in the early neonatal period. 22 (95.7%) boys had signs of hypogonadism (22 cryptorchidism, 6 scrotal hypoplasia). The mothers age of Gr1 children was 25 [21; 31], Gr2 – 38 [32; 42] and Gr3 – 36 [32; 39] years (H=13.4, p=0.001). Gestational age and BW did not differ between groups (p=0.381 and p=0.251). BW percentiles were significantly higher in Gr1 patients (35.8 [17.0; 53.2] versus 15.9 [11.3; 21.4] and 10.3 [2.8; 21.9], p=0.021). Boys’ BW percentiles were 18.2 [7.9; 23.9], girls 41.8 [18.3; 52.4], p=0.031; SDS – -0.91 [-1.41; -0.71] and -0.21 [-0.90; 0.06], p=0.030.

Conclusion: Examined children with PWS characterized by anamnestic data, low BW percentiles and SDS at birth, hypophagia, hypotonia, hypogonadism in boys in the neonatal period. In the dynamics of the analyzed time interval, a decrease in the disease diagnosis time was established.

GH and IGFs

P1-95

Clinical and laboratory characteristics in children with growth hormone deficiency (GHD) and short stature unresponsive to stimulation tests (SUS)

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Background: It has been previously proposed that not all children with short stature displaying an inadequate response to tests for growth hormone (GH) secretion truly suffer from GH deficiency (GHD). Instead, amongst these, solely children with an identifiable monogenic cause of GHD or an identifiable functional or anatomical anomaly in the hypothalamic-pituitary axis should be considered GHD. The remaining patients should be defined as affected by “short stature unresponsive to stimulation tests” (SUS).

Methods: Retrospective analysis on 187 consecutive patients with short stature and pathological response to two stimulation tests for GH secretion, who underwent recombinant human GH (rhGH) therapy in a single Italian centre. Patients were divided into GHD (n=41, 22%; F=32%) and SUS (n=146, 78%; F=29%) groups, with a median follow-up (FU) time of 4.2 years (IQR 3.4-5.1). GH peaks at stimulation tests, height, bone age and serum levels of IGF-1 were compared at diagnosis, at 1 year of treatment and last available FU.

Results: At diagnosis, GHD and SUS populations did not differ significantly in age (11.8 vs 11.9, p=0.68), sex (F 32% vs 29%, p=0.78) and prevalence of short stature (height <-2 SDS) (100% vs 99%, p=0.45). IGF-1 SDS were significantly lower in GHD (-2.41 vs -1.99, p=0.02). The GH peak in the GHD group was lower when the stimulus was arginine (3.8 vs 5.0 ng/mL, p<0.01), but higher with insulin (3.5 vs 2.2 ng/mL, p=0.04). After 1 year of treatment, the prevalence of short stature was equally reduced in both groups (27% vs 25%, p=0.82), while the increase in IGF-1 SDS was greater in the GHD category (2.05 vs 1.52, p=0.01). At the last available FU, solely a minority of patients (52 of 187; 22% vs 29%, p 0.77) had reached the definitive height, none of which <-2 SDS. All 52 patients underwent retesting for GHD, which was positive in a significantly greater portion of GHD patients (33% vs 4%, p<0.01).

Conclusions: The GHD and SUS populations cannot be distinguished by GH stimulation tests alone. Both populations equally benefit from GH therapy in terms of stature. However, the stronger benefit of IGF-1 secretion in the GHD group suggests that deficient GH secretion may not be the sole cause of short stature in the SUS population. This is further corroborated by the finding that a vast majority of SUS patients do not have pathological retesting upon reaching definitive height.

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P1-96

Modified Insulin Stress Test for Assessment of Growth Hormone Secretion – Experience from a University Teaching Hospital

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Introduction: Insulin stress test (IST) to diagnose growth hormone (GH) deficiency is rarely used by paediatric endocrine teams in the United Kingdom, due to concerns over safety. We share our experience of undertaking modified IST in children, with regards to safety and outcomes.

Methods: We adapted the protocol for insulin stress test, proposed by Galloway et al to undertake pituitary stimulation test for our cohort of patients with suspected growth hormone deficiency. The exclusion criteria were were strictly adhered to and comprised the following: children less than 5 years of age, history of seizures, suspected or established adrenal insufficiency and suspected pan-hypopituitarism. An informed consent was taken from the parent(s) prior to undertaking the test and sex-steroid priming was done as per British Society for Paediatric Endocrinology and Diabetes (BSPED) guidance. Each test was supervised by specialist endocrine nurse and consultant. We evaluated the number of modified ISTs undertaken between February 2020 and June 2022. Data was gathered relating to any adverse events, degree of hypoglycaemia achieved, timing of peak responses for GH and cortisol.

Results: 22 ISTs were performed during the study period. The age range of patients was 5.6-16.2 years (15 males and 7 females). 11 patients (50%) had suboptimal GH response based on BSPED cut-off of 6.7 mcg/l. 1 patient (5%) had suboptimal GH and cortisol response and 10 patients (45%) had appropriate GH and cortisol response. Majority of patients (27%) achieved peak GH response at 45 minutes (range 30-150 minutes), post insulin administration. The peak cortisol response was observed at 60 minutes post insulin administration in 50% of patients (range 0-120 minutes). BG dropped to below 3 mmol/l in 19 patients (range 0.7-2.9 mmol/l). The two patients who did not achieve the desired drop in blood glucose (4.2 and 3.4 mmol/l) showed appropriate responses to GH (11.5 and 9.2 mcg/l respectively) and cortisol (849 and 543 nmol/l respectively). Apart from hunger and tiredness, no adverse effect was observed in any of the patient.

Conclusion: Modified IST can be undertaken relatively safely in children over 5 years of age with strict adherence to exclusion criteria and appropriate supervision. Adequate hypoglycaemia was achieved in 86% of cases. Modified IST can eliminate the need for a second stimulation test saving time and cost.

P1-97

Efficacy of long-acting growth hormone preparation in children with growth hormone deficiency

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Objectives: Convenience of growth hormone (GH) use can lead to good adherence and result in satisfactory treatment outcomes. The aim of this study is to compare the long-term efficacy of weekly GH with daily GH in children with GH deficiency (GHD).

Methods: Clinical data of 966 GHD children (773 treated with daily GH and 193 treated with weekly GH) were obtained from the "LG Growth Study", which is an observational Korean multicenter registry for GH treatment. Anthropometric data at baseline and every 12 months follow-up were collected; gender, chronologic age, height, weight, body mass index, bone age, serum IGF-I and IGFBP3. Data are expressed as mean ± standard deviation. The t-test was used to compere the difference of between two groups at each time point and p-value under 0.05 were considered statistically significant.

Results: At baseline, chronological age, mid-parental height SDS, and frequency of pubertal boys in weekly GH group were older, shorter, and higher compared to those of daily GH group (7.46 ± 2.89 vs 8.46 ± 3.44, $p < 0.001$; -0.88 ± 0.73 vs -1.02 ± 0.84, $p = 0.044$; 16.9% vs 34.0%, $p = 0.006$, respectively). However, baseline height SDS, BMI SDS, bone age delay, and IGF-I SDS were similar between the two groups. Height velocity during the first 12 months and changes in height SDS at 12 months were higher in daily GH group (9.06±1.72 vs 8.67±1.98, $p = 0.028$ and 0.78±0.39 vs 0.61±0.41, $p < 0.001$, respectively). Height SDS at 24 months and 48 months were similar between two groups (-1.60 ± 0.79 vs -1.75 ± 0.82, $p = 0.088$ and -1.27 ± 0.93 vs -1.50 ± 1.28, $p = 0.194$, respectively). In LMM analysis, the overall height SDS and height velocity for 48 months follow-up were similar. The percentage of maintaining GH at 48 months was higher in weekly GH group (22.7% vs 36.3%).

Conclusion: This study showed better adherence and comparable long-term efficacy of weekly GH in Korean GHD children.

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P1-98

Evaluation of patients with growth hormone deficiency during the transition period

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Introduction: The transition period between childhood and adulthood in patients with growth hormone deficiency is a vulnerable period during the follow-up. Different consensuses have established follow-up and reassessment protocols for this period in order to clarify whether GHD persists. The benefits of maintaining treatment during this period are widely documented on the metabolic, vascular, bone and in terms of quality of life and well-being.

Aims of the Study: To evaluate the clinical and biological status of patients with growth hormone deficiency followed since childhood during the transition period (14-16 years).

Patients and Method: Out of 255 patients followed in pediatric endocrinology from September 2007 to March 2023, 51 patients reached age of transition (14-15 years). Clinical data were collected. In patients GHD with normal MRI, treatment was interrupted for one month .Iinsulin or glucagon test was performed to reassess growth hormone function. The GH threshold defining GHD is 3µg/L for the insulin test. For glucagon test, the cut off is 3µg/L for patients with BMI <30Kg/m^2 and 1µg/L for patients whose BMI is > 30Kg/m^2. IGF1 values after discontinuation of treatment are interpreted according to age and sex.

Results: The average age of 51 adolescents reaching transition period is 15.83 years with male predominance. 80.3% of patients had an isolated deficiency and 19.6% had other anterior pituitary deficiencies. Hypothalamic-pituitary MRI found pituitary abnormalities in 39%of patients. MRI was normal in the other cases. The average stature gain in terms of standard deviation is 1.88 SD, it is greater in the GHD group with MRI abnormalities ($p<0.05$). The final height after average treatment of 8 years increased from -2.9 SD before treatment to -1.02 SD at the end of treatment. The average bone age in the transition period is 14.89 years. Biological reassessment in 38 patients confirmed the persistence of GHD in 12.7% of patients with normal MIR, leading to the renewal of treatment and the transfer of follow-up by the adult pituitary unit. 13.6% of patients presented with other anterior pituitary deficits during follow-up.

Conclusion: Evaluation in transition phase revealed a satisfactory stature gain. Reassessment of somatotropic function in patients with normal MRI demonstrated persistence of GH deficiency in less than a quarter of the patients which led to the renewal of treatment. Patients aged over 18 still treated were transferred to the adult pituitary unit.

P1-99

Clinicians' perceptions on ease of use and usefulness of Aluetta® Smartdot™ and comprehensive digital health ecosystem in Italy to support patients receiving r-hGH treatment

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Background: Aluetta® Smartdot™ (Merck Healthcare KGaA, Darmstadt, Germany) is first of its kind digitally connected smart injection pen device for recombinant-human growth hormone (r-hGH) administration. Aluetta® pen with Smartdot™ knob attachment integrated with Growzen™ digital ecosystem enables healthcare professionals (HCPs) to remotely monitor adherence and achieve optimal clinical outcomes for patients.

Aim: To explore current landscape of growth hormone deficiency care in Italy, to analyse HCPs' perception on the potential acceptance of health devices and technological evolution, and to identify factors impacting their intent-to-use and recommend digital solutions supporting r-hGH therapy.

Method: A 4-hour participatory workshop was conducted in Rome, Italy on 25th November 2022 with eight HCPs (regardless of previous digital device usage experience) including three adult endocrinologists. They were divided into two teams (each moderated by facilitator) based on professional expertise, age, and gender. HCPs discussed two contexts of self-administration and caregiver-supported administration to identify factors and share opinions according to variety of predefined topics on technology acceptance. Workshop progressed in 5 phases with the introduction of project and participants, views on current context of digitalization, perceived usefulness and ease of use of Aluetta® Smartdot™ device (as example of digital solution), perception of health technology evolution, and combined team recommendation. Data collected via audio-recordings, completed predefined templates, and facilitators' notes were independently analysed by experts in participatory research using thematic analysis and relevant findings were shared and validated with participants.

Results: Four main themes were identified upon analysis: 1) understanding the context for digital transformation: currently, Italian National Health System lack resources to support the growth hormone device ecosystem; 2) relevant digital health design considerations: catering target audience's specific needs, preferences; 3) perceived benefits and risks of using digital solutions for adherence monitoring: can result in reduced costs for healthcare system and patients, may strengthen HCP-patient relationship, digital solution accuracy can impact data driven decisions; and 4) perceived usefulness and ease-of-use: Aluetta® Smartdot™ and Growzen™ ecosystem was perceived simple to use/teach/learn with a potential to improve injection data download and adherence monitoring.

Conclusion: Participants perceived Aluetta® Smartdot™ to be highly useful and easy-to-use. Aluetta® with Smartdot™ enables automatic and real-time injection data transmission to support adherence monitoring and data-driven treatment decisions. The availability of unbiased, accurate data transmitted by device would be of benefit and helps generate new evidence-based knowledge to support clinical decision making and strengthen patient-HCP relationships, empower patients throughout the treatment process.

P1-100

Exploring healthcare professionals' attitudes towards digitalization and the perceived usefulness and ease of use of digital solutions in patients receiving growth hormone therapy: Results of a Korean participatory study

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Background: Aluetta® Smartdot™ (Merck Healthcare KGaA, Darmstadt, Germany) is a novel injection device for administering recombinant-human growth hormone (r-hGH), integrated with a smart knob attachment for data transmission that combines ease of use with advanced capabilities. Integration with Growzen™ digital ecosystem empowers healthcare professionals (HCPs) with remote monitoring of patient adherence, thereby promoting optimal clinical outcomes.

Aim: To explore current landscape of growth hormone (GH) deficiency care in Korea, analyse HCPs' perception on the acceptance of health devices and technological evolution, identify factors impacting their intent-to-use and recommend digital solutions supporting r-hGH therapy.

Method: A 4-hour participatory workshop was conducted in Seoul, Korea on 2nd November 2022 with fourteen HCPs (regardless of previous digital device usage experience). They were divided into two teams (each moderated by facilitator) based on professional expertise, age, and gender. HCPs engaged in discussion on GH administration, identified specific issues and shared their opinions on various predefined topics in contexts of both self-administration and caregiver-supported administration. Workshop progressed in 5 phases with introduction of project, participants, views on current context of digitalization, perceived usefulness and ease of use of Aluetta® Smartdot™ device, perception of health technology evolution, and combined team recommendation. Experts analysed data collected via audio-recordings, completed predefined templates, and facilitators' notes independently using thematic analysis and shared relevant findings validated with participants.

Results: HCPs perceived Aluetta® Smartdot™ with Growzen™ ecosystem as easy to use/handle and adopt by users including children in Korea. HCPs highlighted functionality such as automatic, real-time data transmission, and sending notifications/reminders to patients were important factors; however, its usability can be improved with wireless charging, integrating alarms for missed injections, patient/caregiver training, and visual-case-presentation based feedback. Limited time for intensive consultation during practice with adherence data without proper reimbursement support and internet access restriction by parents could be potential barriers for use of technology. HCPs considered the use of this digital system could result in increased patient/caregiver satisfaction and medication self-management.

Conclusion: Participants considered Aluetta® Smartdot™ with Growzen™ app as user-friendly, intuitive, and easy-to-use digital solution. Aluetta® with Smartdot™ enables automatic real-time injection data transmission to support adherence monitoring and to understand the reasons of suboptimal response or adherence to GH therapy. Availability of unbiased, reliable, and accurate data transmitted by the device would be of benefit and helps generate new evidence-based knowledge to support GH treatment and strengthen patient-HCP relationships, empower patients throughout the treatment process.

P1-101

Withdrawing growth hormone treatment at mid-puberty in idiopathic isolated growth hormone deficiency: baseline characteristics in patient-preference design study

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Background: The majority of children diagnosed with idiopathic isolated growth hormone deficiency (IIGHD) show a normal growth hormone (GH) secretion (assessed by GH stimulation tests) when retested at near adult height (NAH). It appears plausible that if normal stimulated GH secretion is observed in mid-puberty, continuing recombinant human GH (rhGH) treatment may only have a minor effect on NAH. The effect on NAH has never been investigated in a prospective study.

Aim: To evaluate patient preference in the choice to (dis-)continue GH treatment from mid-puberty, and to study whether patients who discontinued treatment differed in baseline characteristics from those who continued treatment.

Methods: The study population consists of adolescents who were diagnosed in childhood with IIGHD (GH peak at diagnosis between 1.7 and 10 ug/L; <1.7 ug/L was excluded) and who had started rhGH therapy between 2005-2018. According to the national treatment protocol, GH secretion was retested in mid-puberty (males: Tanner stage G3/4, testicular volume >12 ml and bone age (BA) 13-16 years; females: Tanner stage B3/4 and BA 11-14 years). In this multicentre prospective patient-preference design study, adolescents who tested GH sufficient at mid-puberty (GH peak of >6.7 ug/L) had the choice to discontinue or continue rhGH treatment until NAH (height velocity <2cm/year).

Results: In total 126 patients (94 male, 75%) participated in this study. Forty-three patients (34%) chose to continue GH treatment until NAH (group 1), and 83 patients (66%) chose to discontinue GH treatment until NAH (group 2). Baseline data were available for all patients. Mean height at inclusion was significantly higher in group 2 (group 1: -0.78±0.68 SDS vs group 2: -0.48±0.85 SDS; P=0.042). Target height SDS (-0.73±0.53 SDS and -0.58±0.53 SDS, respectively (P=0.14)) and age at inclusion (14.0±1.2y and 13.8±1.1y, respectively (P=0.81)) did not differ between groups. Males and females did not differ in these characteristics. Currently, 72 patients (57%) have reached NAH.

Conclusions: The majority of patients (66%) preferred to discontinue GH treatment after sufficient GH retesting in mid-puberty. Adolescents who chose to discontinue treatment were taller at baseline. The between-group difference in height SDS at inclusion is too large to show statistically significant "non-inferiority" of discontinuing GH at mid-puberty. A statistical model of expected height gain during GH treatment from mid-puberty until NAH will be constructed from a historic control group with IIGHD who showed normal GH secretion upon retesting at NAH.

P1-102

Assessment of clinical pediatric perception of short stature in childhood and challenges to treat with Growth Hormone in Brazil: A exploratory evaluation of a developing country daily practice

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Background: Concerns about a child's growth are one of the most common topics parents express during pediatric visits and are a leading cause for referral to a pediatric endocrinologist. For the general pediatric, when short stature is diagnosed, its clinical management remains a challenge.

Objective: The aim of the study was to approach and understand the perception from the general pediatrician about short stature, when is the optimal time to refer to pediatric endocrinologist and what are the challenges of the GH therapy in a developing country.

Methods: The study was observational, cross-sectional, self-completed electronic survey, preceded by an exploratory stage. The questionnaire comprised 27 questions based on evaluation scales and was applied to active general pediatricians in private practice. Exclusion criteria were proportion of private appointments <20% and proportion of patients with low purchasing power (considering that in Brazil, the access to somatropin in not universal). A total of 120 pediatricians were included.

Results: Short stature represented 12% of all appointments in a 30-day period (203 patients). Among this, families were concerned about child growth in 85% of the cases. In 31% of patients, the concerns about height arose from comparing the child with peers. Finally, in 35% of patients, the child himself raised concerns about his height.

84% of pediatricians wait for about 6 months to one year to refer a child to a specialist if height and weight do not suggest severe GH deficiency. Changes in eating habits and physical activities prior referral are usually recommended. Pediatricians believe

that in 62% of cases, decreased adherence to somatropin therapy are related to cost and in 17% to fear of injections and adverse events.

Patient and primary care physicians lack awareness about GH deficiency and frequent changes in physicians reflect on delayed treatment. 83% of patients and 71% of physicians, respectively believe that awareness campaigns and access to guidelines and GH treatment are relevant. In addition, 53% did not see relevance of early treatment with somatropin. The most frequently reported challenges were access to specialists, cost of therapy, and family acceptance regarding GH treatment.

Conclusion: To our knowledge, this is the first observational qualitative survey performed in Brazil to gather perceptions about GH deficiency in primary care practice. From the pediatric point of view, referral to a specialist appears to be a challenge. The need of continued medical education regarding eligibility of GH therapy should be addressed promptly.

P1-103

Assessing the treatment burden and Quality of Life of children receiving daily recombinant Growth Hormone treatment in Greece

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Background: Pediatric growth hormone deficiency (pGHD) is associated with growth attenuation/deceleration, short stature, delayed bone maturation, and metabolic defects. Daily recombinant human growth hormone (rhGH) treatment promotes linear growth and increases growth rate; however, it may present a substantial burden for patients and caregivers. This may lead to low adherence, limiting the clinical effect of treatment. This study assesses the health-related quality of life (HRQoL) of children and adolescents with GHD, as well as rhGH treatment burden for patients and caregivers in Greece.

Methods: This ongoing cross-sectional study enrolls patients aged 3-17 years receiving daily rhGH for at least 12 months. The Quality of Life in Short Stature Youth (QoLISSY) questionnaire assessed patients' HRQoL (higher score denoting better HRQoL) from both patients' and caregivers' perspective, whereas the Life Interference Questionnaire for Growth Hormone Deficiency (LIQ-GHD) evaluated patients' and caregivers' treatment burden (higher score denoting greater life interference).

Results: Overall, 84 patients (77 aged >8 years) from 5 pediatric endocrinology outpatient clinics were included in this interim analysis (July 2022-January 2023). The mean QoLISSY scores reported from patients and caregivers were 81.18 and 74.92, respectively. Coping was the lowest scored domain in both groups, followed by Treatment and Beliefs domains (Table 1). The LIQ-GHD results were similar to literature reports, revealing a mean (SD) overall patient life interference score of 22.36 (±19.36) with no substantial differences among age groups. The mean (SD) caregiver life interference score was 15.86 (±18.48). In a four-week period, 46.43% of patients missed ≥1 injections. Adolescents (>12 years) demonstrated lower adherence than patients 8-12 and <8 years of age (47.62% vs. 60.00% vs. 57.14%, respectively).

Conclusion: This analysis showed an overall good HRQoL and a moderate treatment burden for patients receiving daily rhGH and their caregivers. However, sub-optimal adherence rates may affect clinical outcomes. New treatment options could further improve HRQoL and treatment experience, as well as increase adherence rates that may lead to better health outcomes.

Table 1. Mean overall QoLISSY scores for each domain

QoLISSY scores	Overall (patient report*) N = 77 Mean (SD)	Overall (caregiver report**) N = 84 Mean (SD)
Total	81.18 (±15.05)	74.92 (±18.63)
Physical domain	82.25 (±15.30)	78.37 (±19.28)
Social domain	80.64 (±18.56)	75.74 (±21.63)
Emotional domain	80.64 (±17.01)	70.65 (±20.13)
Coping domain	46.88 (±23.51)	50.54 (±20.39)
Beliefs domain	70.45 (±27.41)	66.67 (±27.43)
Treatment domain	56.19 (±21.36)	61.37 (±19.90)

SD: standard deviation; *patients aged >8 years; **patients aged 3-17 years

P1-104

Healthcare professionals' perceptions on the quality and evolution of digital health devices to support paediatric growth hormone therapy: Results of a French participatory study

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Background: Treatment of growth hormone deficiency (GHD) requires daily injections over many years. Connected digital health devices can facilitate GH treatment by automating the injection process, which reduces anxiety, and collecting injection data in real-time so that accurate adherence information is available to healthcare professionals (HCPs). In developing new digital health solutions, HCP perspectives should be considered.

Aim: To evaluate the next generation easypod® (EP) device (EP3) for the delivery of recombinant human GH (r-hGH) treatment from the HCP perspective, with a focus on usability, data-enabled insights, and usefulness compared with EP2.

Methods: We conducted a mixed-methods participatory workshop (comprising five phases) in Paris, France, to assess the EP3 device, which is currently in development. Participants included HCPs experienced in the management of GH treatment in paediatric patients, regardless of their previous EP experience. Predefined questions and specific case studies were discussed as part of group activities. In addition, participants individually completed a 25-item, 5-scale Likert questionnaire to assess the impact EP3 may have on usability and usefulness for HCPs, caregivers and patients.

Results: Ten HCPs (six paediatric endocrinologists and four nurses) participated in the workshop. Participants perceived the automatic transmission of data as the most significant improvement of EP3, as real-time adherence data could improve treatment monitoring to allow for telemedicine appointments between clinic visits, enabling more personalised care for patients. As data privacy is paramount, participants valued the ability to deactivate the automatic data transmission functionality. The larger and touchscreen interface on the EP3 device was considered a substantial improvement by participants, stating that it is intuitive, very responsive and enables improved visualisation and the use of pictograms, which facilitate the training and usability of the device. The ability to personalise some visual elements was perceived positively by participants but including more personalised features could lead to further patient engagement and, subsequently, improved adherence.

Conclusion: HCPs rated the new capabilities of the EP3 device, such as usability and data transmission, highly, concurring that it was easier to use, easier to learn and easier to teach compared with EP2. EP3 will enhance clinical decision making and will allow for a more individualised approach in paediatric patients receiving r-hGH for growth disorders.

P1-105

Effects of Growth Hormone Therapy on Glucose Metabolism in Children and Adolescents: 1-year follow-up results

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Introduction: It is thought that long-term growth hormone (GH) treatment may impair hepatic glucose production and insulin-dependent glucose utilization, and therefore it is attributed that GH may adversely affect glucose metabolism.

Objective: In our study, we aimed to examine the effects of GH treatment on insulin sensitivity and glucose metabolism in patients with GH deficiency after 1-year of treatment.

Methods: 59 patients (22 female) who were diagnosed with GH deficiency with two stimulation tests and received GH treatment were included in the study. Patients who were born small for gestational age, had chronic diseases and were using drugs other than GH were excluded from the study. Anthropometric measurements and pubertal examinations of the patients were done. Baseline and first year fasting plasma glucose (FPG), insulin, HbA1c levels were checked and oral glucose tolerance test (OGTT) (1.75 g/kg, max. 75 g) was performed. HOMA-IR and Matsuda indices were calculated.

Results: The mean age of the patients at the initiation of GH treatment was 11.6±2.6 years old. Height SDS of the patients was low, body mass index (BMI) SDS was normal. Before treatment, FPG, fasting insulin, HbA1c and c-peptide levels were normal. HOMA-IR was 2.7±1.6, Matsuda-ISI was 5.8±5.6. At the end of the first year, the mean age was 13.1±2.5 years. Height SDS improved, BMI SDS was similar compared to pretreatment. There was no significant difference between the pre-treatment and first year puberty stages of the patients. At the end of the first year, FPG and HbA1c levels were normal. HOMA-IR was 3.2±2.5, Matsuda-ISI was 5.6±8.2. When the values of the pre-treatment and the first year were compared; fasting insulin, peak insulin, total insulin were significantly higher after GH treatment ($p=0.037$; 0.05; 0.017); Matsuda-ISI was found to be significantly lower ($p=0.009$). Although the first year HOMA-IR levels were high, we did not detect any significance.

Conclusion: We observed that short-term GH treatment caused an increase in insulin resistance, but this increase did not reach disease-causing levels. It is important to monitor children receiving GH treatment for insulin resistance. OGTT is a reliable method in these patients; and we recommend to evaluate fasting, peak and total insulin levels and to calculate the HOMA-IR and Matsuda-ISI. We recommend to follow-up patients after treatment discontinuation, since insulin resistance can be reversible.

P1-106

Growth Hormone (GH) Therapy in Children with short stature: A cross-sectional study of indication and treatment outcomes- 12-year single center experience

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Background: GH deficiency remains the main indication for GH therapy in children. GH therapy has subsequently been approved in the USA and Europe for other conditions resulting in short stature, including Turner Syndrome, being born small for gestational age with failure to attain normal growth, Prader-Willi Syndrome, chronic renal insufficiency, short stature homeobox-containing gene deficiency, and in the USA exclusively Noonan Syndrome and idiopathic short stature.

Objectives: to describe the main indications and treatment outcomes of rGH therapy among a cohort of children with short stature followed at the endocrinology clinic at SKMC-Abu Dhabi over the past 12 years. Assessing treatment outcomes using a change in height SDS at 1 year and 3 years post rGH therapy for various indications, in addition to exploring potential predictors for good outcomes.

Methods: A cross-sectional retrospective review of children (age < 18 years) treated with GH and followed between Jan 2011 and Dec 2022.

Results: A total of 416 children received rGH therapy during the study period off of which 369 were rGH naïve at baseline and enrolled in subsequent analysis at 1-year and 3-year follow-ups. Clinical indications were GHD (n=83, 19.9%), ISS (n=142, 34.1%), SGA (n=116, 27.9%), CKD (n=20, 4.8%), TS (n=16, 3.8%). Mean age at GH initiation based on indications were 9.8 years (±3.6) for GHD, 10.9 years (±2.9) for ISS, 6.9 years (±0.87) for SGA, 6.5 years for CKD (±3.5) and 9.2 years (±2.2) for TS. Mean height SDS at baseline was -2.89 ± 0.72, comparable among all groups but worse for TS (-3.38±0.75). Mean height SDS gain at 1year was excellent for all indications mean 0.69±0.45, more significant in SGA (=0.82 SD) but lower than the mean for TS (0.54 SD). The responses at 3 years persisted (Mean height SD gain=1.2±0.7) with an overall 83.3% gain in height. Multivariate analysis revealed that both age and puberty status at GH therapy initiation were inversely correlated with responses at 1 year and 3 years, with P=0.04 and 0.01 respectively however gender had no effect on the outcome.

Conclusion: established our clinic's rGH therapy registry. GHD is the most common indication in our cohort. Results were consistent with those from international surveillance databases. Age and pre-pubertal status at GH initiation were independently associated with a significant response to therapy supporting the importance of early identification and prompt initiation of GH therapy.

P1-107

The Growth Predictive Value of (IGF1/Growth Hormone Peak) Ratio in Children with Idiopathic Short Stature (ISS)

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Introduction: Stimulated GH peak values have been shown to correlate well with nocturnal GH peak values and with nocturnal mean GH values. In addition, the expression level of serum IGF-1 in ISS has been shown to be significantly lower than that in normal children despite their normal GH peak response to provocation. GH stimulates the production of IGF1; however, their metabolic effects are different. GH has lipolytic and anti-insulin actions while IGF1 has insulin-like actions.

Objectives: To investigate the value of using the IGF1/GH peak ratio in the anthropometric assessment of children with idiopathic short stature (ISS).

Patients and Methods: 20 short children with ISS (HtSDS < -2, with normal GH response to provocation) were randomly selected. Their IGF1 level and their peak GH response to provocation were analyzed in relation to their growth data for 1 year of follow-up. followed for 1 year.

Results: Are presented in 3 tables:

IGF1/GHP ratio highly correlated with the growth parameters (HtSDS, BMI, BMISD) before and after a year of follow-up. In addition, IGF1/GHP ratio correlated significantly with weight gain/day and with delta- BMI at 1 year of follow-up.

Conclusion: The IGF1/GHP ratio has significant growth predictive value in children with ISS.

Table 1. Growth and hormonal data of children with ISS are presented in table 1

	Age 1	**Wt 1**	**Ht 1**	**HtSDS1**	**BMI1**	**BMI SDS1**	**IGF-I1**	**GH-P**	**IGF1/GHP**
Mean	9.6	23.6	122.9	-2.1	15.2	-1.1	192.7	18.1	10.4
SD	2.8	7.2	15.6	0.5	1.5	0.8	126.5	5.8	9.0
	Age2	Wt 2	Ht 2	HtSDS2	BMI2	BMI SD2	wt gain g/day		
Mean	10.7	28.5	130.5	-1.8	16.3	-0.7	12.6		
SD	2.6	8.2	14.2	0.4	1.8	0.7	7.9		

Table 2. Correlation of GHP, IGF1 and IGF1/GHP ratio on growth parameters at diagnosis

	Age 1	weight1	Ht1	HtSDS1	BMI1	BMI1 SD	IGF-I 1	GH-P
IGF-I 1	0.54	0.63	0.61	0.46	0.47	0.27	1.00	
GH-P	-0.03	-0.21	-0.02	-0.04	-0.35	-0.36	0.03	1.00
IGF1/GP Ratio	0.37	0.66	0.43	0.39	0.68	0.48	0.51	-0.49

Table 3. Correlation of GHP, IGF1, and IGF1/GHP ratio on growth parameters after 1 year.

	GH-P	IGF-I 1	IGF1/GP Ratio
IGF1/GP Ratio	-0.49	0.51	1.00
Age2	-0.05	0.51	0.35
weight2	-0.24	0.60	0.59
IGF-1 2	-0.16	0.78	0.61
IGF1 incre	-0.21	0.14	0.36
wt gain2	-0.02	0.20	0.27
Height2	0.07	0.58	0.40
HtSDS 2	-0.08	0.55	0.53
BMI2	-0.28	0.43	0.60
BMI SDS2	-0.32	0.25	0.41
Delta BMI	-0.5	0.04	0.36

P1-108

A challenging case of Pituitary Gigantism

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A 4.9-year-old girl presented with a 6-month history of excessive body odour and suspected breast development. Family history was significant for presence of Lynch syndrome in both her father and paternal grandmother.

At presentation, she was pre-pubertal but tall for her age. Her height was 124 cm (SDS 3.5), and weight was 27.1 kg (SDS 2.69). Her height velocity was accelerated at 15 cm/year and bone age was advanced at 7 years. Investigations revealed an elevated IGF-1 (500 ug/L NR 35 – 232), IGFBP3 (7.1 mg/dl NR 1.9 – 5.2) and GH secretion failed to suppress on oral glucose tolerance test (OGTT). LHRH test revealed a prepubertal response. Prolactin, thyroid and cortisol levels were within normal limits. Contrast MRI revealed a pituitary micro-adenoma measuring approximately 3*7*8 cm confirming the diagnosis of Pituitary gigantism.

At 5.66 years of age, she underwent an intra -operative MRI-guided trans-sphenoidal excision of her microadenoma. Histology confirmed a neuroendocrine tumour with widespread expression of growth hormone and little expression of prolactin.

Two months post-surgery, her height velocity and IGF-1 level declined to 9 cm/year and 390 ng/L respectively. She did not develop any other pituitary hormone deficiencies. However, five months post-surgery, IGF-1 started to increase again, suggesting incomplete resection/recurrence. Growth hormone secretion failed to suppress on a repeat OGTT. Contrast MRI scan revealed a 4 mm area of hypo-enhancement in the anterior pituitary gland. A 11C-Methionine PET scan co-registered with volumetric MRI brain scan confirmed presence of a small residual adenoma in the pituitary gland.

She has been started on Pegvisomant and her IGF-1 is showing a downward trend. She is planned to have a repeat MRI scan at 6 months after starting Pegvisomant to re-assess tumour growth and need for repeat surgery.

Her R217 gene panel has been reported to be normal. The results of X-linked acro-gigantism genetic test are awaited. At present, her parents are reluctant for her to undergo genetic testing for Lynch syndrome. Corticotroph and prolactin secreting adenomas have been reported in adults with Lynch syndrome, hence the discussions regarding the importance of having this genetic test are ongoing with the family.

The family have to choose between long-term Pegvisomant therapy (provided her tumour remains under control) or have a repeat surgery with a high-risk of developing pituitary hormone deficiencies subsequently.

This case highlights challenges as well as recent developments in management of paediatric Somatotropinomas.

P1-288

The Growzen™ buddy smartphone application shows positive findings on adherence in Argentinian patients receiving growth hormone therapy for growth disorders

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Background: Digital health solutions, such as the Growzen™ buddy smartphone application (app), can facilitate adherence to recombinant human growth hormone (r-hGH) treatment for patients with growth disorders. The app alerts patients when it's time for an injection and allows patients and their caregivers to self-monitor growth, to build a routine and improve adherence. The app also contains educational resources to empower patients to be active in their treatment.

Aim: To study the impact of the Growzen™ app on adherence to r-hGH treatment in patients with growth disorders.

Methods: Adherence data, invitation dates to the app, activation dates of the app, and height measurements entered in the app were extracted from the easypod™ connect ecosystem. Patients from Argentina who had 12 months of adherence data and were <19 and ≥2 years of age at treatment start were selected both before (Jan 2018-Sept 2020) and after (Oct 2020-May 2022) implementation of the app. Mean adherence in the first year was classified as optimal (≥85%) versus suboptimal (<85%). Logistic and mixed effects logistic regression analyses were performed to test the difference between adherence before and after implementation and the pre-post app effect on adherence, respectively.

Results: Data for 693 patients (GHD, n=415; SGA, n=207; TS, n=46; other/unknown, n=8) were available. Prior to implementation of the app, the proportion of patients with optimal adherence remained stable (179/261 [69%] and 169/254 [67%] patients initiating treatment in 2018 and 2019, respectively). Following implementation of the app, out of 178 patients, 174 (98%) received an invitation with a link to the app, 134 (75%) activated the account, and 75 (42%) entered height data in the app in the first year of treatment. There was a significant increase, already visible early in treatment, in the proportion of patients with optimal adherence following implementation of the app: 83% (148/178), p<0.001. After implementation, the proportion of patients with optimal adherence included 84% (113/134) of those with an active account and 89% (67/75) of those who entered height measurements in the app. Within the group with an active account in the first year, there was a significant and positive pre-post app effect on adherence (p<0.05).

Conclusion: Our results show that using the Growzen™ buddy app has a timely fast positive impact on adherence to r-hGH treatment in patients with growth disorders receiving GH therapy. In particular, patients who were more engaged with the app showed better adherence.

P1-289

Long-term effectiveness and safety of growth hormone therapy in Japanese children with short stature due to Noonan syndrome (NS): real-world data

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Norditropin® was approved for children with short stature due to NS in Japan in 2017. The aim of this post-marketing surveillance study was to evaluate long-term safety and effectiveness of Norditropin® for the approved indication.

This real-world non-interventional study (NCT03435627) was conducted February 2018–January 2022. Seventy patients enrolled: 35 received Norditropin® after study initiation (new patients); 35 were previously randomised to 0.033 or 0.066 mg/kg/day (0.23 or 0.47 mg/kg/week, respectively) during a 4-year clinical trial of Norditropin® for NS (NCT01927861) and continued treatment in this study (existing patients, for whom baseline was start of the prior trial). Treatment duration was up to 4 and 8.5 years for new and existing patients, respectively. All patients who received Norditropin® at least once during the study comprised the full analysis set (FAS). All FAS patients with a height value at baseline and ≥1 follow-up visit comprised the effectiveness analysis set (EAS).

Males comprised 60.0% and 65.7% of new and existing FAS patients, respectively. At study start, most patients in both groups received an average dose range of 0.03–<0.04 mg/kg/day (0.2–<0.3 mg/kg/week). Mean (SD) IGF-I SDS was –0.47 (1.66) for new patients after 3.5 years' treatment. For existing patients, mean (SD) IGF-I SDS was 0.04 (1.45) at start of this study and –0.46 (1.03) after 8 years' treatment. In the EAS, mean (SD) change from baseline in height SDS was 1.01(0.52)/0.92(0.31) for new patients after 3.5 years, and 1.10(0.99)/1.31(0.80) for existing patients after 8 years, according to Japanese/NS standards, respectively. Adult height was reached by 16 and 28 for new and existing patients, respectively.

In the FAS, four new patients experienced five adverse drug reactions (ADR) and one new patient experienced one serious adverse event (SAE). Five existing patients experienced one ADR each and three existing patients experienced one SAE each. One existing patient with cardiomyopathy who experienced an SAE (arrhythmia) died during the study; Norditropin® causality was judged as 'unlikely' by the physician and 'impossible to assess' by the sponsor.

In this real-world study, Norditropin® effectively improved height outcomes and was well tolerated in Japanese children with NS. Dose optimisation is important to maintain improvements in height outcomes. For patients with NS and cardiomyopathy receiving Norditropin®, careful monitoring is advised. No new safety issues were identified.

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P1-290

Optimal injection device settings to achieve high adherence to growth hormone treatment in patients with growth disorders

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Background: Treatment for growth disorders requires daily injections of recombinant human growth hormone (r-hGH) over multiple years, and automated devices may help in this regard. The ability to adjust injection device settings, which are pre-set as default unless changed by healthcare professionals, may improve patient comfort and needle anxiety and thereby improve adherence.

Aim: To study the association between injection device settings and adherence in patients with growth disorders.

Methods: Adherence and device settings were extracted from the easypod™ connect ecosystem. Patients aged ≥2y and <19y with at least 6 months of adherence data were selected. Mean adherence was stratified by high (≥85%) versus intermediate/low (<85%) between 0-6 months of treatment. The factors for device settings were injection depth (4mm, 6mm [default], 8mm); injection speed (slow, medium [default], fast; selection of European data due to sample size); injection time (3-5 sec [5 sec, default], 6-15 sec); needle speed (slow, medium [default], fast; selection of European data due to sample size) and needle type (29G [default], 30G, 31G; selection of European and Asia Pacific data due to sample size). For each patient, most frequently used device settings were calculated between 0-6 months of treatment. Logistic regression analysis was applied with adherence as the dependent variable and device setting factor and age at treatment start (<13y, ≥13y) as independent factors. In addition, geographical region was added to the model to adjust for differences in clinical practice.

Results: Data were available for 9121 patients (<13y, n=7865; ≥13y, n=1256). Mean age (SD) at treatment start was 9.2y (3.3). Overall, the proportion of patients with high adherence was 89.5%. For patients aged <13y at treatment start, adherence was highest when the injection depth was 4mm, injection time was 6-15 sec, needle speed was slow, and needle type was 30G. For patients aged ≥13y at treatment start, adherence was highest when the injection depth was 6mm, injection time was 6-15 sec, needle speed was fast, and needle type was 31G. We found no association between injection speed settings and adherence.

Conclusion: In this observational study, we found that adherence to r-hGH therapy via an automated device was associated with age-specific device settings, with younger patients preferring shorter injection depth, slower injection speed, and smaller gauge needles. This is the first attempt to evaluate preferred injection settings associated with better adherence to daily r-hGH injections by an automated device using a large sample size.

P1-291

Adult heights of the cases whose GH treatment was discontinued at early retesting reached their target heights

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Background: It has been reported that 25–75% of patients with diagnosis of growth hormone deficiency (GHD) may show normal growth hormone (GH) responses in repeated stimulation tests after completion of treatment. Retests are typically conducted following completion of growth phase. In a small number of studies retests are conducted during early stages of GH therapy. Accuracy of early retesting to exclude GHD can be evaluated by adult heights of those whose GH treatment were ceased after a normal GH response at retest. This study's objective is to evaluate how accurately early retesting can exclude GHD.

Methods: 185 patients (77girls) who were treated with GH for a diagnosis of isolated GHD, and retested after first year of treatment were included in the study. Retesting of 75 patients (34girls) revealed a peak GH level ≥10ng/ml, and GH treatment was discontinued in these patients, it was continued in those with a peak response <10ng/ml. All patients were followed until final height. Chronological age, bone age, height-SDS, IGF1 and IGFBP3 levels, serum peak GH level and target height-SDS of all patients, both at beginning of GH treatment, and at retesting were acquired retrospectively from hospital records. Patients were divided into two groups according to peak GH response at retesting (GH<10ng/ml vs GH≥10ng/ml). Adult heights of all patients were recorded.

Results: At diagnosis, means of chronological and bone age, and height-SDS of patients with peak GH<10ng/ml at retesting were lower than those with peak GH≥10ng/ml; while means of IGF1 and IGFBP3-SDS were similar in these groups. GH response was normal (≥10ng/ml) at retesting in 18% of patients with peak GH<5ng/ml at diagnosis, and in 51.6% of patients with peak GH at 5-10ng/ml at diagnosis (p<0.001). Those with a peak GH<10ng/ml at retesting had an increased growth velocity during first year of GH treatment than those with a normal GH response at retesting. On the other hand, growth rates between those continuing and discontinuing GH after retest were not different. Adult height-SDS, height gains and target heights were all similar in both groups.

Conclusion: Patients with isolated GHD, whose GH treatment was discontinued after a normal GH response at early retesting (1st year of treatment), reached adult heights comparable to their target heights as well as to adult heights of those whose treatment was continued. Considering problems in diagnostic accuracy of GH stimulation tests, early retesting may prevent unnecessary treatment in some cases initially diagnosed as isolated GHD who proved to be normal during retesting.

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P1-292

Clinical predictors of good/poor response to growth hormone treatment (GHT) in children with idiopathic short stature (ISS)

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Children with ISS vary in their response to GHT. We conducted a post hoc analysis to identify clinical characteristics associated with very good or poor response during year 1 of GHT in a subset of 1550 GHnaïve children with ISS from NordiNet® IOS (NCT00960128) and the ANSWER Program (NCT01009905).

We included patients aged 3–11 years (males) or 3–10 years (females) at treatment start, prepubertal throughout year 1 of treatment, with height SDS (HSDS) ≤–2 measured <2 months prior to GHT start. Children with gestational age <32 weeks, receiving any investigational medicinal product or with concomitant illness that could influence response to GHT were excluded, except children with ADHD.

Response analysis set comprised 213 patients. Good/poor responders were defined as patients with a change in HSDS >1.0/<0.4, corresponding to >85th/<15th percentile, respectively, in the first year of GHT (n=31, for each group).

Bivariate logistic analyses (Table) suggested age at treatment start, target HSDS and baseline HSDS corrected for target HSDS were the strongest predictors between good and poor responders. In a separate backward stepwise multivariate logistic regression, sex, age at treatment start and target HSDS were shown to be independent predictors of response to GHT (data not shown).

By analysing clinical variables in prepubertal children with ISS who have had good/poor response during the first year of GHT, we identified predictors of response to GHT. Future studies of genetic variants associated with good/poor response to GHT could help identify genetic pathways involved in ISS and would assist in treatment individualisation.

Table. Individual variable comparison

Variable	Poor responders n=31	Good responders n=31	Odds ratio [95% confidence interval] p-value
Sex (female)	25.81%	16.13%	0.55 [0.16;1.93] p=0.35291
Age at treatment start (years)	7.7 (1.8)	6.3 (2.2)	0.70 [0.54;0.92] p=0.00964
Baseline dose (µg/kg/day)	46.2 (19.9)	47.0 (21.6)	1.00 [0.98;1.03] p=0.87056
Gestational age (weeks)	38.8 (2.1)	38.5 (2.2)	0.92 [0.72;1.17] p=0.48822
Target HSDS	−1.10 (0.7)	−0.56 (0.7)	2.94 [1.30;6.66] p=0.00972
Target HSDS – baseline HSDS	1.77 (1.1)	2.33 (0.9)	1.78 [1.01;3.12] p=0.04491
Birth weight SDS	−0.45 (1.0)	−0.48 (0.7)	0.95 [0.53;1.73] p=0.87617
Birth length SDS	−0.29 (1.3)	−0.17 (1.3)	1.08 [0.65;1.78] p=0.77387
Baseline weight SDS	−2.01 (1.4)	−2.25 (1.6)	0.89 [0.62;1.29] p=0.55228
Baseline body mass index SDS	−0.13 (1.2)	−0.14 (1.2)	0.99 [0.65;1.52] p=0.96486
Baseline HSDS	−2.87 (0.7)	−2.95 (0.6)	0.82 [0.37;1.83] p=0.62960

Mean (SD) except percentage. For some items, data were not available for all patients.

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P1-293

Healthcare professionals' perceptions on the quality and evolution of digital health devices to support paediatric growth hormone therapy: Results of a UK participatory study

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Background: Long-term treatment with recombinant human growth hormone (r-hGH) is often challenging for children and adolescents, their caregivers and healthcare professionals (HCPs), as treatment requires daily injections over several years. Connected digital health devices facilitate this by automating the injection process to improve comfort, reduce anxiety and collect GH treatment data so that accurate adherence information is available to HCPs in real-time. For successful adoption of such digital health devices, HCP perspectives should be considered.

Aim: To evaluate the next generation easypod® (EP) device (EP3) for the delivery of r-hGH treatment from the HCP perspective, with a focus on usability, data-enabled insights, usefulness and improvement over the previous EP2 device.

Methods: We performed a mixed-methods participatory study to assess the EP3 prototype. A participatory workshop (comprising five phases) was conducted in London, UK. Participants included HCPs experienced in the management of GH treatment in paediatric patients, either with or without prior experience of using EP. Participants discussed predefined questions and specific case studies as part of group activities. They also completed a 25-item, 5-scale Likert questionnaire to assess the impact EP3 may have on usability and usefulness for HCPs and patients.

Results: Nine HCPs (five paediatric endocrinologists and four nurses) participated in the workshop. The larger and touchscreen interface on the EP3 device was considered a substantial improvement by participants. They stated that the touchscreen aspect improves the usability of the device, with the larger screen enabling better visualisation and clearer instructions for easier and safer administration of r-hGH. Participants perceived that the automatic transmission of adherence data was the most significant improvement of the EP3 device; specifically, the availability of real-time adherence data enabled improved treatment monitoring and clinical decision making, with the potential to increase clinician engagement with the device. However, participants acknowledged that hospitals would require the necessary set up to receive the data. Participants likened EP3 to a smartphone, highlighting that its utility within a wider digital health ecosystem will enhance complementary approaches to r-hGH treatment. The personalisable visual elements on EP3 were commended, with participants advising that reminders and motivational features be integrated into the EP ecosystem to reinforce patient adherence.

Conclusion: HCPs perceived the EP3 device to be more intuitive, comfortable, user-friendly, simpler, and easier to use than EP2. Their feedback suggests that this next generation device will enhance clinical decision making and encourage greater personalised care for children and adolescents receiving r-hGH treatment.

P1-294

A novel variant of IGF1R in a Chinese family with short stature and efficacy of recombinant human growth hormone therapy

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Introduction: Insulin-like growth factor 1 receptor (IGF1R) mutations lead to systemic disturbances in growth due to widespread IGF1R expression throughout the body. IGF1R is expressed by innate and adaptive immune cells, facilitating their development and exerting immunomodulatory roles in the periphery.

Case Report: We detected a novel heterozygous variant c.664 C > T (NM_000875) of IGF1R in a Chinese family with short stature by targeted next-generation sequencing. Although the mutation is a variant of unknown significance, it is highly conserved and was predicted to be harmful by the SNAP and PolyPhen-2 software. The proband received recombinant human growth hormone treatment 0.12~0.15 IU/kg/day for 2 years. During the treatment period, there were no considerable adverse effects during rhGH treatment, his growth velocity was 8cm in the first year and 6.7cm in the second year, with a height gain of 0.93 SDS.

Conclusion: We identified a de novo mutation in human IGF1R related to short stature and expanded the mutation spectrum of IGF1R. In addition, we evaluated the efficacy of IGF1R mutation to recombinant human growth hormone treatment. However, long-term follow-up and more cases are needed to verify the effects of rhGH treatment.

P1-295

Sex steroid priming decreases the frequency of divergent results between spontaneous and stimulated GH tests

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Introduction: The diagnosis of growth hormone (GH) deficiency (GHD) is complicated by the low specificity of GH testing, especially in children before and during early pubertal stages. Sex steroid priming reduces false positive results in pre- and early pubertal children. However, only a small number of studies have assessed its efficacy in improving the diagnostic accuracy of GHD investigations.

Aim: To evaluate the effect of sex steroid priming in GH testing on the prevalence of divergent results of spontaneous nocturnal secretion and arginine-insulin-tolerance test (AITT).

Methods and Materials: This is a retrospective chart review of all 196 children investigated for GHD from January 1, 1993 until February 28, 2023 at the Department of Paediatrics, Örebro University Hospital, Örebro, Sweden. Of them 173 (89%) children had undergone both overnight GH sampling and AITT and 28 of 173 children (16%) had received estrogen priming prior to their tests. A GH peak concentration of ≥ 7.0 μg/L or more was considered normal for both tests.

Results: Children receiving priming (36% girls) had a median age of 12.1 years (6.2–15.0) vs. 8.4 years (1.5 – 15.9) in children not primed (43% girls). Of the 173 children that had undergone both tests, 31 (18%) tested positive (<7.0 μg/L) on both tests, 22 (13%) tested positive on overnight sampling only, and 13 (8%) tested positive on AITT only. Of the 28 children who had received priming, only one child had divergent results, with a positive result solely from AITT. Amongst non-primed children, 34 of 145 had divergent results with 21 (14.6%) testing positive on AITT, and 13 (9%) exhibiting a positive result on the spontaneous GH test. The frequency of divergent tests was significantly lower ($p = 0.016$) amongst primed children (3.6%) compared to non-primed children (23.6%).

Conclusion: Our results show that sex steroid priming prior to GHD testing with overnight sampling and AITT decreases the frequency of divergent results between the two tests and thus suggest that sex steroid priming decreases the risk of false positive results.

P1-296

The efficacy and safety of rhGH treatment combined with letrozole/GnRHa in adolescent boys

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Objective: In boys during puberty who were undergoing recombinant human growth hormone (rhGH) treatment, we compared the therapeutic efficacy and any adverse reactions, of co-therapy with letrozole/gonadotropin releasing hormone analog (GnRHa).

Methods: Fifty-six pubertal growth hormone deficiency (GHD) boys were studied, they were treated with the combination of letrozole and rhGH (letrozole group) or GnRHa and rhGH (GnRHa group) for at least one year. 35 patients attained adult height (AH).

Results: The increase in height of the letrozole group was significantly more than the GnRHa group, however, there was no significant group difference in the advancement of bone age (BA) ($p>0.05$). The mean AH in two groups were similar, but the treatment duration of the letrozole was significantly less than GnRHa ($p<0.05$). There was a significant body mass index (BMI) increase in the letrozle vs GnRHa groups. Of concern, bone mineral density (BMD) decreased in both groups after treatment, but more so in the letrozole cohort.

Conclusion: The combination of letrozole/rhGH in pubertal GHD boys was similar to GnRHa/rhGH in terms of the progression of BA and AH, but the former co-therapy required less treatment time. Disconcerningly, however, this combination may adversely affect BMI and BMD.

P1-297

Evening or morning growth hormone treatment?

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Context: Physiological growth hormone is secreted during the slow-wave sleep. Traditionally, growth hormone (GH) therapy is given in daily GH injections before sleep. This schedule better imitates the physiological diurnal variation of GH secretion and action. Late-night daily injections have been claimed to be associated with sleep disturbances and insomnia, yet there is no hard evidence supporting this contention. Morning and evening GH injections produce comparable effect on growth and IGF-1 levels.

Objective: Our objective was to evaluate evening vs. morning daily GH injections with respect to sleep quality, duration, and activity index in children treated with GH.

Design: An open-label, cross-over, randomized trial of 20 children (11 boys) 5-15 years of age with isolated growth hormone deficiency (n=11) and idiopathic short stature (n=9) treated with daily injections of GH (dose 33±6.9 mcg/kg/d) was performed. Each subject received 2 weeks of evening injections and 2 weeks of morning injections. Patients sleep quality, duration, and activity index were assessed by a 7-d actigraph on the second week of each treatment schedule.

Results: All subjects treated with morning or evening growth hormone injection slept well, within recommended ranges for sleep quality and duration. Total time in bed (min) (529.1±52 vs 519.5±57), total sleep period (min) (515.7±519 vs 507.9±58.4), sleep efficiency (%) (93.2±3.0 vs 94.0±2.4), sleep onset latency (min) (8.7±7.9 vs 7.3±6.6), number of arousals per night (14.0±5.75 vs 13.2 ±5.9), and activity index in 24 hours (67.2±4.0 vs 67.0±5.0) during evening and morning GH injection schedule correspondently were comparable. No difference was found between growth hormone deficient and idiopathic short stature group. No difference was found between boys and girls.

Conclusions: With respect to sleep quality, duration and activity index were not affected by treatment schedules. We recommend injecting growth hormone according to the family convenience morning or evening or otherwise.

P1-298

Quality of life at adult height in adolescents and young adults treated by GH

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Background: short stature can lead to emotional and social stress in children and adolescents. We previously demonstrated in a cohort of 74 children that a one-year growth hormone treatment (GHT) is associated with a significant improvement of quality of life (QoL) especially on emotional and social scales, both in general (PedsQL 4.0) and height-specific (QoLiSSY) questionnaires. Whether this improvement is sustained until adult height remains to be documented.

Objectives: to evaluate the long-term changes in general and height-specific QoL associated with GHT in short patients who have reached adult height.

Methods: monocentric, prospective, observational, non-interventional, clinical study including the patients from the original cohort who reached adult height (growth velocity <2 cm/year and/or bone age ≥15 years for girls or ≥17 years for boys). Patients and families were recontacted in order to perform the same QoL questionnaires. Change in QoL were evaluated by relative variation and tested by Wilcoxon rank test, each patient being his own control.

Results: Fifty-nine out of 74 children had reached adult height. Among them 10 were lost to follow-up and 19 did not return the questionnaires, leaving 20 patients with complete questionnaires (8 boys and 12 girls). Gain in height was in median +1.5 SD (-0.2 to +3.2). Three patients (too young at inclusion) did not have the initial child QoLISSY questionnaire. The initial parent questionnaire was missing in three other patients. Although PedsQL data were not statistically improved from childhood to adulthood, a significant improvement of the QoLiSSY emotional score was observed, of +0.5 SD (-1.6 to +2.4), p=0.031.

Similarly, no improvement was noted on the parental PedsQL data, whereas the parental QoLiSSY questionnaires revealed a significant improvement of children's social score of +0.9 SD (-0.7 to +1.7), p=0.003, emotional score of +1.5 SD (-0.2 to 2.3), p=0.007, and parental concern about their child's future, of +0.7 SD (-0.7 to +2.7), p=0.037.

Conclusion: even though the size of the study population does not allow robust conclusions, GHT seems to be associated with a sustained improvement of specific height-related QoL dimensions until adult height, such as the emotional score. Our results also confirm the relevance of using a specific QoL scale for a careful assessment of the potential benefits of GHT in such a population, instead of a more generic one.

P1-299

Real-world adherence to growth hormone treatment and catch-up growth in children with growth disorders in France: An interim analysis from the SCOPE study

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Background: The SCOPE French retrospective study follows children affected with growth hormone (GH) disorders treated with recombinant human GH (r-hGH) therapy via the easypod® connected injection device for up to 5 years.

Aim: To show the results from an interim analysis of the SCOPE study analysing adherence to r-hGH therapy in a real-world setting and its effect on catch-up growth.

Methods: Adherence data up to 36 months and height data up to 18 months of treatment were extracted from the easypod® connect ecosystem between July 2018 and December 2022. Adherence was classified as optimal ($\geq$85% of injections recorded) versus suboptimal (<85%). To study catch-up growth (Δ height standard deviation score [HSDS]), patients aged $\geq$2 years at treatment start, with a HSDS <-1 at treatment start and $\geq$1 HSDS measurement between 0-18 months of treatment were selected. A linear mixed-effect model was applied to calculate the predicted mean ΔHSDS at 6, 12 and 18 months.

Results: In total, 363 children with adherence data and 199 patients with HSDS data were available from 466 patients. At treatment start, mean age (SD) was 9.7 (3.1) years and mean HSDS (SD) was -2.5 (0.7). Among patients with adherence data available, the proportion of patients with optimal adherence was 94.8% in the first year (n=344/363), 91.1% in the second year (n=195/214) and 85.7% in the third year (n=90/105). Adherence was significantly lower during the summer holidays (July and August) (86.2%) compared with the academic year (September to June) (94.5%) ($p<0.001$, in patients with data available for both time periods; n=311). Predicted ΔHSDS was 0.31, 0.54 and 0.70, respectively, after 6, 12 and 18 months of treatment. ΔHSDS was higher when the patient started treatment at a younger age; e.g., when initiating treatment with r-hGH at age 6, predicted ΔHSDS was 0.38, 0.68 and 0.86, respectively, after 6, 12 and 18 months. Due to the high proportion of patients with optimal adherence, adherence did not have a significant effect on ΔHSDS.

Conclusion: Adherence rates to r-hGH delivered via easypod® are high and remain optimal over 36 months in France. Lower adherence during the summer holidays may reflect difficulties to remain adherent to treatment when not in school or may be due to treatment holidays during the summer. These initial results confirmed the growth response to r-hGH in children and showed that starting GH therapy at a younger age is associated with improved height outcomes.

P1-300

Assessment of the rhGH treatment compliance in children with growth hormone deficiency

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Aim: To identify factors affecting compliance to treatment with recombinant growth hormone (rhGH) in children with growth hormone deficiency (GHD).

Study Population and Methods: The following data were collected during standard visits in 8 endocrine clinics in Poland:

medical history, auxological measurements, laboratory tests and the numbers of empty and full rhGH ampoules dispensed and returned by the patients. The observation covered 6 months of treatment.

The study group consisted of 319 children aged (years) 1.4-17.7 (M=12.06; SD=3.27), including 109 girls.

To examine the impact of a child's personal and familial characteristics on compliance, two generalized linear mixed models were run using the mixed procedure in SPSS 28 (SPSS Inc., 2021) – the first with compliance treated as a linear variable (% of compliance), and the second with compliance treated as an ordinal variable. Both models included a random effect of the data collection site and a fixed effect of the child's age, sex, level of parental education, duration of treatment, mid parental height (MPH), pubertal stage, and rhGH self-administration. Compliance was categorised as: good - one dose per week missed (>86% of doses administered), moderate – one to two doses missed per week (57-86%) and poor – three and more doses per week missed (<57%).

Results: Good compliance was observed in 85,9% of patients (in 84,4% of girls and in 86,7% in boys), moderate in 13,2% and poor in 0,9%. The highest proportion of patients with good compliance was detected in children between 8 and 14 years (91,2%) and the lowest in those above 14 years (76,2%).) More than 80% of patients with normal serum concentration of insulin-like growth factor 1 (IGF-1) presented good compliance.

Mixed model analysis revealed the main effect of the pubertal stage - in the first model (F(2,261)=3.829, p=0.023), indicating that children with more advanced puberty complied with rhGH treatment worse than children with lower puberty stages (Beta= -6.6 (95%CI - 12.25; -0.95) p=0.022. In the second model, the main effect was paternal education (F(2,260)=2.964, p=0.05) indicating that children of fathers with low education had worse compliance (Beta= -1.07(95%CI -2.15, 0) p=0.05.

Conclusion: We found good compliance to rhGH routine treatment in children with GHD. Our results indicate that lower father education and patient's more advanced puberty stage adversely affect compliance.

P1-301

Outcome of growth hormone treatment in growth hormone deficient children over the course of 3 years in Notre Dames Des Secours-University Medical Center Byblos-Lebanon-single center experience

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Keywords: Descriptive study, short stature, Growth Hormone deficiency, Growth Hormone analogue, Lebanon, NDS-UMC, Byblos, single center experience.

Background: There is a lack of national data concerning growth hormone deficiency treatment in Lebanon. The aim of this study is to describe the height gained under growth hormone therapy of 39 patients diagnosed with growth hormone deficiency (GHD).

Methods: Data was collected by one investigator. The group formed of 39 GH deficient children was initially selected from 240 patients presenting to the Pediatric Endocrine Unit at Notre Dame Des Secours University Medical Center (NDS-UMC), Byblos, for short stature between January 1999 and December 2019.

Results: In this study, the height gained was satisfactory over the course of 3 years. The height gained during and after treatment was assessed with an overall gain of 29cm after 3 years for girls compared to 24.8cm for boys.

Conclusion: To be able to maintain an optimal treatment for GH deficient children, awareness concerning short stature, its potential causes and education about GH treatment initiation and adherence is a must. GH treatment should be prescribed to the right patient at the right moment and during an important period of life to prevent short stature during adulthood and its undesirable effects.

P1-302

Influencing Factors on Selection of Initial Treatment Dose in Children Diagnosed with Isolated Growth Hormone Deficiency

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Background: Although it has been recommended to start treatment in the range of 22-35 µg/kg/day in growth hormone (GH) deficiency, individualized dose selection is more preferred for those patients instead of a fixed dose. However, there is no consensus as to which dose should be started for which patient. In this study, we aimed to reveal the factors that affect the clinicians' preferences in the selection of the starting dose of GH treatment.

Methods: Patients aged <18 years, who applied to our department between 2013 and 2022 and were diagnosed with isolated GH deficiency and started treatment, were included in the study. Relevant data were collected retrospectively from the medical records of the patients. Results are presented as median (25-75p).

Results: Eighty-eight patients (56.8% male; 65.9% prepubertal) with a calendar age (CA) of 10.4 (7.4-12.8) years were included in the study. The median bone age (BA) of the cases was 8 (5-10) years and height standard deviation score was -2.7 [(-3.3) – (-2.3)]. Somatropin treatment was started at a median dose of 35 (30-35) µg/kg/day. Patients were divided into two groups according to the treatment dose as <35 µg/kg/day (n=36) and ≥35 µg/kg/day (n=52). The target height was shorter (p=0.033) and the annual height velocity was lower (p=0.008) in the group in which high-dose treatment was initiated. While the ratio of BA/CA was similar in both groups (p=0.730), the difference between BA - CA was significantly higher in the high-dose given group (p=0.018). Other anthropometric measurements, peak response in GH stimulation tests, serum IGF-1 and IGFBP-3 levels did not differ among the two groups (p>0.05). The initial dose of somatropin correlated negatively with annual growth rate (p=0.006), positively to the difference between BA - CA (p=0.009).

Conclusions: In this study, we found that target height, annual growth rate, and the difference of BA - CA were taken into account in the selection of the initial treatment dose in children diagnosed with isolated GH deficiency. We demonstrated that those who were started on high-dose treatment had lower growth rates and more retarded BA. Also, we found that the peak response in stimulation tests or baseline IGF-1 and IGFBP-3 levels were not effective in the initial treatment regimen choices. This result showed that clinical findings rather than laboratory parameters were taken into consideration by clinicians for somatropin treatment dose preferences in children.

P1-303

Further analyses on the role of IGF-I in the diagnosis of GH deficiency (GHD) in children

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Background: The diagnosis of GHD in children is based on auxological, biochemical, neuro-radiological, and genetic tests. Biochemical tests include evaluation of stimulated GH secretion and baseline IGF-1 determination. Although IGF-1 is the most reliable indicator of GH action, its value should always be interpreted in conjunction with other clinical and biochemical parameters. Since IGF-1 has good specificity (about 90%), but low sensitivity (about 70%), normal levels do not always rule out GHD. Our recent studies have shown that the best IGF-1 cut-off for discriminating patients with GHD from healthy subjects is −1.5 SDS.

The aim of our research was to evaluate GH secretion and clinical features in short stature patients subdivided in 4 groups according to their serum IGF-1 levels at diagnosis.

Patients and Method: 514 short patients (height-SDS (HT-SDS) -2,56 (-5,20; 0,42), age 10,20 (2,00; 17,70)y, 308 boys), were included in this analysis.

In all patients median IGF-1 SDS was - 1,13(-6,07; 3,50) and median GH peak (after two stimulation tests (arginine, clonidine, or insulin tolerance test)) was 11,80 µg/L (0,41; 53,00). 6,23% had a GH peak <5 µg/L, 14,79% between 5-8 µg/L, 13,81% between 8-10 µg/L and 65,18% >10 µg/L.

Patients were divided into four groups according to their IGF-1 values: group 1 IGF-1<-1,5 (n= 189), group 2 -1,5<IGF-1<1 (N= 83), group 3 -1<IGF-1<0 (N= 154), group 4 IGF-1> 0 (N= 86). Data are presented as median (range).

To remove confounding factors, such as BMI and pubertal status, and highlight the correlation between GH peak and IGF-1, we performed a multinomial logistic regression.

Results: BMI-SDS and HT-SDS were lower in patients with higher IGF-1 (p= 0,006) and (p=0,0036). The percentage of patients with GH peak below 5 decreases as the IGF-1 value increases: in group 1 12,70% of patients had a GH peak <5 µg/L, group 2 4,82%, group 3 1,95% and group 4 1,16% (p<0,0001). No differences were observed in patients with GH peak between 5-8 µg/L. Multinomial logistic regression showed that a low IGF-1 level increases the probability of a GH peak <5 µg/L, whereas higher IGF-1 concentrations decrease the likelihood of GHD.

Conclusions: Despite the reported low specificity of IGF-1 measurement in the diagnosis of GHD, we have shown in this study that children with baseline IGF -1>0 are at very low risk of GHD.

P1-304

Prevalence and predictors for growth hormone deficiency in children born small for gestational age with short stature

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Introduction: Small for gestational age (SGA) is a common condition affecting around 10% of all newborns, and it is associated with an increased risk of short stature and other health problems later in life. Growth hormone deficiency (GHD) is a well-known cause of growth failure in children, and it is estimated to affect approximately 1 in 4.000-10.000 children. However, the prevalence of GHD in SGA children with short stature is not well established. Early detection and treatment of GHD in children born SGA is essential to optimize their growth potential. Therefore, this study aimed to determine the prevalence of GHD in SGA children with short stature and also to identify potential predictors that could guide clinicians in GH stimulation testing in this population.

Material and Methods: We conducted a retrospective analysis of children who presented to our clinic with short stature and were born SGA in the previous seven years before commencing growth hormone treatment. The children underwent clinical evaluation, auxological measurements, and hormonal testing. GHD was defined as a peak growth hormone level of less than 10 ng/ml in response to two stimulation tests. All patients were assessed for GHD, as well as for potential predictive factors for GHD in these patients.

Results: Of the 163 children (101 male; 62 female) evaluated, 30 (18.4%) were diagnosed with GHD. The prevalence of GHD was slightly higher in boys (10.4%) than in girls (8.0%). The mean age of our investigated cohort was 8.2± 3.7 years. Statistically significant associations between predicting GHD in short SGA children were observed in the following factors: being born with both small body length and weight for gestational age (p-value 0.028), having low body mass index (median in GHD group -0.9 (IQR 2.4) kg/m2; non GHD group -0.7 (IQR 1.8) kg/m2; p-value 0.017) and low IGF-1 levels (p-value 0.029).

Conclusion: This study provides evidence for a relatively high prevalence of GHD in short children born SGA. Our findings emphasize the importance of early detection and treatment of GHD in children born SGA, with special attention to ones born with both small body length and weight for gestational age, with low BMI and low IGF-1. We recommend that all short children born SGA undergo evaluation for GHD with the final goal of optimizing their growth potential. Further studies are needed to determine the optimal timing and duration of treatment in this population.

P1-305

A rare case of microduplication 5q35.2-q35.3, also known as anti-Sotos syndrome, in a female patient

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V.C. was referred to our Centre for short stature. The mid-parental target height was 153 cm (-1,6 SDS). Her mother had one spontaneous abortion and displayed mild short stature (151,5 cm). Her father had Arnold Chiari syndrome type 1 and was 165,9 cm tall. V.C. was delivered at term after in-vitro-fertilization pregnancy with intrauterine growth retardation (IUGR) from gestational week 21. Birth weight was 2160 g (SGA, SDS -3,17); length was 45 cm (SDS -2,92); head circumference 38,5 cm (SDS +3,75). Her past medical history was unremarkable. During the first visit in our Pediatric Endocrinology Centre, the patient's auxological parameters were: age 0,7 years, length 60 cm (SDS -3,56); weight 5250 g (SDS -3,4), CC 39,5 cm (SDS -2,81). Blood count showed a thalassemia trait; liver, renal and thyroid function were normal, screening for coeliac disease was negative. V.C presented a mild psychomotor delay (especially in language abilities) confirmed by child neuropsychiatry evaluation (total IQ 84, verbal-linguistic IQ 70). Echocardiography and abdominal ultrasound resulted normal.

Growth hormone stimulation test with GHRH + arginine showed a normal response with normal IGF-1 levels. Bone-age assessment was equal to the chronological age.

CGH-array showed a microduplication of 5q35.2-q35.3, where the NSD1 gene is located. A loss-of-function of this gene is associated with Sotos syndrome, characterized by overgrowth, distinctive facial features, macrocephaly, and cognitive impairment. In contrast, the duplication of the NSD1 gene appears to be associated with short stature (probably related to downregulation of IGF-1 receptor signaling and altered mTOR signaling), microcephaly, dysmorphic features, and intellectual disabilities with wide phenotypic variability.

The same microduplication was found in the mother.

Due to the persistence of short stature of the patient at an age of 9 years, after the approval of the regional committee, she has been recently started an off-label treatment with recombinant growth hormone.

P1-489

Effects of GH therapy in patients with GHD (Growth Hormone Deficiency) on glucose homeostasis: results of a 10-years follow-up

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Objectives: Among adverse effects of GH, a particular attention should be given to glucose homeostasis. The aim of the study was evaluate the effect of GH therapy on glucose homeostasis in children with GHD after 10 years of treatment.

Methods: 30 patients (8 M/22 F, age 7.00 ± 2.61 years) with GHD at diagnosis and 30 healthy children comparable to patients for age, sex and BMI were enrolled. Glucose, insulin, HOMA-IR and HbA1c were evaluated in patients and controls at study entry. All the evaluations were repeated in patients and controls after 1 and 10 years of treatment or follow-up respectively.

Results: at study entry no significant differences were detected between GHD and controls in glucose (76.40 ± 9.23 vs 75.38 ± 8.45 mg/dl), insulin (6.83 ± 5.44 vs 6.15 ± 2.97 µU/ml), HbA1c (5.5 ± 1.38 vs 5.27 ± 0.34 %), and HOMA-IR (0.96 ± 1.17 vs 0.94 ± 0.44). After the first year of treatment, insulin (11.04 ± 4.8 vs 6.83 ± 5.44 µU/ml, $p=0.03$) and HOMA-IR (1.84 ± 0.88 vs 0.96 ± 1.17, $p=0.011$) values significantly increased in GHD children. Furthermore, these values were significantly higher than those of controls evaluated after 1 year of follow-up (7.01 ± 2.42, $p<0.05$). After 10 years of GH treatment, patients showed a slight reduction in insulin levels in comparison to year 1 (8.63 ± 2.16 vs 11.04 ± 4.8 µU/ml), although the difference did not reach statistical significance. At the same time point, controls showed a significant increase of insulin values compared to year 1 (9.87 ± 2.64 µU/ml vs 7.01 ± 2.42, $p<0.001$), thus becoming similar to patients' values. Fasting glucose and HbA1c values did not change in patients or controls throughout the study.

Conclusions: Our results suggest that long-term treatment with GH is not associated with significant impairment in glucose homeostasis. GH replacement therapy is associated with a transient insulin resistance (IR), already evident after 1 year of treatment. Insulin values do not further increase after 10 years of GH therapy and the slight IR obsereved in GHD subjects in adolescence is comparable to that physiologically occuring during puberty.

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P1-490

Phenotype and genotype of children with biallelic GHRHR gene mutations: a Belgian case series

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Background: Children with biallelic GHRHR gene pathogenic variants share a phenotype of growth failure starting in infancy and resulting in a proportionate short stature and bone age delay due to a complete isolated growth hormone (GH) deficiency. The genotype ranges from rare promotor mutations to the more frequent splicing mutations, some genotypes being specific to certain geographic areas. Diagnosis is mainly made around the age of 7 years and more often in children from consanguineous parents, given the autosomal recessive character of the condition. Our aim is to report the phenotypic and genetic characterization of the children with biallelic pathogenic GHRHR gene variants diagnosed in Belgium.

Patients and Methods: Children with documented pathogenic biallelic GHRHR gene variants were retrieved from BELGROW, a national database of all rhGH treated patients. Their clinical and biological data were extracted. Height SDS was calculated using the Flemish growth study references.

Results: 8 cases (3 males) were retrieved. Four children were from Syrian origin, 2 of which are cousins. Median age at start of growth hormone treatment was 2.4 years (1.1 – 8.6 years). Median height SDS at start of treatment was -4.7 SDS (range -2.6 to -7.7). Serum IGF1 was below the lower limit in 7/8 patient, while peak GH level was below 3.4 µg/L in all patients. Birth weight and length were within normal limits. No frontal bossing or midfacial hypoplasia were seen. None had a breech delivery or neonatal hypoglycemia, although 2 patients had had neonatal icterus. Five patients were homozygous for a pathogenic variant. The 4 Syrian children from consanguineous families, had the same c.367G>T p.(Glu123*) variant in homozygous state. Three of the non-Syrian patients (2 siblings) harbored the c.674_677delinsGCTGTTGGCAGAAG p.(Val225Gly*fs165), either in homozygous (n = 1) or in compound heterozygous state. Brain MRI revealed an anterior pituitary hypoplasia in 6/8 patients. Height velocity during the first year of GH treatment was above 8 cm/year in all patients (above 11 cm in those treated before the age of 3 years).

Conclusion: Anterior pituitary hypoplasia was the most consistent finding in our series of children with GHRHR gene mutations. A dramatic growth response was observed in those who started GH therapy prior to 3 years of age. The c.674_677delinsGCTGTTGGCAGAAG p.(Val225Gly*fs165) mutation might be more prevalent in Belgian patients and the c.367G>T p.(Glu123*) mutation in the Syrian patients.

P1-491

Priming with sex steroids increases the specificity of GH tests in the diagnosis of "True" isolated growth hormone deficiency

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Background and Aim: Priming with sex steroids before growth hormone (GH) stimulation tests is considered to increase the specificity of the GH stimulation tests, however, its use in the diagnosis of growth hormone deficiency (GHD) is still controversial. Purpose of this study is to analyze efficacy of sex steroid priming in the diagnosis of GHD.

Methods: The study comprised 115 peripubertal boys who were diagnosed with isolated GHD as a result of inadequate GH response in two GH stimulation tests (L-dopa and clonidine). Bone ages of all patients were ≥ 9 years, pubertal stages were either Tanner 1 (54/115, 47%) or Tanner 2 (61/115, 53%), and testosterone levels were <200 ng/dl in all patients. Sixty (52.2%) of these patients were primed with sex steroids (125 mg sustanon intramuscularly) one week before at least one of the two GH stimulation tests during the diagnosis of GHD. GH treatment at a dose of 0.033 mg/kg/day was started in all patients and GH stimulation tests were repeated in the first year of treatment. Clinical, auxological, laboratory characteristics, annual growth velocity and annual change in bone age during GH treatment were compared between patients with and without sex steroid priming, among those with a peak GH response <10 ng/ml during the retest.

Results: At diagnosis of GHD mean age was 12.8±2.6 years (10.1-16.2). Chronological and bone age, height-SDS, peak GH, IGF1 and IGFBP3 levels at diagnosis, as well as target height SDS were similar between those who were primed vs not primed. At retest (one year of GH therapy) peak GH during the retest was <10 ng/ml in 70% (42/60) of the patients primed with sex steroids, and in 47.3% (26/55) of those who were not primed (p<0.001). Under GH treatment, the annual change in height SDS of the primed group was higher than the unprimed group (0.7±0.3 vs 0.5±0.3, p<0.001). In addition, the annual progression of bone age in the sex steroid-primed group during GH treatment was slower in comparison to the unprimed group (1.0±0.3 years vs 1.6±0.4 years, p<0.001).

Conclusion: Individuals diagnosed with GHD by GH stimulation test under priming with sex steroids have better height gain and a higher probability of a diagnosis of GHD in the repeat test. In other words, priming with sex steroids increases the specificity of the GH stimulation test in identifying GHD.

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P1-492

GH stimulation testing: is it time to change the paradigm?

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Background: The efficacy of growth hormone (GH) treatment in short, healthy children diagnosed with growth hormone deficiency (GHD) or those meeting the criteria of idiopathic short stature (ISS) suggest that an overlap exists between these two conditions. Although flawed and inconsistent, growth hormone stimulation tests (GHST) are the key diagnostic tool differentiating between GHD and ISS affecting clinical decisions such as treatment eligibility and dose.

Aim: To compare the response to GH treatment in children diagnosed as GHD or ISS based on their GHST results.

Methods: A single-center, retrospective study evaluating the response to GH treatment over 3 years in children diagnosed with GHD or ISS. GHD was defined as Peak $GH<7.5$ng/m in 2 GHST. The response to GH treatment was analyzed by mixed and linear models, in which the children were stratified according to their pubertal status and gender, and the GH dose was adjusted to body weight.

Results: 291 children (mean age 8.92.37; 38.8% females; 77.6% prepubertal) were included in the study. Height (Ht)-SDS significantly improved in all the children during the 3 years of GH treatment ($P<0.001$). In prepubertal children, Ht-SDS at baseline and along the treatment was comparable between the GHD and ISS groups (Pgroup), and the changes in Ht-SDS were similar along GH treatment (Ptime*group). In pubertal boys, Ht-SDS was lower at baseline and along treatment in the ISS compared to the GHD group ($P<0.001$) and comparable between the groups in pubertal girls. The changes in Ht-SDS were similar in pubertal boys and girls along GH treatment (Ptime*group). The response to GH treatment was also analyzed according to peak GH in the GHST by dividing the cohort into 3 groups: peak $GH<6$, $6GH<7.5$, and GH7.5ng/ml, respectively, and was comparable between the groups.

Conclusions: The response to GH treatment is similar in healthy children defined as GHD or ISS based on GHST. These results suggest that the pivotal role of GHST in diagnosing and treating short children should be reconsidered.

P1-493

Use of aromatase inhibitors in short children and adolescents to optimize final height: A current practice survey

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Introduction: Management of pediatric patients with short stature and poor adult height prognosis it's challenging and effectiveness of treatment with growth-promoting agents is controversial when linear growth is ending. Aromatase inhibitors (AI) have become a therapeutic option as they promote slowdown of bone maturation and increase final height, but yet is a non-approved indication.

Aim: To conduct a survey about its current use in short children and adolescents to optimize final height.

Results: Two hundred and thirty-four endocrinologists from 23 countries answered the survey, and 71% used AI to preserve final height, with anastrozole being the most frequently AI used. A 26.4% of the clinicians used AI in prepubertal patients with short stature or significant advanced bone age with poor adult height prognosis, mostly combined with growth hormone (GH). The most common indication in this group of patients was in prepubertal boys with congenital adrenal hyperplasia. Ninety two percent of the endocrinologists use AI in male pubertal patients with short stature and poor adult height prognosis, and 66.5% used it in any boy with these features regardless of the cause. Eighty percent use was combined with GH. Regarding the duration of treatment, half of the clinicians (53.3%) used AI for an average of two years, 6.6% used it for 3 years and 21.4% used it for more years depending on the cause. Almost all endocrinologists (86.5%) requested safety tests every 3-6 months; with a great variability, being testosterone and liver function the most frequent labs requested. One fifth of the clinicians had to discontinue treatment due to adverse effects, being acne the most frequent cause of cessation of AI. Most clinicians felt confident about the effectiveness of AI in reducing bone age advancement and improving adult height prognosis in pubertal male patients. Nevertheless, the use of AI in girls was exceptional and most participants believed that AI had no role in improving adult height prognosis in female patients. The main reason for not using AI was the belief that there was lack of long-term data on effectiveness in improving final height.

Conclusion: Although these drugs remain off label in the pediatric population, its use has become a common practice in pediatric endocrinologists over the last years as more information about their use has been collected. We stimulate future trials to reassure the safety and effectiveness.

P1-494

Comparison of insulin tolerance test and arginine test in the diagnosis of growth hormone deficiency in children

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Background: The diagnosis of growth hormone deficiency (GHD) requires the subnormal responses to two provocation tests. This study evaluated the value of the growth hormone provocation test using arginine and insulin-induced hypoglycemia to diagnose growth hormone deficiency (GHD).

Method: This study included 294 children with short stature (136 girls and 158 boys) who underwent a growth hormone provocation test using the arginine test (AT) and insulin tolerance test (ITT).

Results: The age at the time of evaluation was 7.6 ± 3.0 years, and GHD and partial GHD were diagnosed in 42 and 111 patients, respectively. Weight-SDS and BMI-SDS were significantly higher in the GHD and partial GHD groups (1.52 ± 1.07 vs. -1.64 ± 0.84 vs. -2.0 ± 0.89, p = 0.001; 0.13 ± 1.07 vs. -1.64 ± 0.84 vs. -2.01 ± 0.89, p = 0.001) and IGFBP3 was lower in the GHD group (1742.4 ± 500.4 vs. 1843.7 ± 410.3 vs. 1967.8 ± 498.6, p = 0.011) than in the non-GHD group. Thirty patients showed peak growth hormone levels > 10 ng/mL in both provocation tests, 35 in ITT alone, and 72 in AT alone. Hypoglycemia was not induced in three patients, and one patient showed anaphylaxis due to arginine administration. The specificity and accuracy of AT were 74.8% and 88.0%, respectively, while the specificity and accuracy of ITT were 48.8% and 75.3%, respectively.

Conclusion: The higher specificity and accuracy of AT compared to ITT suggests that it would be beneficial to perform AT as an initial evaluation of the growth hormone axis in children with short stature.

P1-495

Difficulties in interpreting insulin-like growth factor 1 (IGF-1) levels in short stature children born small for gestational age (SGA) treated with recombinant human growth hormone (rhGH) based on data from six clinical centres in Poland

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Introduction: The assessment of IGF-1 concentrations is one of the parameters used for evaluating response to rhGH treatment. An increase in IGF-1 concentration positively correlates with growth improvement. The IGF-1 concentrations significantly above the reference range may increase total the risk of possible side effects. High IGF-1 concentration is one of the reasons for rhGH dose reduction which affects the response to treatment.

Aim: The aim of this study was to evaluate the IGF-1 local reference ranges (LRR) for the rhGH treatment centres concerned, to compare these values with the populational reference ranges (PRR) and to assess the need for modification of the rhGH dose based on the different norms.

Methods: Auxological data of SGA patients treated with rhGH between 2016 and 2020 at six university clinical polish centres were analysed. The IGF-1 levels were assessed at baseline, after 12 and 24 months, using IMMULITE 2000 XPi Immunoassay System, Elecsys® IGF-1 Roche or SM-C-RIA-CT from DIAsource ImmunoAssays S.A. The IGF-1 assay values were compared to the reference ranges provided by the local laboratory, adapted to the method used for the assay and to the populational reference ranges based on the data presented by Bedogni et al.

Results: At baseline, 185 patients (81%) remained within the normal range for IGF-1 with reference to the LRR and 215 (94%) with reference to the PRR. After 12 months, 56 patients (24%) presented IGF-1 values > 97th percentile for LRR, whereas only 8 (3.5%) for PRR; p< 0.001. After 24 months of treatment, the values were respectively: 47 (33%) > 97th percentile by LRR vs 6 (4.2%) by PRR ; p<0.001. Thirty-nine patients had rhGH dose reduced after 12 months, of whom 12 (25%) had IGF-1 > 97th percentile according to the LRR and 5 (13%) > 97th percentile for the PRR. After 24 months, 35 patients required dose reduction - 23

(66%) had IGF-1 > 97th percentile for LRR and 4 (11%) for the PRR.

Conclusions: The different methods used to determine IGF-1 concentration and the different IGF-1 reference ranges result in a significant proportion of rhGH-treated children with elevated IGF-1 concentration and experiencing dose reductions, which may negatively affect growth rate.

It would be optimal to determine IGF-1 levels in all children using the same method and in the same laboratory, but this is difficult to do in a country with a population similar to the Polish one.

P1-496

Comparative Efficacy of Growth Hormone treatment on children with Idiopathic Growth Hormone Deficiency(and Idiopathic Short Stature (A 12year Tertiary Center Experience

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Short stature is one of the most common concerns presented to pediatric endocrinologists. ISS describes a heterogeneous group of children with a height of more than 2 SD score (SDS) below the corresponding mean height for a given age, sex, and population group without underlying aetiology. The primary objectives of GH treatment are acceleration of growth velocity to promote normalization of stature during childhood and attainment of normal FAH.

Objectives: Assess and compare GH treatment response for ISS and GHD groups: measured as height gain at 1st and 3rd year, and FAH SDS. Also, investigate potential predictors for better outcomes of GH therapy.

Methods: A cross-sectional retrospective review of children with short stature treated with rGH at a pediatric endocrine clinic under the indications of ISS and GHD; followed during the period from Jan 2011 and Dec 2022.

Results: A total of 225 were enrolled, 63.1% (n=142) with ISS and 36.9% (n=83) with GHD, of which 69.3% were male. At rGH therapy initiation, the mean age was 11 years (± 2.7) compared to GHD 10 years (± 3.6) with height SDS of -2.5 (± 0.47) in comparison to -2.7 (± 0.6 SD) for GHD subjects (p-value < 0.06). Treatment outcomes at 1 & 3 years, mean height SDS gain for the ISS group was 0.6 (± 0.3) and 1.14 ± (0.46) compared to GHD of 0.77 (±0.6) and 1.5 (± 0.7); respectively (p -value= 0.0004). Adult height SDS was recorded for 96 subjects (42.6%), with better outcomes for GHD -1.15 (±0.65) than ISS -1.3 (±0.6). The majority (90%) of subjects under GHD and ISS achieved AH SDS above -2 SD. Multivariate regression analysis revealed age at GH therapy initiation and height SDS at baseline were inversely correlated with height gain at 1 year, 3rd year and final AH (P < 0.05).

Conclusions: At 1-year and 3-year follow-ups, both had significant increments in height SDS on average. Almost a third of our cohort reached FAH during the study period, and both subgroups attained normal FAH (HSDS>-2). This is consistent with the results of previous observational studies, showing that children with GHD reach a mean height SDS of approximately −1.0, and children with ISS reach a mean height SDS of approximately −1.4. Earlier recognition and referral for short stature, and efforts to start GH treatment at a younger age, would most likely have resulted in greater gains in height and an increase in adult HSDS.

P1-497

First-year response to growth hormone (rGH) treatment and assessment of iGRO software for the prediction of growth velocity

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Objectives: Response to rGH during the first year of treatment is considered indicative of its effectiveness for the improvement of final height. The iGRO software assesses the response to rGH in children with idiopathic growth hormone deficiency (IGHD) or small for gestational age (SGA) based on age, gender, gestational age, birthweight, rGH dose, maximal GH during stimulation tests, as well as weight and height measurements on follow-up visits. The aim was to evaluate the response to rGH and assess the iGRO software as to the prediction of height velocity (HV) during the first year of treatment.

Methods: Retrospective study of preadolescent children monitored at the Endocrinology Department of "P&A Kyriakou" Children's Hospital with IGHD or SGA before and one year after the start of the rGH treatment. Variables recorded in the iGRO were analyzed, as well as the index-derived response rate (IoR), calculated as (observed HV-predicted HV)/standard deviation of predicted HV. IoR <-1.28 indicates low response, i.e. lower response compared to the corresponding reference population, while IoR >1.28 a better than expected response. For the comparison of the variables between groups, the x2 and one way ANOVA tests were used (STATA version 13.1).

Results: In total, 118 children (73 boys) were studied, mean age 7.66 (2.01) years, of which 92.4% with IGHD. A percentage of 78% (n=92) had a good response i.e. the observed growth rate agreed with that predicted by the software (-1.28<IoR<1.28), while 15.3% (n=18) had a worse response and 6.78% (n=8) a better response than that predicted. Among the 3 response-based groups, there was no difference in gender, age at treatment initiation, median height, baseline BMI z-score, diagnosis (IGHD/SGA), peak GH in stimulation tests and the initial rGH dose. Children with good responsiveness had a tendency for lower initial height z-score compared to children with low responsiveness (p=0.085). Children with poor responsiveness had a higher initial predicted growth rate [9.15 cm (1.9)] than children with normal [(8.4 (1.15)]) and good responsiveness [8.1 (0.7)] (p=0.022). The actual growth rate was 6.7 (1.5), 8.2 (2.1) and 10.1 (10.1) cm, p <0.001, respectively.

Conclusion: In our population, high rates of good response indicate a correct application of the clinical criteria for the diagnosis of IGHD. The iGRO software provides realistic expectations of treatment outcome, is easy to use in daily clinical practice and can detect patients with an unsatisfactory response who need re-evaluation of the diagnosis.

P1-498

The relationship between body mass index and therapeutic effect in children with idiopathic growth hormone deficiency

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Purpose: The aim of this study is to investigate the influence of body mass index (BMI) on therapeutic effect in prepubertal children with idiopathic growth hormone deficiency (IGHD).

Methods: We conducted a retrospective study by chart review in a single center. A total of 138 patients (male n=90, female n=48) with idiopathic growth hormone deficiency who were was treated growth hormone for at least 2 years from January 2010 to May 2019 were analyzed.

Results: Among the 138 patients, 128 were normal weight (BMI<85th percentile) and 10 were overweight (95th>BMI≥85th percentile) and obese (BMI≥95th percentile). At the start of growth hormone treatment, birth weight (P=0.020), Weight SDS (P <0.001), BMI (P =0.003), and BMI SDS (P <0.001) were higher in the overweight and obese patient groups than in the normal group. During 2 years of growth hormone treatment, height SDS in normal weight patients increased from -2.64 ± 0.49 to -1.22 ± 0.60, and height SDS in overweight and obese patients increased from -2.58 ± 0.40 to -0.96 ± 0.78 in patients. The height gain for 2 years in overweight and obese group was higher than in normal weight group (P =0.024). In multiple regression analysis, BMI SDS was positively association with growth velocity (P =0.001) and the gain in height SDS (P <0.001).

Conclusion: BMI SDS was positively related with growth velocity and the gain in height SDS during 2 years of growth hormone treatment in IGHD patients. Growth hormone treatment had a better therapeutic effect in obese and overweight IGHD patients.

P1-499

Growth characteristics and final height in survivors of childhood medulloblastoma

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Background and Aim: Medulloblastoma is a highly malignant childhood brain tumor, requiring treatment with high dose cranio-spinal irradiation and aggressive chemotherapy. Survivors of are at high risk for multiple endocrine deficiencies, including growth retardation and growth hormone (GH) deficiency. Previous studies reported decreased final adult height in survivors of childhood medulloblastoma, with height standard deviation score (SDS) ranging from -1.9 to -1.54±1.06 in patients treated with GH, and from -5 to −3.2±1.3 in those not treated with GH. We aimed to describe growth outcomes, response to GH treatment, and final height in survivors of childhood medulloblastoma.

Methods: Retrospective analysis of 85 children, adolescents and young adults (males=54) treated for medulloblastoma in a tertiary care center, with a follow-up of at least one year from diagnosis.

Results: Fourteen patients (16.4%) have already completed linear growth at the time of diagnosis. The remaining 71 patients were included in the current analysis. Sixty-two patients (87.3%) exhibited growth retardation over the follow-up period, of whom 36 (58%) were formally diagnosed with GH deficiency, and 23 have been treated with GH. Twenty-eight patients achieved final height at the time of analysis, with a height SDS of -1.46±1.4. Thirteen of these patients were treated with GH, with a mean final height SDS of -1.29±1.5. One GH treated patient (4.3%) had recurrence of medulloblastoma, and three patients had secondary carcinoma of thyroid. In the group not treated with GH, six patients (12.5%) had recurrence of their disease and two had secondary neoplasms (meningioma and uterine leiomyosarcoma).

Conclusions: Growth retardation and GH deficiency are observed in the vast majority of medulloblastoma patients. Final height SDS in our cohort was higher compared to previously published series. We suggest that with careful follow-up and early intervention, optimization of height outcome can be achieved. Long term safety is still a concern, and should be discussed with the family prior to initiating treatment.

P1-500

Factors influencing response to growth hormone therapy in patients with growth hormone deficiency

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Keywords: recombinant human growth hormone (rhGH), growth hormone deficiency (GHD), short stature

Background: Recombinant growth hormone is used for the treatment of growth hormone deficiency. In children treated early, catch-up growth is excellent, with a normal final height. A final height gain of 30 cm can be expected on average. However, it has long been recognized that there is variability in the magnitude of individuals' responses to GH. Several factors may contribute to this variability, including birthweight, age at start of treatment, extent of this deficiency, duration of treatment, and frequency of growth hormone injections, height at start of treatment, and height at the start of puberty.

Aims: to evaluate factors influencing response to growth hormone therapy in patients with GH deficiency.

Patients and Methods: this is a case series. Children diagnosed with growth hormone deficiency at the Vietnam National Children's Hospital from January 2012 to June 2019 were initiated on GH. Detailed clinical, biochemical, radiological, and treatment parameters were recorded at baseline and follow-up. Data were analyzed using IBM SPSS version 21.

Results: We received 159 patients who were diagnosed with growth hormone deficiency and treated with rhGH. Mean chronological age and bone age at treatment start were 7.7 and 4.4 yr., respectively. Gain in height for the first twelve months of treatment was 9.5 cm (4.5 – 18 cm). Growth velocity was reduced after one year of treatment but still attained a normal catch-up growth. Duration of growth hormone therapy, age at onset and bone age onset independently impacted the first-year growth velocity cm.

Conclusions: Early diagnosis and delayed bone age are determinants of a better response. Growth hormone must be administered as soon as possible for catch up height SDs within target height SD range.

P1-501

The Predictive Value of using IGF1/Growth Hormone Peak Ratio on growth parameters in Children with Growth Hormone Deficiency (GHD) before and after GH treatment

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Introduction: GH stimulates the production of IGF1; however, their metabolic effects are different. GH has lipolytic and anti-insulin actions while IGF1 has insulin-like actions.

Objectives: To investigate the value of using the IGF1/GH peak ratio in relation to the anthropometric data of children with growth hormone deficiency (GHD) before and after a year of GH therapy.

Patients and Methods: 22 short children with GHD (HtSDS < -2, with peak GH response to provocation < 7 mcg/L) were studied. Their IGF1 level and their peak GH response to provocation were analyzed in relation to their growth data for 1 year on GH treatment (0.3 to 0.5 mg/kg/day) for 1 year.

Results: Summarized in 3 tables

IGF1/GHP ratio correlated better with the growth parameters compared to IGF1SDS, both before and after a year of GH. IGF1/GHP ratio correlated significantly with IGF1 increment and weight gain/day after 1 year of GH therapy.

Conclusion: The IGF1/GHP ratio has a good predictive value of growth response to GH therapy in GHD children.

Table 2: Correlations between IGF1, GHP, and IGF1/GHP ratio on anthropometric data before GH treatment.

	Age	weight	Height	HtSDS	BMI	BMI SDS	IGF-I
IGF-I	0.64	0.78	0.73	0.67	0.64	0.36	1.00
GH-P	0.01	-0.12	0.04	0.13	-0.30	-0.32	0.12
IGF1/GHP	0.52	0.78	0.59	0.53	0.80	0.52	0.64

Table 3: Correlations between IGF1, GHP, and IGF1/GHP ratio on anthropometric data after GH treatment.

	GH-P	IGF1SDS	IGF1/GHP
GH-P	1.00	0.19	-0.53
IGF1/GHP	-0.53	0.39	1.00
Age1	0.02	0.01	0.52
weight1	-0.11	0.34	0.78
Height1	0.01	0.18	0.61
Height SD1	-0.06	0.65	0.67
BMI1	-0.24	0.42	0.82
BMISD1	-0.27	0.54	0.60
Age2	0.01	0.02	0.54
weight2	-0.08	0.27	0.79
Height2	0.02	0.14	0.61
HeightSD2	-0.01	0.58	0.67
BMI2	-0.18	0.34	0.83
BMI SD2	-0.08	0.41	0.47
wt gain g/day	-0.15	-0.02	0.61
IGF1-2	0.00	0.64	0.83

Table 1: The growth and hormonal data of children with ISS.

GHD	Age	wt	Ht	HtSDS	BMI	BMI SDS	MPHSDS	IGF-I	IGF1SDS	GH-P	IGF1/GHP
mean	9.99	27.51	124.1	-2.22	16.99	-0.40	-0.98	158.3	-0.99	4.95	37.30
SD	3.07	11.57	18.01	0.69	3.21	1.17	1.14	102.3	1.09	1.59	31.45
	Age2	wt2	Ht2	HtSDS 2	BMI2	BMI SD2	wt gain g/day	IGF-1 2	IGF-1SDS 2	Delta BMISD	Delta HTSD
mean	10.9	32.8	131.9	-1.79	17.88	-0.12	13.03	268	0.85	0.24	0.46
SD	3.25	13.57	19.39	0.65	3.27	0.98	7.59	152.6	1.05	0.42	0.42

P1-502

Integration of Nurse-Led Virtual Reviews with Growth Hormone Device-Linked Adherence: a mixed methods, feasibility study

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Introduction: Easypod-connect™ for childhood growth disorders is a unique connected system that enables the transmission of injection adherence information for recombinant human growth hormone (r-hGH). Although this system has the potential to facilitate greater adherence, observational studies have shown declining adherence over prolonged periods when used without additional support. Supplemental nurse practitioner support has been envisaged but not investigated; in this study, we have undertaken a feasibility analysis of nurse-led virtual reviews (NVR) in combination with easypod-connect™ in a single centre using quantitative and qualitative analyses.

Methods: We aimed to explore feasibility by assessing compliance with NVR, height standard deviation score (SDS) gain, adherence improvement and patient opinions.

Patients using easypod™ r-hGH were recruited prospectively to a 12-month study with two telephone NVR appointments in addition to standard-of-care in-person hospital outpatient visits. A subset was recruited for a semi-structured interview for qualitative thematic analysis.

Results: Forty-three patients of median (range) age 10.7 (6.7, 15.2) were recruited for a period of 1.1 (0.7, 1.8) years. Thirty-three (76.7%) patients fully complied with NVR integration with easypod-connect™, establishing feasibility. Median (inter-quartile range, IQR) height SDS improved from -1.85 (-2.44, -1.37) to -1.48 (-2.14, -1.07) ($p<0.001$) and was negatively correlated with prior length of r-hGH treatment ($r=-0.34$, $p=0.029$) but not influenced by the presence of confirmed growth hormone deficiency. Adherence was high at study start and remained similar in the majority from study start [96.5 (88.8, 100.0)] to end [99.0 (94.0, 100.0)], in contrast with other observational studies lacking NVR.

Qualitative analysis identified themes supporting patient benefit: practicalities of appointments, perceived purpose and significance of virtual reviews, and the importance of optimising growth. Four patients complained of injection pain; two switched to an alternative r-hGH device.

Conclusion: Our study has demonstrated the feasibility of nurse-led virtual review integration with easypod-connect™ in a mixed methods study, laying the foundation for research in larger groups over longer periods. Nurse practitioners supported the application of easypod-connect™ maintained adherence throughout the study period and offers the potential for improved growth outcomes in all r-hGH devices providing adherence information.

P1-503

Risk factors and best predictor of Osteopenia in preterm Neonates: single center experience

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Background: Osteopenia of prematurity (OOP) is serious but common concerns for parents of premature babies. Reduced bone mineralization results in OOP, or low bone density. The incidence of OOP has increased as a result of medical advancements that have allowed more very low birth weight (VLBW) infants to survive. It is inversely proportional to the intrauterine gestational age (GA).

Objective: to study the risk factors and best biochemical marker to predict OOP.

Patients and Methods: Forty preterm infants with GA < 36 weeks and postnatal age > 6 weeks were recruited from Neonatal Intensive Care Unit of Zagazig University Hospitals. Serum parathyroid hormone (PTH), ALP, calcium (Ca), phosphorus (P), and vitamin D were measured during the first six postnatal weeks. Wrist and arm radiography was done for all patients.

Results Statistically significant difference regarding age at reaching full enteral feed ,furosemide uses, corticosteroid use, blood or plasma transfer and phototherapy in osteopenic infants compared with non-osteopenic infants ($p<0.005$). Using the statistically significant univariate variables, a multivariate multiple logistic regression analysis was conducted, and ALP was found to be the only factor independently associated with neonatal osteopenia.

Conclusion: serum ALP is the best marker to predict OOP and risk factors should be avoided to protect the growing bone of preterm babies.

P1-504

The pattern of growth in a girl with short stature and duplication at 5q35.2q35.3 encompassing NSD1

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Introduction: Characteristic features in patients with a duplication at 5q35.2q35.3 encompassing NSD1 are short stature, microcephaly, mild developmental delay, behavioural problems, digital anomalies and defects of internal organs. The above-mentioned features are reversed to Sotos syndrome phenotype, which is associated with a microdeletion in the same chromosomal region. In the literature, 41 patients were reported so far.

Case Report: Our patient was born at a gestation age of 39 weeks. Her birth weight was 2650g (-1,95 SDS), and her length was 49 cm (-0,85 SDS). At the age of 12 years and 2/12, the girl was admitted to the Department of Pediatric Endocrinology and

Rheumatology at Poznan University of Medical Sciences for the diagnosis of short stature. She does not have any chronic illnesses and does not take any medication regularly. Bone age was delayed by half a year. Genetic testing showed a normal karyotype of 46, XX. The patient suffered from school problems and mild psychomotor developmental delay. The physical examination showed a normal and proportional body structure, with noticeable dysmorphic features such as hypertelorism, low-set hairline, bilateral clinodactyly of the fifth finger of the hand, narrow upper lip, and wide nasal base. The thyroid gland was palpable. Pubertal development was: Th2, P1, Ax1. Her height was 131,9 cm (-3,4 HSDS) and her weight was 26 kg (-2,8 SDS). Diagnostic tests showed normal thyroid function, with IGF-1 and IGFBP-3 levels within the normal range. Growth hormone deficiency and celiac disease were ruled out (max. growth hormone after glucagon 14,4 ng/ml). Thyroid ultrasound was normal. The patient's pubertal development proceeded normally, with the menarche occurring at the age of 15 years, and subsequent menstrual cycles were regular. According to auxological data at ages 5 years and 7 months calculated predicted adult height based on bone age was 151,5 cm. Despite significant short stature observed during developmental period, she reached the final height 152 cm (-2,3 HSDS) which is close to the predicted adult height calculated at the age of almost 6 years. The patient improved growth velocity during the pubertal spurt. The corrected final height was -1,61 SDS.

Conclusion: The reported patient in paediatric care demonstrated significant short stature, with the lowest HSDS -3,4. She improved growth velocity during the pubertal spurt and her final height was -2,3 HSDS. This is the first report showing a detailed pattern of growth in patient with confirmed duplication at 5q35.2q35.3 encompassing NSD1.

Growth and syndromes (to include Turner syndrome)

P1-109

Unique proteomic signatures of Noonan Syndrome-associated LZTR1 variants detected by phosphopeptide analysis

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Background: Noonan syndrome (NS) is caused by variants in multiple genes regulating the RAS/MAPK signalling cascade. NS can present with growth failure associated with growth hormone insensitivity (GHI; low IGF-I and normal/elevated GH levels). Variants in *LZTR1* lead to NS, although the interaction of LZTR1 with the RAS/MAPK and the GH-IGF-1 pathways remain to be elucidated.

Objectives: To gain insights into the functional role of *LZTR1* genetic variants by phosphoproteomic analysis.

Methods: A novel heterozygous missense *LZTR1* variant (p.K156E) was identified in a GHI subject with clinical features of NS by our whole genome short stature panel. We also examined a published (but not characterised) *LZTR1* variant causing NS and GHI (p.G248R). *LZTR1* WT, *LZTR1* variants (generated by site directed mutagenesis) and empty vector (EV) constructs were transiently transfected into HEK 293T cells using Lipofectamine™3000. Cell lysates were extracted, phosphopeptides enriched and pellets reconstituted. Differences in phosphorylation patterns between WT, variant and EV constructs were reported as fold over WT and statistical significance assessed using unpaired two-tailed t-tests. Analysis of transcriptomic data was conducted using Ingenuity Pathway Analysis.

Results: Kinase activity estimation (KSEA) demonstrated significant enrichment of MAPK1 (mitogen-activated protein kinase 1) suggesting increased ERK activation in both variants. This corroborates our previously generated *in vitro* data where through Western Blot analysis of transfected HEK293 cell lysates, we observed increase in p-ERK/total ERK ratios in several *LZTR1* variants compared to WT. Ataxia Telangiectasia Mutated (*ATM*) kinase and Checkpoint kinase 1 (*CHK1*), major effectors of the DNA damage response (DDR), were both preferentially activated in *LZTR1* variants. Ingenuity pathway analysis and filtering of molecules based on p-values revealed a target histone acetyltransferase inhibitor, *NOC2L* (NOC2 Like Nucleolar Associated Transcriptional Repressor), upregulated in both variants.

Conclusions: Phosphoproteomic analysis of two *LZTR1* variants, corroborated enhanced MAPK1 signalling and revealed specific phosphopeptide signatures indicative of upregulation of the DNA damage response (DDR) consistent with previous data demonstrating activation of the DDR and chromosomal instability in germline *LZTR1* variants. Upregulation of a novel target, *NOC2L*, was concordant for both *LZTR1* variants. Its involvement in cell cycle regulation makes it a potential regulator of growth either downstream of or independent of LZTR1, although further work is needed to characterise this target. The phosphoproteomic analysis thus reveals unique molecular signatures characteristic of *LZTR1* variants causing NS and growth failure.

P1-110

Comparison of long-term height outcomes in pediatric patients with growth hormone deficiency receiving once weekly somatrogon with those of matched patients treated with once-daily somatropin in the Kabi/Pfizer International Growth Study (KIGS)

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Objectives: Somatrogon is a long-acting recombinant human growth hormone (GH) approved in the EU and other countries for once-weekly treatment of pediatric patients with GH deficiency (GHD). In this analysis, height outcomes of somatrogon-treated patients in a phase 3 trial (CP-4-006) were compared with historical data from matched somatropin-treated patients enrolled in KIGS.

Methods: In trial CP-4-006, patients were randomized to once-weekly somatrogon (0.66 mg/kg/week) or once-daily somatropin (0.24 mg/kg/week) for the first 12 months. After the main study period, patients were enrolled in an open-label extension where they received somatrogon at their current dose or somatrogon at 0.66 mg/kg/week. Somatrogon-treated patients in the CP-4-006 study were matched with patients enrolled in KIGS who received somatropin (0.20–0.30 mg/kg/week), using propensity score matching according to geographic region, gender, age, peak GH levels and height standard deviation score (SDS) (i.e., peak GH levels and height SDS at study entry). All patients in CP-4-006 and KIGS were hGH therapy-naïve. 155 patients were one-to-one matched in the somatrogon-treated and KIGS groups.

Results: Somatrogon-treated patients and matched somatropin-treated patients in KIGS demonstrated similar mean annualized height velocity (HV) throughout 3 years of treatment (**Table**). Similarly, changes in mean height SDS from baseline to Years 1-3 were comparable between somatrogon-treated patients and the matched somatropin patients in KIGS (**Table**). Being ADA+ in study CP-4-006 did not negatively impact mean annualized HV or mean height SDS.

Conclusions: Somatrogon-treated pediatric patients in trial CP-4-006 had similar height outcomes to matched somatropin-treated patients in KIGS, irrespective of the presence of ADAs.

Clinicaltrials.gov:NCT02968004;EudraCT:2016-003874-42

Table

	Somatrogon CP-4-006 study (N=155)			Somatropin-treated matched KIGS cohort (N=155)	
	All matched patients	**ADA+**	**ADA–**	**All matched patients**	**Matched to ADA+ patients**
Annualized HV (cm/year), mean (SD)					
Year 1	10.03 (2.37) n=81	10.09 (2.50) n=70	9.66 (1.28) n=11	9.57 (2.11) n=81	9.61 (2.13) n=70
Year 2	7.70 (1.82) n=125	7.63 (1.75) n=89	7.86 (2.01) n=36	7.33 (1.80) n=125	7.34 (1.91) n=89
Year 3	7.15 (1.80) n=47	7.24 (1.78) n=35	6.87 (1.91) n=12	6.56 (1.44) n=47	6.69 (1.48) n=35
Height SDS change from baseline, mean (SD)					
Year 1	0.92 (0.54) n=81	0.95 (0.57) n=70	0.76 (0.25) n=11	0.86 (0.45) n=81	0.86 (0.45) n=70
Year 2	1.69 (0.79) n=125	1.75 (0.85) n=89	1.53 (0.59) n=36	1.20 (0.71) n=125	1.20 (0.75) n=89
Year 3	2.00 (0.81) n=47	2.13 (0.88) n=35	1.63 (0.41) n=12	1.32 (0.80) n=47	1.34 (0.81) n=35

P1-111

The phenotypic spectrum of Kenny-Caffey type 2: a case series and literature review

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Context: Kenny–Caffey syndrome (KCS) is a rare condition characterized by proportionate short stature, cortical thickening and medullary stenosis of tubular bones, delayed closure of the anterior fontanelle, ocular and dental anomalies, and variable hypocalcemia due to hypoparathyroidism. KCS is classified into two types according to its clinical features and inheritance pattern. KCS Type 2 (KCS2) is caused by mutations in FAM111A and is distinguished from KCS Type 1 by the absence of microcephaly and mental retardation.

Objective: To highlight the clinical characteristics and early genetic diagnosis of KCS2.

Methods: We present 8 new affected individuals with KCS2 from 6 families, including one family with three individuals found to be a father-to-daughter transmission, adding to the limited literature. We performed a review of genetically confirmed KCS2 cases in PubMed and MEDLINE.

Results: There were 6 females and 2 males in our cohort. All the patients present with short stature (100.0%). Facial dysmorphisms included prominent forehead, small eyes, depressed nasal bridge and micrognathia, consistent with the typical features of KCS2. Ocular defects included hypermetropia (5/8, 62.5%), astigmatism (3/8, 37.5%), amblyopia (2/8, 25.0%) and pseudopapilledema (2/8, 25.0%). Dental problems included defective dentition (3/8, 37.5%) and dental caries (3/8, 37.5%). Skeletal and brain features included delayed closure of anterior fontanelle (6/8, 75.0%), cortical thickening (3/8, 37.5%) and medullary stenosis (4/8, 50.0%) of tubular bones, and cerebral calcification (3/8, 37.5%). Two patients suffered from hypocalcemic seizures. Endocrinologic abnormalities included hypoparathyroidism (5/8, 62.5%) and hypocalcemia (4/8, 50.0%). One male patient had micropenis and microorchidism. All cases harbored missense mutations of FAM111A, and nucleotides c.1706 arose as a mutational hotspot, with 7 individuals harboring a c.1706G>A (p.Arg569His) mutation and one child harboring a c.1531T>C (p.Tyr511His) mutation. Literature review yielded a total of 45 patients from 19 papers.

Conclusions: Our results indicates that there is a marked prevalence of short stature, cortical thickening and medullary stenosis of tubular bones, delayed closure of the anterior fontanelle, ocular and dental anomalies, hypoparathyroidism and hypocalcemia. This study provided strong evidence for the pathogenicity of missense mutations of FAM111A gene, refines the associated clinical phenotypes, and highlights implications for genetic counseling of affected individuals.

P1-112

Treatment of Short Stature in Aggrecan Deficient Patients with Recombinant Human Growth Hormone: Three-Year Growth Response

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Background: Aggrecan (ACAN) is a proteoglycan found in the extracellular matrix of articular and growth plate cartilage. Animal studies have shown that mutations in the ACAN gene lead to premature hypertrophic chondrocyte maturation, causing accelerated cartilage ossification. Patients with ACAN deficiency present with dominantly inherited short stature, often with advanced skeletal maturation and premature growth cessation, as well as early-onset joint disease. The objective of this study was to evaluate therapy with recombinant human growth hormone (rhGH) on linear growth in children with ACAN deficiency.

Methods: This was an open-label, single-arm, prospective study examining the effects of rhGH (50 mcg/kg/day SQ) in treatment-naïve pediatric patients with ACAN deficiency. Main inclusion criteria: confirmed heterozygous mutation in ACAN, age ≥ 2 years (yr), pre-pubertal, bone age (BA) ≥ chronological age (CA), and normal IGF-I concentration. Main outcomes measured: height velocity (HV) and change in (Δ) height standard deviation score (SDS).

Results: Ten patients (six females), ages 2.4-9.7 yrs were treated with rhGH. At baseline, mean height SDS was -2.55 (range, -4.27 to -1.07), mean HV was 5.2 cm/yr (range, 3.8 to 7.1) and median BA advancement was 1.2 yrs (range, -0.9 to 1.9 yrs). Mean HV during the first year increased to 8.9 cm/yr (range, 7.3 to 11.2 cm/yr), 7.4 cm/yr (range, 5.9 to 8.8 cm/yr) during the second year, and 6.7 cm/yr (range, 4.9 to 8.6 cm/yr) during the third year. The Δ height SDS was +0.74 (range, +0.35 to +1.39) during the first year, +0.40 (range, +0.21 to +0.55) in the second year, and +0.16 (range, -0.11 to +0.53) during the third year. Four female subjects entered puberty (but weren't treated with pubertal blockade), with two starting menses towards the end of the trial. Nevertheless, the overall rate of skeletal maturation was similar to change in CA, with Δ BA / CA of -0.1. Joint complaints were infrequent, with one patient experiencing a possible anterior cruciate ligament tear with a sports injury. There otherwise were no unexpected adverse events.

Conclusion: Treatment with rhGH was tolerated well and showed improved linear growth in a cohort of patients with ACAN deficiency. On average, catch-up growth was largest in the first

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year of treatment, less in the second year, and afterwards still at least maintaining normal HV for age. Longitudinal follow-up is needed to assess the long-term efficacy of rhGH and impact on adult height.

P1-113

Etiology of extreme tall stature and auxological cues at presentation

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Background: Tall stature is a frequent concern in pediatric endocrine clinics. However, no representative reports addressing etiology and auxological diagnostic cues at specialized healthcare presentation currently exist. We report the etiology of extreme tall stature and describe auxological cues indicative of a growth disorder.

Methods: We identified 145 subjects (girls/boys: 78/67) with extreme tall stature from our institute's growth database. We applied the criteria: ≥2 measurements with HSDS≥+3 after the age of three years. Subjects born 2012-2018 in the Helsinki University Hospital catchment area with complete medical records were included. We reviewed the medical records, laboratory, genetic, and auxological data. Age at presentation was defined as the first assessment for tall stature in specialized healthcare.

Results: A primary or secondary growth disorder was diagnosed in 64 (44%) children. The frequency of primary growth disorder (girls/boys: 13/21), secondary growth disorders (girls/boys: 21/9), and idiopathic tall stature (ITS) (girls/boys: 44/37) differed between sexes, p=0.03. The most prevalent monogenic syndromes were Sotos (n=5) and Marfan syndromes (n=4). Syndromic tall stature with a neurodevelopmental disorder such as intellectual disability, developmental delay, or autism spectrum disorder lacking a definitive genetic diagnosis was frequent (n=24, 17%) and a male-dominant (67%) phenotype. Molecular genetic studies were relatively frequently used (genetic studies other than karyotype: n=53, 37%) in the diagnostic workup. The most frequent secondary causes were premature adrenarche (n=16) and central precocious puberty (n=9). ITS was diagnosed in 81 (56%) children and was considered mostly non-familial (n=60). Twenty-one subjects with ITS had a tall parent (parental HSDS≥+2). Patients with primary growth disorders presented at a younger age (mean 3.2 years) compared to secondary disorders (mean 5.7 years, p<0.001) and ITS (4.4 years, p=0.021), and patients with secondary causes older than ITS (p=0.014). HSDS (medians 3.1-3.4, p=0.28) or HSDS-TH (medians 2.5-3.1, p=0.18) at presentation did not differ between the groups. Patients with secondary causes had a smaller TH (mean 0.0SD) compared to primary causes and ITS (both, mean 0.7SD, p<0.001), p=0.55 between ITS and primary causes.

Conclusions: We show that primary and secondary growth disorders are frequent in extremely tall children and show sex-specific distribution. Children with extremely tall stature and neurodevelopmental features were prevalent, though a genetic diagnosis was established infrequently in the diagnostic practice. The most functional cues to differentiate the diagnostic groups were age at presentation and TH, whereas HSDS and HSDS-TH did not differ between the groups.

P1-114

Sex-dimorphic associations of the Prader-Willi imprinted domain with prenatal and postnatal growth in healthy infants

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Background: Infants with Prader-Willi syndrome (PWS) exhibit stunted growth. However, little is known about the role of genes expressed from the imprinted PWS domain in healthy infants. This study aimed to analyze the relative gene expression of the SNURF-SNRPN/UBE3A cluster in the imprinted PWS domain in umbilical cord tissue, and its potential association with prenatal and postnatal growth in apparently healthy infants.

Methods: The relative gene expression of the paternally expressed genes MAGEL2, NDN, SNURF-SNRPN as well as the small nucleolar RNA (snoRNA) SNORD116 and SNORD115 were determined by RT-qPCR in umbilical cord tissue from 122 healthy newborns (59 girls and 63 boys) included in a cohort of mother-infant pairs in a region of northeastern Spain. Gene expression values were correlated with auxological measures at birth and during the first year of infancy.

Results: The relative expression of MAGEL2, NDN, SNORD116 and SNORD115 in umbilical cord associated independently and negatively with weight and length of the infant at birth, and with weight of the placenta (p<0.0001). Postnatally, the relative expression of these genes associated independently and positively with weight and length at age 3 months (p<0.001) and also with weight gain from birth to age 1 year (p<0.01). The negative associations at birth were stronger in girls (p<0.0001), and the positive associations during infancy were stronger in boys (p<0.001). In the latter, the postnatal growth curves during the first year of life diverged

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depending on the cord expression of MAGEL2, SNORD116 and SNORD115 (infants with values above the median being those with more postnatal growth).

Conclusion: The relative expression of the paternally expressed genes from the imprinted PWS domain in umbilical cord was found to associate negatively with prenatal growth and positively with early-postnatal growth in healthy infants, conceivably conferring a perinatal advantage, first to the mother-fetus pair and then to the young infant. In boys, the cord expression of such genes could help predicting weight gain during the first year of postnatal life.

P1-115

How are gestational age and size at birth related to pubertal timing and adult height? - Results from the GrowUp Gothenburg studies

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Background and Aim: How gestational age and size at birth are related to the timing of puberty and the adult height of an individual is not well known. Children born small, either preterm or small for gestational age (SGA), are known to be shorter than their peers during childhood. Both adult height and pubertal timing depends on both genetical and environmental factors, have changed over time with broad individual variations. Previous studies have shown conflicting results regarding the associations between characteristics at birth and the pubertal timing. The aim of this study was to investigate associations of gestational age and birth size with the timing of puberty and adult height in a population-based study.

Material and Methods: A study population of individuals from both GrowUp1974 and GrowUp1990 Gothenburg was used. 6781 individuals (3370 girls) were included, born between 25 and 45 weeks of gestation (302 preterm and 107 post term, less than 20 individuals were born before 32 weeks of gestation). Medical birth records registering gestational age, birth weight/length, parental heights and longitudinal growth data from well-baby clinics and school health records were collected. Pubertal timing was defined by age at peak height velocity, PHV. Reaching target height was defined as a height of ±1 SDS from mid-parental height. Statistical analyses were conducted using linear regression models.

Results: Gestational age had no association with adult height nor pubertal timing. Neither birth length nor birth weight was found to be significantly associated with pubertal timing. 50% of children born SGA based on birth length did not reach target height. Birth length and birth weight had 25% and 21% ($p< 0.001$) explanation, respectively, of the variation for adult height when corrected for mid-parental height. Without correction was the explanation for the variation of adult height by birth-length and weight 13% and 7.5% respectively ($p< 0.001$).

Conclusions: This study suggests that gestational age is not associated with adult height or pubertal timing. However, the study population mainly consisted of individuals born term, including moderately premature born babies. The larger the birth size, the taller the adult height, with the main influence being birth length. No significant association between birth size and timing of puberty was seen, however, may non-linear correlations be present. Future studies including larger numbers of premature born individuals and more sophisticated analyses of growth may give more detailed answers.

P1-116

Phenotypic differences in Noonan syndrome based on PTPN11 mutation status

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Introduction: Noonan syndrome (NS) is one of a group of diseases known as rasopathies, which share a common molecular substrate: alterations in the RAS-MAPK signaling pathway. NS is characterized by clinical and genetic heterogeneity. Up to 50% of cases are caused by variants in the PTPN11 gene, although more than 10 genes have been identified as involved in the pathogenesis of this disease with marked clinical overlap.

Objectives: To establish phenotypic differences in patients with NS based on whether it is caused by PTPN11 or another gene.

Materials and Methods: Retrospective observational study that included all patients diagnosed with NS (genetic and/or clinical) between 2005 and 2022 in the Paediatric Endocrinology unit of a single tertiary health care centre. The IBM SPSS software package was used for statistical analysis, using the chi-square test for quantitative variables, and Fisher's exact test when expected values were <5.

Results: A total of 56 patients were included, with a median age at diagnosis of 4.3 years (IQR 1.4-10.4). The genetic cause was identified in 53 patients (94.6%), with 34 of them having variants in PTPN11 (66.1%), 5 in SOS1 and RIT1 (8.9% respectively), 2 patients in RAF1 (3.6%) and one patient in KRAS, MAP2K1, RASA2, and LZTR1 (1.8% respectively). Regarding clinical features, 75.5% of patients had typical facial features. 89.3% had some type of cardiovascular abnormality, with pulmonary stenosis (62.5%) and hypertrophic cardiomyopathy (8.9%) being the most frequent and characteristic. Short stature was observed in 55.3% of patients, with 55% of them receiving growth hormone treatment. Other less characteristic abnormalities included lymphatic disorders (21.4%), cryptorchidism (80%), palmoplantar keratosis (23.2%), musculoskeletal anomalies (76.8%), and hematologic abnormalities (23.3%). The statistical association of all phenotypic characteristics with the presence or absence of mutation in PTPN11 was studied. Only a significant result was obtained in the association of low height and mutation in PTPN11 ($p=0.022$).

Conclusions: Since NS is an entity with great clinical variability and all known causative genes participate in the same signaling pathway, it is difficult to establish phenotypic differences based on the affected gene. The phenotypic overlap described in the literature is confirmed.

P1-117

Evaluating the Beneficial Role of Nutritional Intervention (NI) Trials in Improving Growth in Children with Beta Thalassemia Major (BTM)

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Introduction: Patients with thalassemia have a high prevalence of malnutrition and low body mass index (BMI), and nutritional intervention studies are scarce.

Aim: We performed an electronic search in PubMed, Google Scholar, and Web of Sciences to review nutritional intervention studies and their possible beneficial effect on children and adults with BTM.

Results: 17 controlled and/or longitudinal studies fitted the search criteria. Two NI studies investigated the effect/s of increasing mean energy intake by 20 and 30-50%, respectively, in 12 and 15 children with BTM for 4 and 8 weeks, respectively. Authors reported significant increases in body weight, BMI, fat-free mass, fat mass, and accelerated height velocity associated with increased IGF-1.

On the other hand, NI using micronutrients discovered variable clinical and biochemical effects. One controlled study proved that zinc (Zn) supplementation for 18 months increased serum Zn and bone mineral content of patients with BTM (n = 40) versus controls. Longer term-controlled trials using Zn supplementation (n = 32 patients, aged 1-7 years) increased linear growth compared to thalassemic children without Zn supplementation. A study on 64 patients found that Zn supplements reduced anti-heat shock protein (anti-HSP27) titers in patients with BTM suggesting potential antioxidant and anti-inflammatory effects. Another placebo-controlled study (n = 120) showed that supplementations of Zn and vitamin E increased BMI and total antioxidant capacity.

In 3 nutritional intervention (NI) studies, vitamin E supplementation for 1- 9 months improved the antioxidant/ oxidant balance in plasma and red blood cells, counteracted lipid peroxidation processes, and increased red blood cells membrane fluidity. Daily vitamin C supplementation for a year potentiated the efficacy of DFO to reduce iron overload. (95)

In 3 studies, vitamin D supplementation (intermittent mega dose, oral or IM, or daily oral dose) was associated with increased serum 25-OHD level and significant improvement of symptoms related to vitamin D deficiency in adolescents with β-TM.In one study oral vitamin D and calcium supplementation for 1-year increased bone mineral content.

Oral supplementation of L-carnitine for 6 months improved pubertal development, cardiac performance, and physical fitness and in BTM adolescents. One study suggested a positive role of folic acid in preventing the progression of arteriosclerosis and decreasing thromboembolic events.

Conclusion: Besides increasing Hb level and effective chelation therapy, nutritional support and follow-up of nutritional status including weight gain, BMI, height velocity and bone health appear very important to maintain normal growth

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P1-118

The effect of growth hormone therapy on body composition in girls with Turner syndrome – a 10-year follow-up

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Background: Obesity and a thicker layer of subcutaneous adipose tissue are more common in Turner syndrome (TS), however, it is assumed that growth hormone (GH) treatment has beneficial effect on their body composition (BC).

Objective: To investigate the effect of GH therapy on BC and its relation with metabolic syndrome components in girls with TS during a 10 year-follow-up.

Patients and Methods: 21 girls with TS were described by weight, height, body composition (muscle mass/MM, fat-free mass/FFM, body fat/BF, total body water mass/TBW) and biochemical parameters (glucose, insulin, HDL-cholesterol, triglycerides, total cholesterol) at the beginning of GH therapy (V0) and after 1st(V1), 3rd (V3), 5th (V5) and 10th (V10) year of GH therapy. BC was determined using TANITA MC-980 and waist circumference (WC).

Results: BMI and BMI z-score increased over time on GH therapy ($p<0.05$). Increase in MM by 31.6% (V5), in FFM by 32.8% (V5) and 42% (V10) compared to V0 was observed ($p=0.031$, $p=0.013$, $p=0.021$, respectively). BF was reduced after 10 years by 31.5% ($p>0.05$). TBW increased in each measurement compared to V0 ($p<0.05$). Correlations between the components of the metabolic syndrome and other analyzed parameters are presented in the Table. No significant correlations were found between body composition parameters, glucose and total cholesterol during GH 10-year follow-up.

Conclusion: GH therapy affects body composition and metabolic criteria in girls with TS, especially during first years of treatment.

		BF					MM					TBW					FFM				
		V0	V1	V3	V5	V10	V0	V1	V3	V5	V10	V0	V1	V3	V5	V10	V0	V1	V3	V5	V10
BMI	r	.765	.856	.800	.588	NS	.737	.850	.778	.588	.899	.764	.850	.724	.581	.955	.641	.849	.779	.576	.927
	p	<0.001			<0.01		<0.001			<0.01		<0.001			<0.01		<0.01	<0.001		<0.01	
BMI z-score	r	0.780	.801	.725	.643	NS	<0.01	.663	.420	NS			.661	NS				.662	.423	NS	
	p	<0.001			<0.01			<0.01	<0.05				<0.01					<0.01	<0.05		
WC	r	.832	.764	.491	NS		.656	.820	.858	.703	.831	.728	.831	.785	.696	.894	.604	.830	.860	.749	.831
	p	<0.001	<0.01	<0.05			<0.05	<0.001		<0.01	<0.05	<0.01	<0.001		<0.01	<0.05		<0.001		<0.01	<0.05
Insulin	r	.522	NS	.537			.597	NS	.519	.766	NS	.572	NS	.765	NS				.519	.765	NS
	p	<0.05		<0.01			<0.01		<0.01	<0.05		<0.05		<0.05					<0.01	<0.05	
HDL-C	r	NS	-.496	NS																	
	p		<0.05																		
TG	r	NS																		-.524	NS

P1-119

Clinical features and response to rhGH treatment in ten patients with heterozygous *IGF1* variants

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Introduction: Patients carrying homozygous *IGF1* loss-of-function mutations are extremely rare and show severe pre- and postnatal growth failure, microcephaly, developmental delay, retrognathia and sensorineural deafness. Heterozygous variants in *IGF1* appear to be more common in short stature, but only few cases have been reported in detail. Therefore, clinical features and growth response to recombinant human growth hormone (rhGH) therapy are still incompletely defined. We aimed to perform an extensive characterization of patients with *IGF1* haploinsufficiency in terms of phenotype and their response to rhGH treatment.

Methods: We present the largest case series to date of patients with heterozygous variants in *IGF1*. Ten patients are included (four girls), with either ACMG class 5 (n=5 whole gene deletions, n=3 frameshift variants) or class 4 (partial gene deletion or base substitution) variants. Eight patients had received rhGH for 1 to 12 years. Height, sitting height/height (SH/H) ratio, head circumference and weight for height were expressed as standard deviation score (SDS) for Dutch references. Predicted adult height was determined with the validated software program Bonexpert. Serum IGF-I was expressed as SDS for national standards.

Results: Mean birth length and weight were -1.3 and -1.5 SDS, respectively, and five (of ten) children were born small for gestational age. A history of feeding difficulties or low BMI was present in seven. At an median age of six years (range 1.1-11.9 yr and one adult), height was -3.7±0.7 SDS with a normal SH/H ratio, weight for height was -1.7±1.1 SDS, and average bone age delay 1.8 years (range 0.4-4.0 years). Head circumference was -2.5±0.6 SDS. Mild developmental delay was present in six patients. Serum IGF-I was -1.6±1.3 SDS while serum IGFBP-3 and the GH response to stimulation testing were normal. In six children a predicted adult height could be calculated with a mean of -3.2±0.9 SDS. In the eight rhGH-treated patients, height increased by +0.3-1.2 SDS (median 0.7 SDS) after one year and +0.5-2.0 SDS (median 1.7 SDS, n=5) after two years of treatment. One patient has reached adult height and gained a total of +1.4 SDS compared to height SDS at start.

Conclusion: The phenotype of children with *IGF1* haploinsufficiency consists of borderline low birth size, feeding problems and mild developmental delay, proportionate short stature, and low head circumference and serum IGF-I. RhGH therapy significantly increases growth velocity in a majority of patients and may increase adult height.

P1-120

Personalized behavioral change technique intervention with TUITEK® patient support program to support caregivers of children treated with growth hormone in Korea

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Background: Growth hormone (GH) treatment requires long-term self-management and optimized recombinant-human growth hormone (r-hGH) prescription. Patient support programs (PSPs) are vital in educating, providing personalised support to caregivers and enhancing patient care to achieve optimal growth outcomes. Nurse-led PSP calls using behavior change techniques (BCTs) and motivational interviewing principles have demonstrated a meaningful behavior change across different health conditions.

Aim: To report the impact of the TUITEK® PSP, a multi-component service involving BCTs on caregivers' knowledge, beliefs, and perceptions supporting treatment adherence in patients with GH.

Method: TUITEK® PSP was evaluated in Korean caregivers of children with growth disorders prescribed with r-hGH (Saizen®, Merck KGaA, Darmstadt, Germany) using Aluetta™ pen device approved by MFDS, Korea. Two PSP nurses were trained by psychologist and applied personalization screener to caregivers to identify issues and challenges faced by patients and caregivers. Caregivers in the high-risk group were offered a set of personalized telephone calls and resource packs with a range of BCTs over 3 months. Caregivers were asked to answer same screener to evaluate the progress at the final survey.

Results: Of 34 participants, 97% caregivers (n=33) who managed patients with disease of partial GH deficiency (n=22), idiopathic short stature (n=6) or small for gestational age (n=5) completed the survey. In total, 94% caregivers (n=31) were initially categorized as 'high-risk'. The percentage of caregivers classified as high-risk for emotional burden (n=23), treatment-related anxiety (n=22) and lower confidence of self-administration (n=23) was reduced significantly by 65%, 77% and 70%, respectively at follow-up. Of 3 caregivers with lower disease coherence, 2 showed improvement in disease coherence at follow-up and lower treatment coherence of 1 participant was improved with nurse coaching. Caregivers of children with co-morbidities (n=7) showed a tendency of requiring interventional calls more frequently than the group without co-morbidities (mean number of calls was 2.6 vs 2.0). Regardless of co-morbidities, the percentage of caregivers scoring as 'high-risk' (n=31) was reduced by 82% in at least one of the risk factors at follow-up after educational interventions. Half of the caregivers (52%) were low-risk on all factors at follow-up as compared to 6% at baseline.

Conclusion: TUITEK® PSP addressed potential treatment barriers and provided effective interventions with personalized BCT motivational contents. Thus, such PSPs could help caregivers to understand and improve treatment-related knowledge, perceptions, and beliefs and better support adherence-related needs at different stages of GH treatment.

P1-121

First year reponse to growth hormone (GH) therapy is related to long term outcome in GH deficiency (GHD) but not in children born small for gestational age (SGA)

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In the history of biosynthetic GH, first prediction models on long term outcome of therapy were based on large multinational cohorts of various growth disorders and have concentrated on GH dose.

In this study we analyzed the 1st year and final height (FH) data in a large single center cohort (center of expertise for rare growth disorders) and compared patient outcome and predictions in GHD and SGA. Our aim was to predict treatment outcome using simple previously suggested parameters using linear regression models for group comparisons adjusted for age and height SDS at treatment start. Patients with ongoing treatment were extrapolated using multiple imputation.

GHD and SGA were defined according to international consensus guidelines (cut-off 7ng/ml in GHD, birthweight or length < -2,0 SDS in SGA). The sample consisted of 103 patients with GHD and 53 patients with SGA, median age 6,5 and 7,7 years, respectively (p 0,0968 ns).GH dose was 25 mcg/kg/d in GHD and 35mcg/kg/d in SGA. Height at start of GH therapy was -3,08 (-3,73/2,44 upper/lower quartile) SDS in GHD and -2,88 (-3,63/-2,57) SDS in SGA (p=0,771). DeltaHSDS 1st year was 0,92 (0,83/1,01) SDS in GHD and 0,69 (0,57/0,82) SDS in SGA (p 0,004). DeltaHSDS from start to FH was +2,15 (1,93/2,63) SDS in GHD and 1,16 (0,86/1,45) SDS in SGA (<0,001), corresponding to target height adjusted FH of -0,44 (-0,67/-0,2) SDS in GHD and -1,19 (-1,53/-0,86) SDS in SGA.

A prognostic model including age and height SDS at start as well as deltaHSDS 1st year predicted deltaSDS at FH in GHD with an R-square of 0.47 but of only <0.1 in SGA. In GHD, the addition of deltaHSDS at FH increased the R-square from 0.38 (age and height SDS at start only) to 0.47.

Summary and Conclusions: As expected, both short term and long term effects of GH therapy were significantly higher in GHD compared to SGA. In contrast to GHD, long term effect of GH could not be predicted by the 1st year height SDS increase in SGA.

Overall, long-term results in our center with GH dosing in the low-dose segment yieled favourable results when compared to recently published multinational trials* .

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P1-122

Near Adult Height in a 14-year-old boy with ACAN Deficiency treated with Growth hormone and Anastrozole

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Background: Aggrecan (ACAN) deficiency is a cause of autosomal dominant short stature with bone age advancement and premature growth cessation. There is limited data on the use of growth hormone (GH) treatment and aromatase inhibitor (AI) in this condition and their effect on adult height.

Objective: To describe the improvement in predicted adult height (PAH), height SDS, and near adult height (NAH) in a 14-year-old boy with ACAN deficiency treated with GH for 8 years and AI for 3 years.

Case Report: Growth hormone treatment was started at 6 years and 1-month in a pre-pubertal boy at a dose of 0.3 mg/kg/week. His bone age (BA) was 8 years resulting in a PAH of 142 cm (Ht SDS -5.1). His height was 102.2 cm (Ht SDS -2.67), weight 17.1 kg (Wt SDS -1.6), BMI 16.3 kg/m2 (BMI SDS 0.66), and growth velocity 4.8 cm/year (9%) at initiation. His untreated mother with ACAN deficiency has height of 147 cm (Ht SDS -2.4) and his unaffected father's height is 170 cm (Ht SDS -0.88). His midparental target height is 165 cm. His untreated maternal grandfather with ACAN deficiency stands 147 cm (Ht SDS -4.4). After 1 year of GH treatment, height was 111 cm (Ht SDS -2.15), weight 21.6 kg (Wt SDS -0.5), BMI 17.6 kg/m2 (BMI SDS -1.1), and growth velocity 8.4 cm/year (>97%). After 5 ½ years of growth hormone treatment, his height SDS improved from -2.67 to -1.19, weight SDS -0.18, and BMI SDS 0.73. BA was 13 ½ years at a chronologic age of 11 years 7 months. AI (Anastrozole) 1 mg daily was added to GH when he entered central puberty at 11 ½ years. After 3 years of the combined GH and AI therapies, at 14 yrs and 8 months, his height is 154.5 cm (Ht SDS -1.66), weight 60.8 kg (Wt SDS 0.55), BA14-15 years, with growth velocity of 2.1 cm/year.

Conclusion: After 8 years of GH treatment and AI for 3 years, there is a height gain of 1 SD and 12 cm improvement above the pre-treatment PAH. The use of GH and AI in this patient led to improvement in near adult height (154.5 cm) compared to the pre-treatment PAH (142 cm). No significant side effects were observed in this patient. More data are needed on the effect of growth hormone and AI in boys with ACAN deficiency.

P1-123

Aromatase Inhibitors May Increase the Risk of Cardiometabolic Complications in Adolescent Boys

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Introduction: Aromatase inhibitors (AIs) are increasingly used in children and adolescents to augment adult height. Given the potential risks of these drugs in women with breast cancer, detailed cardiovascular examinations in adolescents using these treatments are needed to ensure their safety in the pediatric group. The aim of this study was to investigate the effects AIs on cardiac morphology, functions and their relation to several metabolic parameters in adolescent boys.

Methods: Three groups matched for sex (boys, n=67), age (median age 13.5 years), weight, height, body mass index, and puberty stages were enrolled: (i) Group 1: 23 patients using AIs (only AI (n=6) or in combination with growth hormone (GH) (n=17)) for at least 6 months; (ii) Group 2: 22 patients using only GH, and (iii) Group 3: 22 healthy individuals. Two-dimensional, M-mode conventional Doppler and tissue Doppler examinations of the left ventricle (LV) were performed. Bioelectrical bioimpedance analyses was conducted and follicle-stimulating hormone, luteinizing hormone, total testosterone, lipid, and hemogram parameters were obtained. An a priori power analysis was conducted to determine the minimum sample size required to test the study hypothesis.

Results: Patients in Group 1 had significantly higher serum total testosterone (p<0.001) and hemoglobin (p<0.001) levels, fat free mass (p=0.005), LV mass (LVM) (p=0.002), with increased LV posterior wall diameter (LVPWD) (p=0.0016), interventricular septum diameter (IVSD) (p=0.019), and myocardial systolic wave velocity (Sm) (p=0.02) compared to the two other control groups. No significant differences were observed in terms of diastolic and systolic functions and lipid profiles (p>0.05). There were positive correlations between total testosterone, hemoglobin levels, and LVM, LVPWD and IVSD (p<0.05).

Conclusion: This is the first study to date evaluating the cardiac morphology and functions of adolescent boys using AIs. In this study, we found that (i) LVM, LVPWD, IVSD and Sm were significantly higher in the patient group receiving AI therapy compared to the control groups and that (ii) these parameters were significantly correlated with serum total testosterone and hemoglobin levels. These significant differences and correlations were evaluated as potential side effects of AIs.

P1-124

Caloric intake of 6 months-12 years old children with Prader Willi Syndrome under growth hormone treatment at a reference center

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Introduction: Prader-Willi Syndrome (PWS) is the most frequent cause of genetic obesity. It has been described that these patients require a reduction in caloric intake of 20- 40% compared to general population.

Since 2000, with the approval of growth hormone (GH), the evolution of obesity has changed and it seems that caloric requirements could be different.

Methodology: Observational, descriptive, cross-sectional and retrospective study about caloric intake in children 6 months-12 years old diagnosed with PWS and under growth hormone treatment. Dietary records were used to estimate energy intake and the difference between their caloric intake and the theoretical accepted for healthy children was calculated.

Results: 25 participants were included. 52% (n=13) were boys and 48% (n=12) girls. The mean age was 6.72 years (±2.81 SDS). The median age of initiation of GH was 1.4 years (IQR: 0.78, 2.29). 68% (n=17) were of normal weight and 32% (n=8) were overweight or obese. The mean daily energy intake was 1,208 kcal/d (±186 SDS), 96.83% (±18.66 SDS) compared to that recommended by the Henry predictive equation.

Conclusions: Patients with Prader-Willi Syndrome treated with growth hormone consume an average of 96.83% calories of those needed by a healthy child. We should rethink the classic reduction of 20-40% in these children

P1-125

Significant Linear Growth Impairment in a carrier of an interstitial deletion of *356-kb within cytogenetic band 22q11.21 with good response to growth hormone therapy

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Introduction: The 22q11 deletion is one of the most commonly recognized deletion syndromes in humans (~ 1/4000 live births). Most of the reported defect generally involves a deletion at breakpoints LCR22A and LCR22D causing DiGeorge or velo-cardio-facial syndrome. In deletion syndromes, the phenotype ranges from unspecified dysmorphic features to severe cognitive/behavioral deficits, but normal features can occur depending on the size and amount of gene dosage. We are reporting a case of interstitial deletion within 22q11.21, and its response to growth hormone therapy.

Case Presentation: A 7 years old male boy, presented to the pediatric endocrinology clinic for assessment of short stature. He was born at term, with a birth weight: of 3.1 kg and a length of 48 cm. He had no history of chronic illnesses or previous hospitalization. His development was normal for his age. His weight SDS (WAZ): -0.9, height SDS (HAZ):- 2, BMISDS: 0.65, mid-parenteral height SDS (MPHTSDS): +1.2, and growth velocity: 4.7cm/yr. Clinical examination revealed: subtle dysmorphic features, broad thumb, and mild pectus carinatum, with normal heart and abdominal examination and normal pre-pubertal genitalia. Investigations showed normal hemogram, and renal and liver profiles. Insulin-like growth factor: 49.5 ug/L (-2 SD). The clonidine stimulation test revealed a normal Growth hormone peak (13.9 ug/L). He had normal thyroid function and calcium homeostasis. His bone age corresponded to his chronological age. Microarray analysis revealed an interstitial deletion of *356-kb within cytogenetic band 22q11.21, the deleted segment includes the PRODH gene. A trial of growth hormone therapy (0.05 mg /kg/day) for 2 years increased his IGF1 to 102 (-0.2 SD), enhanced his growth velocity to 8 cm and 6.5 cm per year respectively, and increased HtSDS to -1.37 and BMISD to 0.

Discussion: This case revealed that interstitial deletion within 22q11.21 is associated with significant short stature compared to MPHTSDS (-3SD) with normal GH release after provocation but significantly low IGF1. The significant effect on final adult height appears to arise from reduced gene dosage.

Conclusion: We are reporting linear growth impairment in a child carrying an interstitial deletion of 356-Kb within cytogenetic band 22q11.21. with low IGF1 level and normal GH response to provocation. High-resolution microarray testing should be recommended in children who present with HtSDS < -2 from their MPHtSDS especially those with subtle dysmorphism.

P1-126

A Rare Coexistence of Turner Syndrome and Mycosis Fungoides: A Case Report

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Introduction: The frequency of solid and hematological malignancies has been reported to be higher in children with Turner syndrome than in the general population. Mycosis fungoides (MF) represent the most common type of cutaneous T-cell lymphoma, which is a low-grade lymphoproliferative disease. To the best of our knowledge, the coexistence of Turner syndrome and MF has not yet been reported. Here, we report a girl with Turner syndrome and MF.

Case Report: An 11.2–year–old girl presented to the outpatient clinic with the complaint of substantial weight gain (approximately 10 kg in the last two years). She had no significant medical history, and her family history was unremarkable. Height, weight, and body mass index (BMI) were 132.8 cm (-2.1 SDS), 40.5 kg (+0.2 SDS), and 23 kg/m^2 (+1.4 SDS), respectively. Physical examination revealed a plethoric face, low posterior hairline, acanthosis nigricans on the nape, and purple striae on the thighs, as well as shortening of the 5th metacarpals. Puberty was Tanner stage 2. The dexamethasone suppression test and 24-hour urinary cortisol were normal. Impaired glucose tolerance on oral glucose tolerance test was detected and metformin treatment was started. Other laboratory examinations including LH, FSH, and E2 were 2.2 mIU/mL, 12.2 mIU/mL, and 12.4 pg/mL, respectively. Karyotype analysis revealed mosaic Turner syndrome (mos 45, X/46, X,i(Xq)/46, XX[8/3/49]). Growth hormone (GH) treatment (50mcg/kg/day) was initiated. In the third month of GH treatment, persistent, erythematous, itchy skin lesions were observed and a skin biopsy confirmed the diagnosis of MF. GH treatment was discontinued, and a topical steroid was initiated. On follow-up, no additional treatment was required, since the lesions were under control with topical steroids.

Conclusion: Skin lesions should be carefully evaluated in patients with Turner syndrome due to the increased risk for malignancy and MF should be also considered in these patients who present with skin lesions. A dermatologic evaluation may be necessary to confirm the diagnosis and guide treatment.

P1-127

Effects and safety of growth hormone (GH) treatment in 6 children with pycnodysostosis

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Background: Pycnodysostosis is a very rare autosomal recessive skeletal dysplasia caused by cathepsin K deficiency. It is characterized by extreme short stature resulting in an adult height in males typically <150 cm and in females <134 cm. Bone-fragility and frequent fractures are present. There are few case-reports on the effects of GH treatment.

Objective: To evaluate the effect and safety of GH in 6 patients with pycnodysostosis treated according to the Dutch national pycnodysostosis guideline.

Patients: 6 subjects (4 boys, 2 girls) with pycnodysostosis, treated for ≥1 year with GH (~1.4 mg/m^2/day). Endocrine evaluation before start of GH was normal.

Results: Median (IQR) age at start of GH was 10.4 years (5.3; 12.1) and median height 113.5 cm (97.1; 129.3) (Table 1). All children were prepubertal at start of GH. After 1 year of GH, median height gain was 8.0 cm (6.4; 8.5). Three subjects, relatively old at start of GH, reached adult height. Subject 4 (treated for 4.8 years) reached a height of 138.0 cm. Subject 5, reached a height of 157.0 cm (treated for 6.3 years). Subject 6 reached a height of 148.0 cm after 6.4 years of GH and additional GnRH analogue, which is much higher than typically described in females. No SAE's were reported. Fractures occurred in 3 subjects. Frequency of fractures did not increase during GH treatment. Serum IGF-I remained below +2 SDS.

	Gender	Age at start of GH	Height (cm) at start of GH	Height gain (cm) after 1 year of GH	Adult height (cm)	Total height gain (cm)
1	M	4.1	88.2	8.3		
2	M	5.7	100.0	8.2		
3	M	13.7	139.3	8.9		
4	F	9.5	111.2	6.8	138.0	26.8
5	M	11.7	125.9	5.5	157.0	31.1
6	F	11.4	115.8	7.8	148.0	32.2

Conclusion: Pycnodysostosis is an extremely rare disorder and it is, therefore, impossible to perform a randomized control trial to evaluate the efficacy and safety of GH. Our data suggest that GH can prevent the decline in height SDS which is observed in children with pycnodysostosis. Further research is needed to confirm this. Also, the effect of other growth promoting strategies such as treatment with a GnRH analogue needs to be investigated.

P1-128

Delayed puberty as a core feature of POLE1: The Irish Experience

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Recently, pathogenic biallelic variants in the gene encoding DNA polymerase epsilon catalytic subunit 1 (POLE1), have been described in 15 individuals from 12 families, including members of 3 Irish families. These loss-of-function mutations cause POLε deficiency, thus impairing DNA replication. All reported cases share the same heterozygous intronic variant (c.1686þ32C>G) as part of a common haplotype, in addition to a different loss-of-function variant in the other allele. Phenotypically, these individuals have clinical features closely resembling IMAGe syndrome (intrauterine growth restriction [IUGR], metaphyseal dysplasia, adrenal hypoplasia congenita, and genitourinary anomalies [in males]). In addition, these mutations also display distinctive facial features and immunodeficiency characterised by lymphocyte depletion.

In Ireland to date, there are 6 reported cases of POLE1. We report on the 3 cases who are now adolescents or adults; two females aged 44 and 14.5 years respectively, and one male aged 15 years (cases 1, 2 and 3 respectively). All cases were born to Irish parents. In each case, the intronic POLE gene variant c.1686+32C>G was detected, with a loss-of-function mutation identified on the alternative allele. All presented with severe prenatal growth failure and postnatal short stature. There is subtle but clinically insignificant immunodeficiency in our cases. Clinical features are summarised in Table 1.

Pubertal delay has universally been reported in our cohort with case 1 reaching menarche age 22 years following a normal LHRH stimulation test. Case 2, now 14.5 years, has pubic hair Tanner stage III, breast I, premenarchal. She has normal gonadotrophins and oestradiol levels (83pmol/L at age 13.5 years), pelvic ultrasound is pre-pubertal and bone age appropriate for age. Puberty was delayed in case 3 resulting in pubertal induction at age 15. Insulin resistance was found in cases 1 and 3, the latter is treated with metformin.

POLE1 is a newly described condition of primordial dwarfism and adrenal insufficiency. In our case series, severe delayed puberty despite an apparently normal hypothalamic pituitary gonadal axis, and insulin resistance, are features which have not been previously described.

Table 1.

Clinical Features	Case 1	Case 2	Case 3
IUGR	Yes	Yes	Yes
Growth hormone trial?	Yes - Unresponsive	No	Yes - Unresponsive
Metaphyseal Dysplasia	No	No	No
Adrenal insufficiency	Yes	Yes	Yes
Genitourinary anomalies	N/A	N/A	Bilateral cryptorchidism, unilateral hydronephrosis and pyeloplasty
Puberty (Tanner stage)	complete	B1	1
Other	DDH, 11 ribs, café au lait patches	DDH, gastrostomy, atrial septal defect, café au lait patches	Osteopenia, Alopecia

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P1-129

Qatar population-specific centile charts of placental weight to birth weight (PW/BW) ratio in 80 722 newborns born between the 37 th and 42 nd Weeks of Gestation: Relation to Gestational Age, and Gender

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Background: Data about placental weight (PW) in relation to birth weight (BW) and gestational age (GA) are lacking in Arab countries.

Objectives: To report the specific centile charts of PW/BW ratio in a large cohort of mother/baby pairs (n = 80277) born between 37th and 42nd weeks of gestation in relation to neonatal growth characteristics and gender.

Methods: Retrospective cohort study of 80722 mothers, placentas, and newborns delivered in Hamad Medical Corporation Hospitals for 4 years (1-2016: 12- 2019) in Qatar. The information was collected from medical records. The inclusion criterion for this analysis was term singleton live births, 37+0 to 42+6 weeks gestation. According to birth size babies were divided into SGA (<10th percentile), AGA (between 10th and 90th percentiles) and LGA (> 90th percentile) Using intergrowth-21st standards

Results: The PW/BW centiles are constructed (table 1) in full term boys and girls. The PW/BW ratio is significantly bigger in SGA infants versus AGA and LGA. In addition, the PW/BW ratio was slightly but significantly in girls versus boys.

Conclusion: Increased PW/BW ratio in SGA infants may be represent a compensatory mechanism to increase the efficiency of transport functions to the growth compromised fetus. PW/BW centiles for FT infants are reported.

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Table 1. Placenta to Birth weight ratio centiles by gestational age (weeks) for boys and girls (SGA, LGA and AGA)

	All babies								
Intergrowth-21st	**mean**	**SD**	**p5**	**p10**	**p25**	**p50**	**p75**	**p90**	**p95**
AGA	0.203	0.026	0.158	0.169	0.187	0.203	0.219	0.235	0.245
SGA	0.219	0.039	0.154	0.165	0.192	0.224	0.245	0.264	0.276
LGA	0.195	0.025	0.157	0.165	0.179	0.193	0.208	0.226	0.238
Total	0.203	0.028	0.158	0.168	0.185	0.202	0.219	0.236	0.248
Males									
Intergrowth-21st	**mean**	**SD**	**p5**	**p10**	**p25**	**p50**	**p75**	**p90**	**p95**
AGA	0.200	0.026	0.157	0.167	0.185	0.201	0.217	0.232	0.241
SGA	0.216	0.039	0.152	0.162	0.187	0.220	0.242	0.260	0.274
LGA	0.193	0.024	0.154	0.163	0.177	0.192	0.206	0.222	0.235
Total	0.200	0.027	0.156	0.166	0.183	0.200	0.217	0.233	0.244
Females									
Intergrowth-21st	**mean**	**SD**	**p5**	**p10**	**p25**	**p50**	**p75**	**p90**	**p95**
AGA	0.205	0.027	0.160	0.171	0.189	0.206	0.222	0.237	0.248
SGA	0.223	0.039	0.156	0.170	0.197	0.227	0.248	0.267	0.278
LGA	0.197	0.025	0.160	0.168	0.181	0.195	0.210	0.229	0.241
Total	0.205	0.028	0.160	0.170	0.188	0.205	0.222	0.239	0.251

P1-130

The differences of clinical characteristics and effect of growth hormone treatment according to karyotype classification in Turner syndrome patients

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Objectives: Short stature is the main characteristics for Turner syndrome (TS) patients, and growth hormone (GH) therapy has been used as an essential treatment for developing final adult height. However, there are only a few studies on the difference responsiveness to GH therapy according to the karyotype of Turner syndrome in Korea. The aim of this study was to analyze the effect of different types of TS karyotype abnormality on the response of GH therapy.

Methods: The clinical parameters of 185 TS patients registered in the LG Growth Study (LGS) were retrospectively reviewed. Data for four group of subjects were obtained as follow: X-monosomy (n=52); X mosaicism without structural abnormality (n=40); X mosaicism with structural abnormality (n=68); Structural abnormality (n=25). Parameters of clinical characteristics and growth responses were compared during 3-year GH treatment.

Results: The baseline height standard deviation score (SDS), body mass index SDS, bone age (BA) – chronological age (CA) were significantly higher in the X-monosomy group than in other karyotypes. Height SDS and growth velocity (GV) were evaluated annually. The height increment in the first year was highest, and after that, it tended to decreased over time in all TS groups. The GV is highest in TS patients with X mosaicism without structural abnormality, followed by the structural abnormality, followed by the X mosaicism with structural abnormality and the lowest in the X-monosomy. The age at start GH treatment was inversely correlated with height SDS in third year in multiple regression analysis ($p<0.05$).

Conclusions: Our results indicate that there are difference in response to three years of growth hormone therapy according to karyotype of TS. X-monosomy determined a poorer response than in other karyotypes. On the other hand, the best response to the GH therapy was observed in TS patents with X mosaicism without structural abnormality. Moreover, early growth hormone administration with TS is helpful to improve height response to the treatment.

P1-131

Perinatal features of children with Silver-Russell syndrome due to 11p15 loss of methylation

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Context: Silver-Russell syndrome (SRS) is a rare imprinting disorder responsible for foetal and postnatal growth restriction. It is a clinical diagnosis based on Netchine-Harbison clinical scoring system in patients presenting with ≥ 4 items out of 6. Some of the items in this score are not assessable until the age of two years, such as growth retardation or feeding difficulties and body asymmetry can be difficult to identify in the first months of life. Children born small for gestational age (SGA) due to SRS have a different evolution than children born SGA due to placental insufficiency and require appropriate follow-up and management. It is therefore important to make the diagnosis of SRS as early as possible.

Objective: to determine the perinatal characteristics to differentiate between children born with severe foetal growth retardation due to placental insufficiency and children with SRS, to allow earlier clinical and/or molecular diagnosis of SRS and subsequent management.

Methods: We retrospectively compared the perinatal characteristics of children with SRS (n=17) with those of children born SGA by placental insufficiency (n=22). Results. Children with SRS have earlier and more severely altered foetal weight and length than those born SGA due to placental insufficiency from the second trimester of pregnancy. The presence of uterine artery Doppler anomalies, a parameter classically used to orient the cause of foetal growth restriction towards placental vascular insufficiency, did not rule out the diagnosis of SRS, since 23% of patients with SRS had vascular anomalies. SRS children were significantly smaller at birth (birth length <-3DS in 77% of cases in the SRS group versus 15% in the placental insufficiency group, p=0.0001) with relative macrocephaly in 100% of cases in SRS children versus 59% in those born SGA by placental insufficiency (p=0.002).

Conclusion: The diagnosis of SRS must be evoked in the neonatal period in newborns SGA presenting a growth delay present from the second trimester of pregnancy with a birth length lower than -3 DS and a relative macrocephaly. Doppler anomalies must not systematically drive to placental vascular insufficiency diagnosis. Other clinical signs in favour of the diagnosis such as a protruding forehead and body asymmetry may be present from birth.

P1-132

One-year growth response and cost-effectiveness to Human recombinant growth hormone in girls with Turner Syndrome: Results from a large Egyptian retrospective study

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FDA licensed the use of human recombinant growth hormone (hGH) in girls with Turner Syndrome (TS) in 1997 as short stature is a consistent feature of this syndrome.

Objective: we aimed to assess our 1-year experience of treating short girls with TS, to calculate their growth velocity, to analyze the patients' characteristics and to investigate the possible factors that might affect their height gain.

Methods: we studied a cohort of 190 girls with TS. Anthropometric measurements were reported regularly for one year. The cost in dollars for height gain in (cm) in one year was identified using Markov cost-effectiveness simulation model.

Results: This retrospective study included 190 girls with TS (their age at the start of the study was 11.99±3.24 years. Mosaic TS represent 47 patients (24.7 %) & 60% (114) of total patients were dysmorphic, 70% of our cases had 45+X0 karyotyping & 24.7% had 45+X/46+XX karyotyping & 5.3% had other different karyotyping (45, X/47, XXX). Peak GH by Clonidine and Insulin 5.62 ± 4.82 and 8.69 ± 2.39 respectively. The predicted adult height of the first visit, last visit & delta predicted adult height between the first & last visit in our study (143.33 ± 6.59, 145.45 ± 4.67 & 2.12 ± 2.06 respectively). The cost in dollars for height gain in (cm) in one year was identified to be 99.07 ± 37.83 dollars/cm, the height gain in 1 year 5.04 ± 1.62 cm/year costed a total of 499.34 ± 190.71 dollars with hGH dose of 0.04 ± 0.01 mg/kg/d (1.36 ± 0.52 mg/day). Positive correlation between height gain during the study period and duration of therapy and height at presentation SDS (P-values = 0.027 and 0.015 respectively) and negative correlations with age at diagnosis and dose of hGH (mg/kg/d) (P- values = 0.006 and 0.02 respectively) were detected.

Conclusion: hGH is effective in height and growth velocity improvement of short girls with TS. Height at presentation SDS and hGH dose seem to be effective predictors for height gain in our girls with TS.

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P1-133

A case of Noonan's syndrome and Combined Pituitary Hormone Deficiency: a new potential association?

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Noonan syndrome (NS) is an autosomal dominant, variably expressed, multisystem disorder with an estimated prevalence of 1 in 1000–2500. In 2001, PTPN11 was the first gene associated to Noonan syndrome; now, at least 20 other genes have been discovered especially in the RAS–MAPK signalling pathway. More recently, missense mutations in RIT1 have been reported as causative of NS.

A six-years female patient was referred to our Hospital for short stature (<-2 sds) and peculiar phenotype (upper eyelid ptosis). At the age of 3 years old, a clinical diagnosis of Noonan syndrome was suspected. She was submitted to provocative tests for growth hormone (GH) secretion that resulted pathological (arginine with GH peak of 0.75 ng/ml and clonidine with GH peak of 0,78 ng/ml) and she started rhGH therapy at the dosage of 0,18 mg/kg a week until the age of 14, reaching a final height of 148,5 cm (-1.72 SD) and weight of 49 kg (-0,54 SDS). One-year after menarche, she developed secondary amenorrhea, with a normal LHRH test. Endocrine assessment at the age of 17 years showed a GH deficiency at GH retesting (peak of GH after GHRH and arginine: 6,9, ng/ml), low IGF-1 levels (<25 ng/ml) and a secondary hypoadrenalism at ACTH-low-dose test (peak of cortisol: 13,27 mcg/dl). Pituitary MRI revealed an hypoplastic pituitary gland and thin pituitary stalk. Therapies with rhGH (25 mcg/kg/week) and hydrocortisone (8 mg/mq/day) were immediately administered. At the age of 20 years she started levothyroxine therapy (1 mcg/kg/day) for a central hypothyroidism (FT4 0,75 ng/dl and TSH 4,43 mcUI/ml). NGS panel for rasopathies (PTPN11, SOS1, BRAF, RAF1, MEK1, MEK2, KRAS, NRAS, HRAS genes) was performed and resulted normal. Finally, whole exome sequencing (WES) revealed a point mutation (c.284G>C p.Gly95Ala) in heterozygosis in the RIT1 gene, confirming the diagnosis of Noonan syndrome, and a point mutation in the LIM homeobox gene 4 (LHX4) responsible for combined pituitary hormone deficiency. The location of the two genes is in the long arm of chromosome 1(1q22 and 1q25.2, respectively).

To our knowledge, this is the first case of association of Noonan syndrome due to RIT1 mutation and panhypopituitarism; further genetic studies will be necessary to evaluate whether the two-point mutations are just a random association or there is another explanation due to their proximity in chromosome 1.

P1-306

Annual Hearing Screening in Children with Achondroplasia: Results from the First 4 Years in Glasgow

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Objectives: Hearing loss and ENT problems are frequently seen in children with Achondroplasia. Current international consensus guidance recommends audiological assessment before the age of one year and thereafter in childhood in presence of speech delay, hearing difficulties or features of middle ear effusion. In January 2019, we began a programme of annual hearing screening for children with Achondroplasia residing in Glasgow who attend the Complex Bone Clinic (CBC) at Royal Hospital for Children Glasgow (RHCG). Our aim is to assess whether this screening programme is an effective use of resources, with a worthwhile rate of detecting new otological problems.

Methods: Data was collected on age, ear and hearing symptoms, audiometric test results and subsequent outcomes for the first four calendar years of the screening programme. The Primary outcome was the pick-up rate of new hearing screening problems at each screening visit.

Results: 10 Children with a diagnosis of achondroplasia were identified who lived within Greater Glasgow and Clyde. Seven Children (Five Females) participated in the in the annual hearing screening programme at some point with a Median Age of 10.8 years (Range 6.1 to 18.4 years). The pick-up rate of new problems was as follows:

Of the seven children who participated, six had an episode of hearing loss documented at some point, with prevalence in individual years ranging from 25-80%. One child had normal hearing throughout. One Child had pre-existing conductive hearing loss which remains managed with hearing aids. Three had a new episode of hearing loss detected by screening and were referred to ENT (Ear, Nose, and Throat) surgeons. An additional child was also referred to ENT for treatment. One Child had hearing loss which resolved following treatment then recurred.

Year	2019	2020	2021	2022	Total
Attended	6	4	4	5	19
Hearing Loss	2	1	2	4	9
New Hearing Loss or Ear Disease	1	0	3	2	6
Referred to ENT	2	1	1	2	6
Pick-up rate of new problems	2(33%)	1 (25%)	3 (75%)	3 (60%)	9 (47%)

Conclusions: Results at this stage suggest there is a worthwhile pick-up rate of new otological problems and continued detection beyond inaugural year highlights annual screening is likely beneficial for this cohort, although larger case numbers are required.

P1-307

A unique combination of Klinefelter syndrome and Three M Syndrome in a boy with short stature

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Introduction: Klinefelter syndrome (KS) is most common sex chromosomal aneuploidy in males. The typical clinical features are tall stature with long extremities, small testis, and learning disabilities. Three M syndrome is an extremely rare genetic disorder characterized by short stature, craniofacial abnormality and skeletal malformations. We report a unique case of short stature in KS due to three M syndrome.

Case: A 9-year-old boy previously diagnosed with KS, visited the department of pediatric endocinology due to his short stature. He was born at gestational age of 40 weeks through normal delivery and with a birth weight of 2840 g (5th percentile). There were no specific findings other than cryptorchidism at birth. Orchiopexy was performed at the age of 4, and at that time he was accompanied by developmental delay. Chromosomal analysis revealed a 47,XXY karyotype. When he presented to our clinic, his height were 119.2 cm (-2.70 standard deviation score [SDS]) and weight was 18.8kg (- 3.72 SDS). The mid parental height is 170cm (father's height, 171cm; mother's height, 156cm). There was no family history of short stature. The head circumference was 49cm (near 50 percentile), and it was relatively large compared to the height and weight. Both testicles were palpable with 2cc. His bone age was 9 years. There was no skeletal malformation other than mild scoliosis. Serum levels of insulin-like growth factor 1 (IGF-1) was 106.0 ng/mL (normal range : 136-308 ng/mL). The other pituitary hormone levels including thyroid hormone were normal. In the GH provocation test, the peak GH levels after arginine and L-dopa were 6.69 and 7.87 ng/mL respectively. Next generation sequencing for short stature revealed a compound heterozygous CUL7 mutation, c.1823A>G (p. Glu608Gly) and c.364C>G (p.Leu122Val). Recombinant human GH therapy was initiated (0.64 U/kg/wk). After 1 year of GH therapy, his height was 127.3 cm (-1.97 SDS), and his height velocity increased from 3.4 to 8.1 cm/yr. No adverse events were observed during GH treatment. We will monitor the progress of growth and puberty of patient and consider the sex hormone replacement.

Conclusion: This study reports a boy with short stature, in which a unique combined case of KS and compound heterozygous CUL7 mutation was identified. We report that growth hormone therapy is effective in this patient.

P1-308

Birth Size and Postnatal Growth in Infants with Solitary Kidney: Does the disease affect Growth?

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Introduction: Infants with solitary functioning kidney (SFK) may be prone to develop growth problems, which are not well represented in the literature.

Objectives: The aim of this study was to evaluate birth size and postnatal growth in infants with SFK.

Patients and Methods: We measured the weight, Weight SDS (WAZ), length SDS (LAZ), and weight for length SDS (WLZ) at birth and every 6 months for 2 years postnatally in 26 infants born with SFK, without other congenital anomalies. In addition, we recorded their blood pressure (BP), and their biochemical data including blood urea, creatinine, albumin, bicarbonate, Na, and K levels.

Results: Of the 26 infants with SFK, 19 (70%) had unilateral agenesis, 7 (30%) had Multicystic dysplastic kidney (MCDK).

At Birth (gestational age = 38.8 +/- 2 weeks) 8/26 had WLZ <-2 (underweight for length), 1/26 had LAZ <-2. At 1 year of age 6/26 had WAZ and WLZ >2 (obese) and none had LAZ <-2. At 24 months of age 5/26 had WLZ >2. WAZ and WLZ increased from -0.4 and -1.4 respectively at birth to 0.72 and 0.95 respectively at 2 years. LAZ was maintained normal from birth to 2 years (normal linear growth rate) (Table 1).

Nine out of 26 infants had elevated BP at birth and 5/26 at 2 years of age. At 2 years 5/26 had high creatinine level (> 95th centile for age) and 4 of them had high BP. Macroalbuminuria was detected in 4/26, and hypoalbuminemia in 2/26. The BMI at 2 years was correlated significantly with renal length and width (R = 0.49 and R= 0.70 and respectively, p < 0.01). The LAZ at 2 years was correlated significantly with the renal length and width (R = 0.23 and R = 0.445 respectively P<0.05)

Conclusions: Infants with SFK had significantly low WLZ at birth. Postnatal growth for 2 years showed normal growth in length and catch up in WAZ and WLZ. 19.2 % of these infants were obese at 2 years of age.

Table 1: Postnatal growth data of infants with SFK

age		WAZ	LAZ	WLZ
Birth	mean	-0.39	0.32	-1.41
	SD	0.9	1.2	1.8
6 mon	mean	0.41	0.3	0.42
	SD	1.2	1.2	1.1
12 mon	mean	1	0.28	1.1
	SD	1.1	1	1.1
18 mon	mean	1.15	0.21	1.35
	SD	1.2	1	1.1
24 mon	mean	0.72	0.11	0.95
	SD	1.3	1.8	0.8

P1-309

Molecular and phenotypic spectrum of cardio-facio-cutaneous syndrome in Chinese patients

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Background: Cardio-facio-cutaneous (CFC) syndrome is a RASopathy subtype that presents with unique craniofacial dysmorphology, congenital heart disease, dermatologic abnormalities, growth retardation, and intellectual disability. This study describes the phenotypic spectrum of CFC in China and its association with CFC syndrome gene variants.

Results: Twenty Chinese CFC patients, aged 0.6 to 9.5 years old, were included in this study and their clinical phenotypic spectrum was compared with that of 186 patients with CFC from non-Chinese ethnicities. All 20 Chinese patients with CFC carried de novo heterozygous BRAF, MAP2K1, and MAP2K2 variants. Two novel variants were detected and consistently predicted to be deleterious using bioinformatic tools. The clinical features of CFC in the Chinese patients included hypertrophic cardiomyopathy (2/20, 10%), pulmonary valve stenosis (2/20, 10%), curly or sparse hair (7/20, 35%), epilepsy (1/20, 5%), and hypotonia (10/20, 50%); these features were less frequently observed in Chinese patients than non-Chinese patients ($p<0.05$). In contrast, feeding difficulties (19/20, 95%) were more frequently observed in the Chinese patients. Absent eyebrows and severe short stature were more common in patients with BRAF variants than in those with MAP2K1/2 variants. Facial recognition software was used to recognize most CFC patients using artificial intelligence.

Conclusion: This study identified novel and common variants in our cohort of 20 Chinese patients with CFC. We uncovered differences in clinical features between Chinese and non-Chinese patients and detected genotype-phenotype correlations among the BRAF and MAP2K1/2 variant subgroups. This is the largest cohort of Chinese CFC patients to our knowledge, providing new insights into a subtype of RASopathy.

P1-310

Persistence to growth hormone treatment and clinical characteristics of paediatric patients with growth hormone deficiency: A retrospective database study

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Background: For many years, raising awareness on early referral to endocrinologist, early diagnosis, and treatment continuation for paediatric patients with growth hormone deficiency (GHD) has been continued in Japan. However, the current status of trends in age at diagnosis and of treatment continuation have not been fully clarified.

Aim: The aim of this study is to estimate the persistence to growth hormone treatment (GHT) in Japanese patients with paediatric GHD. Proportion of days covered (PDC), demographics and clinical characteristics are also explored.

Method: This was a retrospective cohort study using the JMDC claims database. Patients with paediatric GHD were identified using disease codes and those who cannot be observed 12 months prior to or 3 months after the initial diagnosis were excluded. To evaluate persistence, we selected patients with paediatric GHD receiving GHT and GH stimulation tests. Persistence was defined as the proportion of patients without interruptions (no prescription for more than 6 months) to all patients at a given point. Discontinuation of GHT was defined as a prescription-free period of at least 6 months after last prescription of GH in the observation period. PDC was defined as the ratio of the length of the period with GHT to the length of the observation period.

Result: A total of 1,594 patients were identified. Regarding persistence, the time to initial treatment interruption for 50% of the patients was less than a year (307 days). 87.0% of patients who interrupted GHT had resumed GHT. Time to discontinuation for 50% of the patients was about 6 years (1,780 days).

The factors affecting longer time to treatment interruption and their hazard ratio (95%CI) were higher number of patients per facility (0.80[0.70-0.93]) and concomitant use of pituitary hormonal agents other than GH (0.62[0.39-0.99]). Mean PDC was 52.7±32.9% and proportion of patients without interruption was only 22.5%. The mean age at initial diagnosis was 7.8±3.8 years. The age at diagnosis decreased until 2016 and afterwards tended to increase.

Conclusion: Most of Japanese paediatric GHD patients experienced at least one treatment interruption and PDC was almost half. Although most of patients who experienced interruption had resumed GHT, challenges with real life treatment persistence still exist. Adequate support and education on the importance of continuation of therapy would be needed to maintain the benefits of GHT, while limitations of database analysis should be considered. Continued efforts for early referral and early diagnosis are important.

P1-311

Management of rhGH treatment in children with CKD in current clinical practice: a multicentric study

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Introduction: Growth retardation < –2 SDS is frequently observed in children with chronic kidney disease (CKD) and is a marker of severity of CKD. Recombinant human growth hormone (rhGH) treatment has been approved since 1995 in CKD patients. The aim of this study was to describe the growth outcomes and treatment patterns in children with congenital CKD.

Methods: Patients were recruited from transplantation records in three pediatric academic centers in Ile-de-France. They received a first transplant between 3 and 18 years of age from 2015 to 2020. Patients suffering from cystinosis, a comorbidity or syndromic disease associated with growth failure, patients who had already received a graft and patients transplanted less than 1 year after diagnosis were excluded. Clinical data were collected at 4 time points : diagnosis of the nephropathy, rhGH start, initiation of dialysis and transplantation.

Results: In this retrospective cohort of 87 patients, 42 patients (48%) were treated with rhGH 3.9 years after the diagnosis at a median age of 7.4 years. Before the treatment start, they had a significant loss of height of –0.7 SDS (p<0.0001), 48% of them exhibiting growth failure < –2 SDS. Over 1.7 years of treatment, the median height gain was +0.7 SDS (p<0.0001). Growth outcome was negatively associated with an older age and end-stage renal disease at rhGH initiation. The 45 untreated patients during the same period experienced a loss of height of –0.6 DS (p=0.02) from diagnosis to transplantation besides a normal median height of +0.22 SDS and –0.42 SDS respectively. At transplantation, 26% of the treated and 9% of the untreated patients had growth failure < –2 SDS. RhGH therapy was initiated by a nephrologist in 52% cases and an endocrinologist in 48% cases. The initial prescription deviated from the marketing authorization criteria in 68% cases, mostly for 2 criteria (HtSDS > –2 SDS and age < 2 years). Median rhGH dosages were 0.044 and 0.036 mg/kg/day at initiation and during follow-up respectively.

Conclusion: RhGH therapy is effective in improving growth in CKD patients. However, the late initiation of rhGH therapy in patients with end-stage renal disease, the short duration of treatment and the insufficient rhGH dosage adjustment during follow-up might explain the lower gain of height observed in these patients than previously published results. This study highlights the need for a tight collaboration between pediatric nephrologists and endocrinologists in the management of short CKD patients.

P1-312

Associations between weight-related anthropometric measurements and occurrence of breast development, pubic hair and menarche

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Background: The timing of puberty is influenced by different factors, one of which is body composition. The aim of the current study was to investigate if anthropometric indicators of body composition, body mass index(BMI), waist circumference(WC), subscapular skinfold(SSF) and body fat percentage(BF%) were differentially associated with occurrence of breast development, pubic hair and menarche in Norwegian girls.

Methods: A total of 540 girls aged 8-16 years were examined in the cross-sectional Bergen Growth study 2 (BGS2) in 2016. Pubertal assessments included Tanner Breast (B2–B5) and Pubic hair (PH2–PH5) stages, menarche(no/yes), and ultrasound assessments of breast development (US B2-B5). Associations between BMI, WC, SSF and BF% and occurrence of the pubertal milestones were investigated with binary logistic regression adjusted for age. Anthropometric measurements were categorized as low(-1SD), average(-1≤SD≤1) or high(>1SD). Girls with high and low anthropometric levels were compared to average.

Results: Girls with high levels of weight-related anthropometric measurements were more likely to have reached all pubertal markers compared to those being average. Girls with low levels were less likely to have reached pubertal status according to the different anthropometric measurements. Findings were most consistent for BMIsd. For the consecutive stages of breast (B3-B5) and pubic hair (PH2-PH5) development, girls with high levels of anthropometric markers were more likely to have more advanced stages of puberty compared to girls with average levels, and the opposite was found for girls with low levels.

Odds ratios(OR) of having reached pubertal status according to anthropometric measurements and markers of puberty.

Conclusions: The associations between anthropometric indicators of body composition in early puberty appear similar, although weaker when compared to the late pubertal marker menarche. Our findings support a maturational effect on BMI from pubertal onset.

		Tanner≥B2			US B≥2			Menarche		
		OR	95%CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
BMIsd	low	0.3	0.1-0.8	0.016*	0.33	0.1-0.8	0.010*	0.15	0.1-0.4	0.000*
	high	2.8	1.2-6.4	0.018*	3.67	1.4-9.3	0.007*	4.7	1.8-12.1	0.001*
SSFsd	low	0.5	0.2-1.0	0.062	0.40	0.2-0.9	0.034*	0.13	0.1-0.4	0.000*
	high	1.7	0.9-3.5	0.123	1.96	0.9-4.1	0.075	3.66	1.6-8.4	0.002*
WCsd	low	0.5	0.2-1.2	0.188	0.41	0.2-1.1	0.082	0.18	0.1-0.5	0.002*
	high	3.4	1.4-8.4	0.009*	5.32	1.7-16.9	0.005*	4.2	1.7-10.4	0.002*
BF%sd	low	1.16	0.53 -2.5	0.714	1.10	0.52-2.4	0.768	0.15	0.1-0.4	0.000*
	high	2.22	0.96-5.1	0.062	2.48	1.0-6.2	0.052	3.05	1.0-9.2	0.049*

P1-313

Genetic aetiology of short stature in children from consanguineous families from Kurdistan, Iraq

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Introduction: Linear growth is a complex process involving the interplay of genetic, epigenetic, and environmental factors. Current knowledge sheds importance to the GH-IGF-1 axis, chondrocyte regulation and extra-cellular matrix in the growth plate, and other fundamental intracellular processes. Despite these advancements, the genetics of short stature are not fully understood. This study aims to contribute by investigating a unique cohort of children from consanguineous families from Sulaimani, Iraq.

Patients and Methods: Fifty-one probands (30 females) with height ≤-2.3SD, examined at the paediatric endocrine outpatient clinic, Dr. Jamal Paediatric teaching hospital between January 2018 and February 2020, were included in the study. Their median height was -3.3 SD (IQR -4.15SD to -3SD) and median age 8 years (IQR 5-10). DNA of the proband, both parents, and health/affected siblings (when available) was obtained with informed consent. Probands' DNA was analyzed by Whole Exome Sequencing. Data was processed by a bioinformatic pipeline and variants were filtered using variant analysis software. Prioritized potentially pathogenic variants were evaluated by the ACMG standards and confirmed using Sanger sequencing. Probands without detected causal variant further underwent MLPA and arrayCGH testing to look for Silver-Russell Syndrome and micro-deletions /micro-duplications respectively.

Results: A pathogenic cause of short stature was elucidated in 33/51 (65%) probands. In addition, one proband had uniparental isodisomy of chromosome1 of uncertain significance. Two probands had Silver-Russell and one had DiGeorge syndrome respectively. In the other 30 probands, pathogenic or likely pathogenic variants (17 novel) were found in genes involved in the GH-IGF-1 axis (*GHR*, *SOX3*), the thyroid axis (*TSHR*), the growth plate extracellular matrix (*COL1A2*, *COL10A1*, *FLNA*, *FN1*, *MMP13*, *LTBP3*), the regulation/function of chondrocytes (*DYM*, *NPR2*, *PTPN11*, *CTSK*, *SHOX*), cell and DNA/RNA replication and repair (*LIG4*, *CCDC8*, *GZF1*, *DNAJC21*, *PCNT*, *CFAP410*), transport (*SLC34A3*, *SLC7A7*) and enzyme coding genes (*CYP27B1*, *GALNS*, *GNPTG*). Majority of variants (24) are homozygous, while 6 are autosomal dominant (*NPR2*, *COL1A2*, *FN1*, *SHOX*), including de-novo variants (*PTPN11*, *FLNA*).

Conclusion: The genetic cause of short stature was elucidated in 65% of probands in a unique cohort from a highly consanguineous region. The spectrum of causative genes is varied when comparing to non-consanguineous regions. As expected, most variants were recessive. Many cases of syndromic short stature were diagnosed even though they were initially referred as idiopathic short stature with either mild or undocumented phenotypic features, enabling active screening for possible concomitant conditions and timely management.

P1-314

A case report of Noonan-like syndrome and refractory treatment for increasing growth

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Introduction: Noonan syndrome-like syndrome with loose anagen hair (NSLH) is a RASopathy due to a missense mutation in the SHOCK2 gene. NSLH is distinguished by facial dysmorphisms, growth retardation, various neurocognitive impairment, and cardiac defects. Extremely short stature is frequently observed in patients with SHOC2 gene mutation. Treatment by growth hormone (GH) due to moderate GH deficiency or IGF-1 due to GH insensitivity may be insufficient. We report on a genetically diagnosed NSLH patient manifesting severe short stature with refractory treatment with GH and mecasermin.

Case Report: The presented case is a girl born 3rd in a family of healthy parents (target height -1.15 SD) at 37 gestation weeks. The birth weight was 3474 g (1.0 SD), length – 48 cm (-0.83 SD). An atrial septal defect was diagnosed at birth. Karyotype was 46, XX. At the first endocrinologist evaluation at 12 months: a length of 64 cm (-3.68 SD), a weight of 6.5 kg (-3.86 SD), and continuous growth retardation were observed, and evaluation was performed at the 3 yr. age: IGF-1 7.5 nmol/L (<-2 SD), normal thyroid function, and retarded bone age (-1 y.). Hypopituitarism was diagnosed and treatment with recombinant human GH (rhGH) was started after GH stimulation tests: GH peaks were 9.51 mU/L and 16.45 mU/L. Height at the beginning (4 yr. of age) of rhGH treatment was 86 cm (-4.61 SD). According to physical examination and dysplastic features, the genetic syndrome was suspected, and NSLH was diagnosed at 11 yr. Due to poor response to rhGH, treatment stopped at the 12 yr. (height 117.4 cm (-4.36 SD)). During treatment with rhGH, the IGF-1 concentrations remained low, severe primary IGF-1 deficiency was diagnosed, and treatment with mecasermin was prescribed with increasing doses 40–120 µg/kg twice daily for 3 years. Height at the beginning (13 yr.) of rhIGF-1 treatment was 124 cm (-5.18 SD). Nevertheless treatment, her growth velocity was between 2.25–4.25 cm/yr. At 16 yr., the treatment was discontinued achieving a height of 132 cm (-5.25 SD).

Conclusion: In this case, we present a poor treatment efficiency of rhGH and IGF-1 for the patient with NSLH affected due to SCHOC2 mutation. The deepest literature review of NSLH and treatment outcomes for growth is needed to compose the genotype-phenotype relationship and treatment response in NSLH.

P1-315

Which Method is More Effective in Predicting Adult Height in Pubertal Girls Treated with Gonadotropin-Releasing Hormone Agonist?

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Purpose: The aim of the present study was to determine the efficiency of three different predictive models [Bayley-Pinneau (BP), Roche-Wainer-Thissen (RWT), and Tanner-Whitehouse 2 (TW2)] by comparing their predictions with near-adult height (NAH) data of girls who received gonadotropin-releasing hormone agonist (GnRHa) therapy.

Methods: Clinical findings were retrospectively analyzed. Bone age (BA) was determined by three different investigators (AA, KD, AA) using the Greulich-Pyle (GP) atlas and TW3-RUS method, which were obtained from left wrist radiographs taken at the time of diagnosis. Predicted adult height (PAH) was calculated using the BP, RWT, and TW2 methods for each patient at the beginning of therapy.

Results: The median age at diagnosis of the forty-eight patients included in the study was 8.8 (8.9-9.3) years. The mean height standard deviation (SD) score of the patients was 1.1±1.4 [(-1.8) - (4.5)]. There was no significant difference between the mean BAs evaluated separately with the GP atlas and the TW3-RUS method (p=0.34). The mean target height and NAH SD scores of the patients were -0.6±0.9 [(-3.0) - (2.0)] and -0.5±1.1 [(-2.5) - (2.2)], respectively (p=0.56). Among the PAH methods, only PAH measured by the BP method was very close to and no different from NAH [159.8±6.3 vs. 158.8±9.3 cm. p=0.3; (-0.5±1.1) vs. (-0.7±1.6) SD score, p=0.1]. The sensitivity, specificity, and accuracy rates of methods in predicting the difference between the NAH SD score and the target height SD score higher than -0.5 SD score were determined as 77%, 46.2%, and 68.8% for BP; 73%, 36.4%, and 64.6% for RWT; and 65.8%, 10%, and 54.2% for TW2, respectively. Accordingly, the BP method was the most accurate prediction tool in girls with puberty treated with GnRHa.

Conclusion: The BP method is more effective at predicting adult height than the RWT and TW2 methods in female patients who received GnRHa treatment.

P1-316

The effects of androgen treatment on growth in patients with 5-α-Reductase type 2 deficiency

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Introduction: 5-α-Reductase type 2 deficiency (5αRD2) is 46,XY disorder of sex development that requires androgen treatment for normal male external genitalia development. Despite concerns regarding precocious puberty and stunted growth associated with androgen treatment, limited research has been conducted on its effects on individuals with 5αRD2. The present study aims to evaluate the impact of androgen treatment on bone age (BA) and height status in children with 5αRD2.

Methods: The study involved 19 participants who were followed up for an average of 10.6 years (range 1.4 to 20.0 years). Out of these, 12 received androgen treatment. We compared BA and height SDS between the treatment and non-treatment groups, as well as between the dihydrotestosterone (DHT) treatment and testosterone enanthate (TE) treatment groups.

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Results: Although the height of the 19 patients with 5αRD2 was above average, the height standard deviation scores (SDS) relative to BA were below average, particularly in the androgen treatment group. This can be attributed to the advancement of BA after androgen treatment. The DHT treatment did not lead to BA advancement and an increase in height SDS for BA, whereas TE treatment resulted in a tendency for BA advancement and a decrease in height SDS for BA. The increase in height SDS for BA during DHT treatment was greater whereas the height SDS for BA during TE treatment was reduced in prepubertal period.

Conclusion: Based on the findings, DHT treatment is more favorable for height, while TE treatment leads to BA advancement, particularly during the prepubertal period in patients with 5αRD2. Therefore, the age and type of androgen used should be carefully considered to minimize the risk of height reduction in these patient groups.

P1-317

Growth hormone treatment in a case of Melnick-Needles Syndrome

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Background: Melnick-Needles syndrome (MNS), a rare genetic disorder characterized by skeletal and craniofacial abnormalities. It is caused by mutation of the gene FLNA, which results in disrupted production of filamin A and affects skeletal development. Short stature can be one of the clinical features of MNS.

Case Presentation: An 8-year-old girl who underwent multiple surgeries for gait disturbance was referred to the department of pediatric endocrinology for short stature. Her body weight and height at the first visit was 18kg (-3.24SD) and 118.3cm (-2.56SD), respectively. Delayed bone age and multiple bony anomalies were noted in the X rays of facial, skeletal, and extremities. Peak growth hormone (GH) levels performed by insulin-stimulation test and arginine-induced test were 4.18 ng/mL and 2.11 ng/mL, respectively. Growth hormone treatment was begun with dose of 2.67-3.33mg/week. Annual growth velocity which was 3.6 cm prior to GH treatment, improved to 6.9 cm/year, 7.7 cm/year, and 7.3 cm/year during the 1st, 2nd, and 3rd year of GH treatment, respectively. Recent height was 140.2 cm (-1.71 SDS). Weight also improved from 17.4 kg (-3.51 SDS) to 27.4 kg (-2.53 SDS).

Conclusion: Patients with MNS need multidisciplinary supports to enhance their quality of life. It is important to evaluate growth and growth velocity periodically with the suspicion of GH deficiency. This case showed that 3-year GH treatment was beneficial to enhance the growth velocity in MNS.

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15-year experience with the IGF1 generation test in the Netherlands

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Introduction: Among children with short stature, some show persistent IGF-I levels <-2.0 SDS despite a normal growth hormone (GH) response in a stimulation test. This may be caused by conditions that could benefit from recombinant human GH (rhGH) therapy (e.g. GH neurosecretory dysfunction, bioinactive GH, partial GH insensitivity). Therefore, the IGF-I generation test (IGFIGT) was implemented in 2006 using a national, standardized protocol. Children with a positive response in the IGF1IGT started rhGH treatment. In this study, we describe the long-term outcome of this strategy.

Methods: Our retrospective cohort includes children with height <-2.5 SDS, repeated IGF-I <-2.0 SDS, maximum GH peak >10 µg/L, BMI >-2.0 SDS, and a positive IGF1IGT as indicated by an IGF-I rise of ≥1.0 SDS after one week of rhGH at 0.7 mg/m2/day or (in case of insufficient rise) 1.4 mg/m2/day or 2.8 mg/m2/day. The rhGH dose at which a sufficient IGF-I increase was observed determined the starting dose for therapy. Children who were treated for ≥1 year were included.

Results: We identified 111 children in our National Registry (28% females), aged 2.4-16.7 years. Mean birthweight and birth length were -0.3 SDS. At start of treatment, mean height was -2.9 SDS, with normal BMI and sitting height/height ratio. Bone age delay was 0.9-2.5 years (interquartile range). Available genetic analyses identified Okur-Chung syndrome (n=1), Noonan syndrome (n=1), and *FGFR3* variants (n=5). Fifty-eight patients responded to the 0.7 mg/m2/day dose in the IGFIGT, 38 to 1.4 mg/m2/day, and 15 only to 2.4 mg/m2/day. Most patients (84.2%) were prepubertal at start of therapy. After one year of rhGH therapy in patients who remained prepubertal (n=86), height increased by 0.8±0.3 SDS. After three years, height increase in patients who remained prepubertal (n=56) was 1.5±0.5 SDS and their predicted adult height increased by 1.1±0.4 SDS. In 50 patients who reached

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near adult height (NAH) after an average of 7.1 years of rhGH therapy, height increased from -3.1±0.7 SDS at start to -1.6±1.2 SDS at NAH. The dose of response in the IGF1GT had no direct correlation with outcome, but better growth responses (NAH) were seen with earlier age at start of treatment.

Conclusion: Patients with short stature, reduced IGF-I levels, normal stimulated GH response, and a positive IGFIGT respond well to rhGH therapy. The IGFIGT may identify a subgroup among children with short stature that benefit from rhGH therapy.

P1-319

Progressively impaired prepubertal growth in children with APECED

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Background: Autoimmune-polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED; APS-1) is a disorder arising from mutations in the autoimmune regulator (AIRE) gene, that lead to the development of circulating autoreactive T-cells and deficiency of regulatory T-cells. Multiple manifestations, such as primary adrenocortical insufficiency, and their treatments may disturb growth in children with APECED. However, no previous data on prepubertal growth in children with APECED has been reported.

Methods: Fifty-nine children [30 (51%) girls] from a national APECED cohort were followed from 1952 to 2021. Height and weight development, progression of APECED, duration of glucocorticoid treatment, and infections were retrospectively collected from birth until the end of prepuberty. Birth size z-scores were calculated according to the exact gestational age in preterm pregnancies and according to 40+0 weeks in full-term pregnancies (≥37+0 weeks). Height, weight-for-height, and mid-parental target height z-scores were calculated according to national growth references.

Results: The mean birth weight was 3340 g (z-score -0.80) and 12 patients (20%) were small for gestational age (z-score <-2.0). Of the 59 children with APECED, 38 (64%) had a height z-score below 0 during the whole prepuberty, and 7 (12%) had a z-score below -2.0. Height measurements were compared between three time points (birth, diagnosis of first endocrinopathy, and end of prepuberty) and in relation to mid-parental target height. Birth length z-score (mean, -0.67) did not significantly differ from mid-parental height (mean, -0.59) but was shorter than the population mean. From birth, the mean height z-score declined progressively being -1.34 at the time of first endocrinopathy and -1.86 by the end of prepuberty. Meanwhile, the weight-for-height z-score increased from -0.80 at birth to -0.06 at the time of first endocrinopathy and +0.12 at the end of prepuberty. The height z-score at the end of prepuberty correlated negatively with the total number of manifestations [r (95% CI), -0.27 (-0.49 – -0.011), p = 0.041], but no correlation was found with the duration of glucocorticoid treatment or the number of infections. Altogether, eight patients were treated for growth hormone deficiency from the mean age of 9.6 years; they were shorter than the others at the end of prepuberty (mean height z-score, -2.80 vs. -1.71, p = 0.03).

Conclusions: Children with APECED are shorter than their peers already at birth and their height z-score progressively declines during childhood and prepuberty. APECED predisposes children to short stature and growth disturbances, warranting careful follow-up during childhood to ensure optimal height gain.

P1-320

Achondroplasia: a novel deep intronic variant of the FGFR3 gene, c.1075 + 95C>G, disrupts mRNA splicing

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Background: In the vast majority of cases, achondroplasia and hypochondroplasia are attributable to hotspot missense mutations in the FGFR3 gene. 96% of patients have a G(1138)A and 3% have a G(1138)C point mutation. We report on a family whose members have a deep intronic mutation that leads to a novel cryptic splicing variant of the FGFR3 gene, and via this pathway results in new pathogenicity manifesting as achondroplasia.

Case Presentation: A family of two affected parents and two children with achondroplasia presented to us for treatment. The parents' second-born child, a boy with thanatophoric dysplasia, had died previously. Both surviving children, a 7-year-old girl and a 2-year-old boy, were of short stature height standard deviation scores of −6.7 and −7.2 SDS, respectively. The girl also exhibited typical signs of achondroplasia on x-ray imaging. Trio exome sequencing (proband and both parents) of all four family members identified a new de novo intronic variant, c.1075 + 95C>G, in the mother and the two surviving children with achondroplasia-like features. The father was found to have the classic c.1138G>A variant. A recently published case report revealed that the new intronic variant alters mRNA splicing by causing retention of a 90-nucleotide segment of intron 8 in the mRNA, resulting in a 30-amino-acid insertion in the extracellular domain of the protein. The family we studied is the first known family with demonstrated inheritance of this newly described, likely pathogenic splice variant identified in the FGFR3 gene. Based on a recent report on three boys with the de novo c.1075 + 95C>G variant and the first identified example of a two-generation family pedigree as described above, the novel intronic variant is classified as likely pathogenic from a human genetics perspective.

Conclusions: Our genetic studies confirm previously reported results strongly suggesting that c.1075 + 95C>G is a recurrent mutation and should be included in genetic testing for FGFR3 mutations, especially in patients with unclear clinical findings and no identifiable exonic variant. We conclude that genetic testing for achondroplasia requires intronic sequence analysis of exome data, if available. In the absence of such data, or if no intronic disease-causing variant is detected, whole-genome sequencing or other diagnostic methods, such as long-read sequencing, can be useful.

Reference

Xu T, Shi L, Dai W, Gu X, Yu Y, Fan Y. An intronic variant disrupts mRNA splicing and causes FGFR3-related skeletal dysplasia. J Pediatr Endocrinol Metab. 2021;34(10):1323-1328. https://doi.org/10.1515/jpem-2020-0679.

P1-321

Questionnaire concerning the process of puberty induction among patients with Turner Syndrome

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Introduction: Characteristics of the Turner syndrome (TS) include congenital gonadal dysgenesis resulting in disturbed sexual maturation. Only 20 % of patients with TS menstruate spontaneously. In most cases pharmacological puberty induction is required to maintain female secondary sex characteristics and menarche. Preferred age of start of estrogen replacement is between 11 and 12 years with gradual increase of dose during 2–3 years.

Aim: The aim of the study is to obtain information about the process of puberty induction among patients with TS, their breast satisfaction and side effects of the therapy.

Material and Methods: In the period from August 2020 to April 2022, adult women with ZT and parents of patients with TS were contacted via the messenger application and encouraged to take part in a 15-question anonymous survey regarding the use of estrogen-progesterone replacement therapy. Participation in the survey was voluntary and free of charge.

Results: 108 participants answered the questions. 23 (21.3 %) of respondents had estrogen therapy started at the age between 10 and 12 years, 26 (24 %) between 12 and 14 years, and 27 (25%) between 16 and 18 years. The remaining group consisted of patients who did not start puberty induction yet or matured spontaneously. In the group of patients under 18 years old– 69% started replacement therapy between 10 and 12 years of age. Oral natural estradiol was chosen in 38.9% of cases, transdermal estradiol in patch in 37% of cases and oral ethinyl estradiol in 27.8% of cases. The pubertal induction took less than 1 year in 30.1% of cases, in 25.4% it took between 1 and 2 years, in 21.8 % of cases it took 2-3 years. 59.2% of respondents answered positively when asked about satisfaction with breast development, however the answer "Yes" was less frequent when the puberty induction was made with transdermal estradiol (52.5%) than with natural oral estradiol (71.4%) or ethinyl estradiol (66.7%). What also can be observed, the later the therapy was started, the less satisfaction with breast development was. The most frequently noted problems during puberty induction were: irregular menstrual bleeding (13%), weight gain (8.3%) and local side effects after use of transdermal preparation (8.3%), 40.7% of participants did not report any side effect of hormonal therapy.

Conclusion: Time and way of puberty induction should be carefully considered to bring the satisfying effect and reduced complications.

P1-322

Postnatal Linear Growth Among Very Low Birthweight Infants (<1.5kg) in the first 2 years of life

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Background: Very Low birthweight (LBW) is defined as birthweight below 1.5 kg) and compared to AGA they are reported to be at a higher risk to develop slow postnatal growth outcomes.

Objectives: To describe the postnatal growth of 120 VLBW newborns who had birth weight < 1.5 kg. linear growth trajectories of VLBW infants were compared with normal infants (WHO curves) during the first 24 months of life.

Methods: All LBW infants born during the year 2019 were included in the study. A total of 120 LBW infants were included and their length, length for age z-score (LAZ) score, weight for age (WAZ), and head circumference SDS (HCZ) were followed for 24 months.

Results: Postnatal growth of VLBW infants showed the following: Both WAZ, LAZ and HCZ steadily and progressively increased during the postnatal 24 months. The WLZ remained normal between -0.2 and 0.2 during the same period.

Among the VLBW infants, 95% showed catch-up growth for LAZ and WAZ > 0.67 SD at 6 months of age. At 6 months age, 44% had WAZ < -2 and 68% had LAZ < -2. At 18 months 11% had WAZ < -2 and 33% had LAZ < -2. By the age of 2 years 12.3% had WAZ <-2 and 7.5% had LAZ <-2 (table 1).

Conclusion: The majority of VLBW infants (<1.5 kg) had significant catch up in LAZ, WAZ and HCZ during the first 6 months of life. By the age of 2 years only 7.5% of them had LAZ <-2 and 12.5 % remained underweight (WAZ < -2).

Table 1.

	WAZ <-2	WAZ<-2 %	LAZ < -2	LAZ < -2 %
At 6/12	45/102	44%	67/98	68%
At 12/12	11/98	11%	30/89	33.7%
At 18/12	12/89	13.5%	20/89	22.5%
At 18/12	7/57	12.3%	79/79	7.5%

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A systematic review of core outcomes reported in clinical trials of growth hormone therapy in children with growth hormone deficiency

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Introduction: Although the safety and effectiveness of recombinant human growth hormone therapy (rhGH) has been reported for several years, the level of consensus on the outcomes that should be reported is unclear. The aim of this systematic review is to study the frequency of reporting of these outcomes in children with GH deficiency (GHD).

Methods: A systematic review was performed in Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Reviews, WHO International Clinical Trials Registry Platform (ICTRP) portal, ClinicalTrials.gov, Wan Fang and Chinese Medical Journal between January-February 2023. Eligibility criteria included all studies published between 2013 and 2023, with participants who started rhGH before the age of 16 years for GHD; cross-sectional and case reports were excluded. These criteria were met in 109 studies, of which 77 were in English, 29 in Chinese and 3 in Spanish.

Results: Of the 109 studies, 81(74%) were cohort studies, 25 (23%) were controlled trials and 3 (3%) case-control studies. Studies originated from six continents, and 27 (25%) were multinational. The median age of the participants at start of the study was 9 years (10th,90th: 6.8,10.8 years). Frequently reported outcomes in the 109 studies included: change in height velocity in 56 (51%), change in height SDS in 53 (49%), IGF-1 in 38 (35%), IGF-1 SDS in 30 (28%), height in 29 (27%), bone age and injection site adverse events in 21 (19%), weight in 19 (17%), IGFBP-3 in 16 (15%) and headache in 15 (14%). The most frequently reported frequency of measurement of the above outcomes was annually, varying from 34% (10/29 studies) for height to 56% (15/27 studies) for IGF-1 SDS, with the exception of IGF-1 and IGFBP-3 which was 6-monthly (13/36 studies, 36% and 7/14, 50% respectively). Of the 276 different outcomes reported in total, 144 (52%) were on efficacy, 122 (44%) on safety and 10 (4%) on quality of life. The 144 effectiveness outcomes consisted of 88 (61%) biochemical, 19 (13%) auxological, 13 (9%) radiological, 5 (4%) body composition and 19 (13%) other clinical outcomes.

Conclusions: The current systematic review identifies the range of outcomes that are used to assess the safety and effectiveness of rhGH therapy in childhood GHD. These results demonstrate a level of consensus regarding which outcomes should be tracked and can be used to promote the development of a core outcome set that can standardise the routine collection of outcomes in a clinical setting.

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PROGRES, a multi-country, non-interventional, prospective study of patients receiving human growth hormone treatment under routine clinical care: Study update

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Objectives: Children with growth hormone deficiency (GHD) are usually treated with once-daily injections of recombinant human growth hormone (rhGH). Somatrogon is a long-acting rhGH (LAGH) approved in the EU and other countries for once-weekly treatment of children with short stature. The Pfizer Registry of Outcomes in Growth hormone RESearch (PROGRES) study will assess the long-term safety and effectiveness of once-weekly somatrogon and once-daily rhGH preparations for treating children with growth abnormalities under routine clinical care; PROGRES will also enable comparisons across different once-daily rhGH preparations.

Methods: This non-interventional, prospective, phase 4 study aims to enroll eligible patients (male/female; any age) from >20 countries. Enrollment is from September 2021-October 2029, with data collected until October 2030 (minimum 1-year follow-up). Study inclusion criteria include prescription of once-weekly somatrogon or one of the daily rhGH preparations (Genotropin, Norditropin, Humatrope, or Omnitrope) and provision of informed consent. Somatrogon-treated patients are eligible for inclusion if somatrogon is approved and commercially available in their country. Primary safety outcomes include adverse events (AEs), serious AEs, and AEs of special interest. Primary effectiveness outcomes include annual height velocity (HV) and change in HV standard deviation scores (SDS) from baseline.

Results: One hundred and thirty-eight patients were enrolled as of 31 March 2023, with idiopathic GHD the most common primary diagnosis in all treatment groups (**Table**). Most patients are from Japan (majority receiving Genotropin) or the USA (majority receiving another daily rhGH). Overall, the mean age (SD) of patients was 12.1 (2.59) years and 23.2% were female; mean height SDS and BMI SDS (SD) at enrollment were -1.16 (0.95) and -0.14 (0.91), respectively.

Conclusions: To date, 138 patients from 5 countries are enrolled in PROGRES, most having a primary diagnosis of idiopathic GHD.

Table.

Demographic and baseline characteristics	Somatrogon (n=2)	Genotropin (n=97)	Other daily rhGH (Norditropin, Humatrope, or Omnitrope) (n=39)
Age, mean (SD), years	11.8 (0.59)	12.5 (2.45)	11.2 (2.81)
Female, n (%)	0	18 (18.6)	14 (35.9)
Country			
Australia	0	1 (1.0)	0
France	0	7 (7.2)	3 (7.7)
Japan	2 (100.0)	65 (67.0)	4 (10.3)
United Kingdom	0	0	2 (5.1)
USA	0	24 (24.7)	30 (76.9)
Height SDS			
n	2	92	38
Mean (SD)	-1.92 (0.15)	-1.33 (0.82)	-0.71 (1.11)
BMI SDS			
n	2	92	38
Mean (SD)	0.37 (0.65)	-0.17 (0.89)	-0.09 (0.99)
Primary diagnosis			
Idiopathic GHD	2 (100.0)	87 (89.7)	29 (74.4)
Prader-Willi Syndrome	0	5 (5.2)	0
Other	0	5 (5.2)	10 (25.6)

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Clinical and Genetic Analysis of Ten Short Stature Patients with ACAN Variants

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Objective: To explore the clinical manifestations and genetic characteristics of 10 patients with ACAN variants presented as short stature, and analyze the efficacy of recombinant human growth hormone (rhGH) and/or combined with gonadotropin-releasing hormone agonist (GnRHa) in some patients with premature thelarche.

Methods: We reviewed clinical data of 10 patients with ACAN variants. Genetic testing was performed on probands and their parents. Exome capture and T-A cloning were performed on two variants. We summarized the clinical characteristics of 126 Chinese patients with ACAN variants. Nine patients were treated with rhGH alone and/or combined with GnRHa.

Result: Ten patients were admitted to hospital for "growth delay" at the age of (8.2±1.4) years. All of them presented with proportionate short stature, eight had flat nasal bridge, four each had bossing forehead and scoliosis, three were midface hypoplasia, two with brachydactyly, one had short neck, pigeon breast and another had cubitus valgus. There were three patients had central precocious puberty (CPP), three had early puberty, one had incomplete precocious puberty, five had advanced bone age, two had growth hormone deficiency. Eight ACAN variants (c.1_2delAT, c.7276G>A, c.488G>A, c.5185del, c.1429+1G>C, c.2831dupT, c.6337delG, c.3127_3642del) were detected in ten patients. Among them, seven were new variants. Exon capture showed c.1429+1G>C results in ACAN protein (Val465Glyfs*13) frameshift. T-A cloning showed one patient had 515bp deletion in exon 12 (c.3127_3642del), the same variant point had not found in the parents, which was a de novo variant. Compared with Europe and the United States, short fingers, short neck, broad toes, midface hypoplasia and early-onset osteoarthritis were less frequently in Chinese patients. Five patients were treated with rhGH alone for (0.55±0.11) years, the height standard deviation score (HtSDS) increased from (-2.35±0.42) to (-1.85±0.45). Two patients of CPP/early puberty were treated with rhGH combined with GnRHa for 2.5 years and 0.75 years, respectively. Two patients progressed significantly in bone yage, and were combined with GnRHa at 0.25 and 1.0 years of rhGH therapy. Combined treatment was (1.42±0.99) years, HtSDS increased from (-2.43±0.31) to (-1.84±0.44).

Conclusion: Seven novel variants were reported for the first time. ACAN variants should be considered in patients presented with short stature, premature thelarche, advanced bone age, and with or without special facial features. Diagnosis was comfirmed by genetic testing. rhGH and/or combined with GnRHa can improve the height of patients with ACAN variants.

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Sex Non-Specific Growth Charts and Potential Clinical Implications in the Care of Transgender Youth and Rare Disease Populations

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Background: Although Centers for Disease Control and Prevention (CDC) and World Health Organization growth charts, dichotomizing "girls versus boys," are commonly used, scenarios exist where this binary approach may not be ideal. These scenarios include care for transgender youth undergoing transitions, non-binary youth, and rare diseases where sex-specific growth chart creation is impractical. There is a need for growth charts and z-score calculators that age smooth differences in pubertal timing between sexes to determine how youth are growing as "children" versus "girls or boys."

Objective: To develop age-adjusted, sex non-specific growth charts for height, weight, and body mass index (BMI), and z-score calculators for these parameters using similar statistical techniques and datasets used to create CDC 2000 growth charts.

Methods: We analyzed data from five US cross-sectional nationally representative surveys including National Health Examination Surveys II-III and National Health and Nutrition Examination Surveys I-III. We used the Lambda, Mu, Sigma semi-parametric approach in a Generalized Additive Models for Location, Scale, and Shape (GAMLSS) technique to model growth. Box-Cox Power distribution families in GAMLSS with additive age splines were used to calculate estimates of our sex non-specific height, weight, and BMI reference data tables.

Results: Data from 39,119 participants (49.5% female; 66.7% non-Hispanic White; 21.7% non-Hispanic Black were included in development of our growth charts, reference ranges, and z-score calculators. Respective growth curves were largely superimposable through age 10 after which, coinciding with pubertal onset timing, differences became apparent. Age-adjusted sex non-specific z-score calculators for height, weight, and BMI are available on this website (http://tsaheight2020.shinyapps.io/gender0growthcharts).

Conclusions: Given the increasing prevalence of youth seeking transgender care and recognized limitations of current approaches, a need has arisen in terms of accurately and appropriately tracking

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growth parameters in these individuals. For transgender youth, our growth charts could help in terms of properly assessing a transgender youth's near adult height prediction and expectations surrounding this, weight classification, and decisions regarding further therapy related to growth and weight status that is more robust than the common practice of comparing male and female charts side-by-side in clinical decision-making. These tools provide an intermediate reference between male-specific and female-specific data points, and will help assess growth outcomes in a systematic fashion until transgender-specific, longitudinal data are available. Moreover, these growth charts may have utility as they relate to rare diseases where it can be challenging to create separate growth charts given overall low prevalence.

P1-327

Growth results after GH treatment of children with juvenile idiopathic arthritis

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Introduction: Short stature is a very common complication of juvenile idiopathic arthritis (JIA). Chronic inflammation, long-term corticosteroid therapy, hepatic impairment and malnutrition can reduce the biological effects of IGF-1 and GH.

Growth hormone (GH) treatment may improve height growth outcomes in patients with severe juvenile idiopathic arthritis (JIA).

The aim of the study was to assess the response to growth hormone (GH) treatment in patients with JIA.

Material and Method: 10 children (09 females, 06 males) with JIA and severe short stature were enrolled and followed up (measured in standard deviation (SD) scores). Clinical characteristics of baseline growth were compared with data after 12 months of GH treatment.

Results: The average age was 08.54 ± 2.30 years, There was a significant increase in mean patient height (-2.9 ± 0.7 vs -2.1 ± 0.68, P< 0.01) after 12 months of GH treatment. The mean GH dose was 0.037 mg/kg/day.

Conclusion: GH treatment significantly increased total growth in JIA patients after 12 months of treatment. To maximize final height, GH treatment should be initiated early.

P1-328

CEP57 variant associated with MVA2 syndrome in two Moroccan brothers

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Mosaic variegated aneuploidy (MVA) syndrome represents a rare autosomal recessive disease characterized by aneuploidies with gain and loss of multiple chromosomes. We describe case of two Moroccan brothers with MVA2, due to CEP57 mutations.

Patients are 17 and 13-year-old male siblings of a Moroccan healthy consanguineous couple. Oldest brother was delivered at 35 gestational weeks after IGR diagnosis, small for gestational age (SGA, 1300 grams, -3 SDS). Younger patient's delivery was 38 gestational weeks and he also resulted SGA (2165 grams, -2.4 SDS).

Siblings were evaluated for marked growth delay (<-4 SDS, genetic target -1.32 SDS). Physical examination showed prominent forehead with frontal bossing, sparse hair, dolichocephaly, triangular face, simple low-set ears and broad nasal tip. Additional features included mild rhizomelic limb shortening, diffuse café-au-lait spots, amelogenesis imperfecta, bilateral cryptorchidism (surgically corrected) and mild psychomotor retardation.

Older sibling presented pituitary gland hypoplasia without GH deficiency at specific tests, IGF-1 stably over normal limits (>> 2 SDS). During follow-up marked growth delay with reduced growth velocity persisted, he showed insulin resistance requiring metformin, hypertriglyceridemia and liver steatosis; furthermore, partial hypergonadotropic hypogonadism and ultrasound dysthyroidism were detected, not requiring specific therapies.

Younger patient presented partial GH deficiency with pituitary hypoplasia, IGF-1 levels significantly increased for age (>> 2 SDS). Partial hypergonadotropic hypogonadism, isolated thyrotropin elevation and insulin resistance, requiring metformin, were similarly identified.

No GH therapy was administered in both patients for IGF-1 levels and unknown neoplastic risk.

According to clinical features, 100-metaphase chromosome evaluation from lymphocyte cultures was performed, showing in both patients a male karyotype with several chromosomal aneuploidies and multiple trisomies; array-CGH, gene sequencing of IGF1R and BUB1B genes were negative. WES analysis revealed in both patients a homozygous frameshift loss of function mutation in CEP57 gene, related to MVA2. Parents were both carriers of identified mutation.

Only 13 patients with pathogenic CEP57 variant have been previously described. Our patients presented hallmarks of MVA2 phenotype: prenatal growth problems, skeletal abnormalities, typical facial features, intellectual disability. Furthermore, our siblings showed partial hypergonadotropic hypogonadism and insulin resistance, which apparently were not previously described in MVA2. MVA1 and MVA3 variants are commonly associated to increased risk of childhood malignancies (rhabdomyosarcoma, Wilms tumor), but neoplastic lesions have not been observed in reported cases (oldest one was 29 years old) and in our patients. A longer follow-up and further studies occur to correctly clarify tumor risk and genotype-phenotype correlation in MVA2 patients.

P1-329

Long-term (9-year, 8-year and 3.5-year) follow-up of treatment with rhGH in three patients with Noonan syndrome due to PTPN11 mutation and confirmed growth hormone deficiency

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Introduction: Noonan syndrome (NS) is relatively common genetic disorder caused by mutations in the PTPN11 (50%), SOS1 (10-13%), and RAF1 (3-17%) genes responsible for disturbances in the activation of the RAS/MAPK signaling pathway. NS is characterized by facial dysmorphic features (90%), congenital cardiac disturbances and short stature (<3c) - the average final adult height is 162.5 cm for male and 153 cm for female. In some, but not all of the NS patients, growth hormone deficiency is observed. Considering the literature, growth hormone replacement therapy (GRHT) improves the final height in this patients whereas the treatment remains safe. However, long-term follow-up concerning the growth rate, final height (FH) and puberty process in NS patients is still to be obtained. The objectives of this work is to reveal GHRT outcomes in patients with long-term follow-up.

Patients and Methods: This is a retorspective study of three patient cases conducted in the Department of Endocrinology and Metabolic Diseases in Polish Mother's Memorial Hospital - Research Institute in Lodz (Poland) over a period of 3,5-9 years, from June 2013 to February 2023.

Results: We collected 3 NS patients with PTPN11 gene mutation and growth hormone deficiency (GHD) treated with GHRT for 3.5, 8 and 9 years. The onset of GHRT occurred with a median age of 8.3 years. In all cases height SD score (HSDS) during treatment improved (ΔHSDS mean±SD: 1.6±0.67; min-max: 1,08-2,27). In one patient near FH was obtained consistent with the target height (TH). In two patients rapid bone age (BA) advancement and deteriorating growth prognosis lead to pharmacological inhibition of sexual maturation and epiphyseal ossification. In the last two cases the final results are uncertain despite current improvement.

Conclusions: GHRT improved growth outcome in NS patients, however the final results depends on various factors, thus demands personalized therapy.

P1-330

A complex phenotype due to the overlap of two rare conditions: miller-mckusick-malvaux (3M) and chung-jansen syndrome

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Introduction: I. was born at term by emergency caesarean delivery due to foetal distress, by unrelated parents. Birth weight: 2160 g (-3.18 SD), length 41.5 cm (-4.47 SD), head circumference 35.4 cm (0.57 SD). He was admitted in the neonatal intensive care unit (NICU) for the severe growth retardation associated to dysmorphic features. Neonatal screening, echocardiography and brain ultrasound normal. Karyotype: 46,XY.

Case Presentation: I. came to our observation for the first time when he was 12.88 years old for obesity associated with severe short stature. Height: 124.3 cm (-4.07 SDS), weight: 51.1 kg (1.04 SDS), BMI: 25.6 kg/m^2 (3.15 SDS). Bone age: 12 years; Tanner pubertal stage: I. At physical examination he presented harmonic short stature, dysmorphic features such as lunar lunar-freckled face, prominent eyebrows, depressed nasal bridge, large ears and earlobes, anteverted nares and full lips. He also had short broad neck chubby, small hands with brachydactyly, cubitus valgus and knee valgus. His parents reported behavioural problems such as easy loss of self-control, impulsiveness, hyperactivity and aggressiveness with a progressive tendency to worsen. His academic performance was poor.

Blood count, lipid profile, electrolytes, renal, hepatic and thyroid function were normal. In consideration of the severe obesity associated to acanthosis nigricans, an oral glucose tolerance test was performed with evidence of marked hyperinsulinism associated with normal glucose tolerance.

The patient was tested through a NGS panel including genes involved in short stature and genetic obesity. The analysis revealed the novel pathogenic variant c.2494-1G>T at the homozygous state in the CUL7 gene, at the splicing consensus site, predicted to produce an aberrant transcript. Moreover, a heterozygous missense mutation in the PHIP gene, namely c.494T>A, that causes the aminoacidic change p.Val165Asp,classified as variant of uncertain significance, was identified.

Discussion: Mutations in the CUL7 gene are associated to the 3M syndrome, an autosomal recessive disorder characterized by characteristic facial features, severe pre- and postnatal growth restriction and normal mental development whereas mutations in PHIP gene are associated to the Chung-Jansen syndrome, an autosomal dominant disorder, mainly characterized by developmental delay, learning difficulties, behavioural abnormalities, facial dysmorphism and obesity.

Conclusion: I. presents a phenotype resulting from the overlap of 3M and Chung-Jansen syndrome, both very rare and caused in this patient by novel genetic variants. Co-occurrence of genetic disorders should be kept in mind especially in the presence of very complex phenotype.

P1-505

Changes in carbohydrate and lipid metabolism during 10-year follow-up of patients with Turner syndrome treated with growth hormone

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Background: Disorders in carbohydrate and lipid metabolism are more common in girls with Turner syndrome (TS) than in general population. Metabolic disorders have been identified as risk factors for the development of cardiovascular diseases. Additionally, TS patients are usually treated many years with growth hormone (GH) that affects the parameters of carbohydrate-lipid metabolism. Therefore cardiovascular risk factors should be monitored in TS girls.

Objective: To establish changes in carbohydrate and lipid parameters from the beginning of GH treatment through the subsequent years of therapy.

Patients and Method: Clinical and laboratory data was available for 89 TS patients at the beginning of GH therapy (V0) and after 1st(V1), 3rd (V3), 5th (V5) and 10th (V10) year of GH therapy for 60, 76, 50 and 22 patients, respectively. The patient's biochemical phenotypes were determined by glucose and insulin in OGTT (0'&120'), HOMA-IR, Ins/Glu (0') ratio, HDL-cholesterol and triglycerides (TG) concentration.

Results: BMI z-score V5 and V10 were higher to BMI Z-score V0 (pV0-V5=0.043, pV0-V10=0.023). Prediabetes was diagnosed at V0 point – in 3.4%, V1 - 6.7%, V3 - 6 7.9%, V5 - 8.0%, V10 - 9.1%. No patient met diagnostic criteria for diabetes. Changes in carbohydrate metabolism are presented in the Table. No statistically significant difference in the serum TG and HDL-cholesterol level during GH therapy were found.

Conclusion: Monitoring the basic parameters of carbohydrate-lipid metabolism in girls with TS seems to be particularly important. Our study confirmed the development of reversible insulin and carbohydrate metabolism impairment during GH therapy in girls with TS.

	Duration of GH therapy					
	V0 n=89	**V1 n=60**	**V3 n=76**	**V5 n=50**	**V10 n=22**	**p-value**
Glucose mg/dl	85.0 (78.0; 90.0)	91.0 (84.0; 98.0)	88.50(81.0; 95.8)	90.5 (84.5; 97.3)	85.5 (81.5; 95.5)	pV0-V1<0.001 pV0-V3=0.006 pV0-V5<0.001 pV0-V10=NS
Glucose 120', mg/dl	110.0 (89.0; 122.0)	119.4 (99.5; 139.8)	111.0 (100.0; 130.0)	107.9 (98.5; 126.0)	102.5 (93.3; 125.0)	pV0-V1=0.034 pV0-V3=NS pV0-V5=NS pV0-V10=0.046
Insulin 0', mIU/L	6.00 (3.0; 9.0)	14.5 (6.5; 78.5)	10.3 (7.0; 14.6)	13.0 (9.0; 17.1)	13.2 (9.8; 19.4)	pV0-V1=0.035 pV0-V3=0.011 pV0-V5=0.007 pV0-V10=0.008
Insulin 120', mIU/L	34.8 (14.0; 59.0)	37.0 (22.3; 74.8)	56.9 (35.0; 70.7)	59.0 (32.1; 84.2)	68.3 (46.1; 121.0)	pV0-V1=NS pV0-V3=0.001 pV0-V5=0.001 pV0-V10=0.001
HOMA-IR	0.94 (0.42; 1.44)	2.22 (1.36; 3.59)	2.03 (1.30; 3.07)	2.36 (1.61; 3.10)	2.44 (1.87; 3.08)	pV0-V1<0.001 pV0-V3<0.001 pV0-V5=0.001 pV0-V10<0.001
Ins/Glu	0.05 (0.02; 0.07)	0.12 (0.06; 0.15)	0.12 (0.08; 0.16)	0.11 (0.08; 0.17)	0.16 (0.11; 0.21)	pV0-V1=0.003 pV0-V3<0.001 pV0-V5<0.001 pV0-V10<0.001

P1-506

Characteristics, effectiveness and safety data for patients with growth failure treated with recombinant IGF-1 and achieving adult or near-adult height: results from the Increlex® Global Registry

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Background/Objective: Severe primary insulin-like growth factor-1 deficiency (SPIGFD) is a rare growth disorder. Recombinant human insulin-like growth factor (IGF-1) (rhIGF-1; Increlex® [mecasermin]) replacement therapy is EU- and US-approved for treating growth failure due to SPIGFD. The long-term therapeutic objective of rhIGF-1 treatment in SPIGFD is to improve adult height (AH).

Objective: to describe the characteristics, safety and effectiveness data for patients with growth failure receiving rhIGF-1 achieving AH or near-AH and elucidate the factors that predict treatment response.

Methods: The ongoing Global Increlex® Registry is a multicentre, open-label, observational study (in ten European countries and the USA) monitoring the long-term safety and effectiveness of rhIGF-1 in children and adolescents with SPIGFD (NCT00903110). Eligible patients: aged 2–18 years, received rhIGF-1 for growth failure due to SPIGFD.

Results: At data cut-off (03 October 2022), 101 patients reached AH; 66.3% (n=67/101) were male. SPIGFD diagnosis was reported in 86.1% (n=87/101) of patients; at Baseline, 56.4% of patients were treatment-naïve (n=57/101) and 45.5% (n=46/101) were naïve prepubertal patients (NPP). 58.2% (n=57/98) performed a genetic test. 18.8% (n=19/101) had Laron syndrome. **Table 1** summarises results for the overall and NPP populations. Multivariate analysis revealed height standard deviation score (SDS) (HtSDS) gain from rhIGF-1 initiation to final AH (FAH) in the NPP population (n=26) was higher in patients with lower Baseline HtSDS ($p<0.001$), higher predicted AH (PAH) ($p=0.028$) and higher biological mother height (BMH) ($p=0.039$). In the overall population, 66.3% (n=67/101) presented ≥1 treatment-emergent adverse event (TEAE). Hypoglycaemia was the most frequent TEAE and serious targeted TEAE.

Conclusions: There was a significant gain in HtSDS from rhIGF-1 initiation to FAH in patients with SPIGFD receiving rhIGF-1. Baseline HtSDS, PAH and BMH were predictive of HtSDS gain at FAH in NPP patients. Safety data are consistent with the profile of mecasermin.

Table 1.

		Overall population (N=101)	NPP population (N=46)
Age (years) at rhIGF-1 treatment	Initiation n Mean (SD)	101 11.7 (3.4)	46 10.0 (3.3)
	End n Mean (SD)	101 16.1 (2.7)	46 15.2 (2.9)
Treatment duration (years)	n Median Q1;Q3	101 3.9 2.3;5.9	46 4.6 3.5;7.0
Year 1 annualised height velocity (cm/yr)	n Mean (SD)	77 6.8 (2.4)	36 7.6 (2.3)
FAH SDS	n Mean (SD)	101 −2.8 (1.7)	46 −2.2 (1.4)
Difference between FAH SDS and HtSDS at rhIGF-1 initiation	n Mean (SD) 95%CI	91 0.9 (1.1) 0.7;1.1	42 1.4 (1.0) 1.1;1.7

CI: confidence interval; SD: standard deviation; Q1;Q3: lower/upper quartile

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P1-507

Identification and characterisation of novel *HMGA2* variants expand the clinical spectrum of Silver-Russell syndrome

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Background: Silver Russell syndrome (SRS) is a heterogeneous disorder characterised by intrauterine and post-natal growth retardation, relative macrocephaly, protruding forehead, feeding difficulties and body asymmetry. Variants in *HMGA2* are a rare cause of SRS and despite strong evidence for the crucial role of HMGA2 in growth regulation, its functional role in human linear growth is unclear.

Methods: Patients with variants in the *HMGA2* gene were phenotyped. Single nucleotide substitutions were created by mutagenesis of an N-terminal FLAG tagged-*HMGA2* cDNA whilst a frameshift construct was customized to recapitulate reading frame extension. HMGA2 protein expression and nuclear localisation were assessed by immunoblotting and confocal microscopy. Two *Hmga2* knock-in mouse models were generated by CRISPR/Cas9 technology.

Results: We report five novel variants in five unrelated individuals (height SDS ranging from -3.2 to -3.9) occurring in different critical regions of the *HMGA2* gene. These include two stop-gain nonsense variants (c.49G>T, c.52C>T), two frameshift variants (c.144delC, c.145delA) leading to an identical prolonged protein and a missense variant, c.166A>G (p.K56E), located in the linker 2 region of HMGA2. Phenotypic features were highly variable. However, microcephaly appeared to be a highly penetrant and consistent feature in these patients. Nuclear localisation was markedly reduced or absent for all variants except c.166A>G. Transgenic mice homozygous for *Hmga2*$^{\text{K56E}}$ present with significant growth impairment and demonstrate for the first time, that a single amino acid change located outside of AT-hook domains, can modulate growth in mice. A further *Hmga2*$^{\text{Ter76}}$ knock-in mouse model for a Hmga2 protein lacking a functional third AT-hook and the C-terminus, results in a pygmy phenotype and infertility.

Conclusions: We report a heterogeneous group of individuals with SRS harbouring variants in *HMGA2* and describe the first *Hmga2* missense knock-in mouse model (*Hmga2*$^{\text{K56E}}$) causing a growth restricted phenotype. In undiagnosed patients with clinical features of SRS but negative molecular/genetic analysis, *HMGA2* testing should be considered, particularly in those presenting with microcephaly.

P1-508

Placental measurements in relation to gestational age (GA) and fetal growth Characteristics (SGA, AGA and LGA) in a large Cohort in Qatar(n = 80722)

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Background: Epidemiological studies have shown associations between placental weight (PW) and perinatal and postnatal linear growth and weight gain.

Objectives: To report trimmed placental weight (PWT) and evaluate their association with birth weight (BWT), and gestational age (GA) in a large cohort of mother/ baby pairs in Qatar. (n = 80722).

Methods: Retrospective data analysis of 80722 births, in Hamad Medical Corporation Hospitals for 4 years (2016 - 2019) in Qatar. The data was retrieved from routinely collected hospital data. The inclusion criterion for this analysis was term singleton live births, 37+0 to 42+6 weeks gestation.

We classified newborn sizes based on gestational age and birthweight, into SGA (<10th percentile), AGA (between 10th and 90th percentiles) and LGA (> 90th percentile) using intergrowth-21st standards. In addition, we also explored placenta to birth weight ratios and estimated newborn proportions (%) for each gestational age group (sex not included).

Results: Overall, the mean birth and placenta weights were 3282 ± 439 and 661 ± 104 grams respectively. For each newborn size, these were AGA (3223 ± 313), SGA (2512 ± 247), and LGA (3938 ± 273) while placental weights were AGA (651 ± 88), SGA (550 ± 103) and LGA (766 ± 106) grams. Birth weights and placenta weights were directly proportional to the size of the baby. This relationship was converse in the placenta weight to birth

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Table 1: Placenta to Birth weight ratio in SGA, AGA & LGA

GA	Newborn size (Intergrowth-21st)	Proportion (%) <10th centile	Proportion (%) between 10: 90th centile	Proportion (%) >90th centile
37 weeks	AGA	9.4	81.8	8.7
	SGA	12.9	54.4	32.7
	LGA	11.2	82.8	6.0
38 weeks	AGA	9.7	81.2	9.2
	SGA	12.4	54.0	33.6
	LGA	10.7	83.3	6.0
39 weeks	AGA	9.4	81.8	8.8
	SGA	12.2	48.6	39.2
	LGA	12.7	82.3	5.0
40 weeks	AGA	9.5	82.3	8.2
	SGA	10.1	47.5	42.5
	LGA	13.2	81.5	5.3
41 weeks	AGA	9.6	82.3	8.1
	SGA	10.3	50.1	39.6
	LGA	12.8	82.1	5.1
42 weeks	AGA	8.1	85.1	6.8
	SGA	11.5	60.7	27.9
	LGA	24.2	69.7	6.1

weight ratio where the SGA babies had higher mean PW/BWT ratios; AGA (0.203), SGA (0.219) and LGA (0.195) (table 1). The proportion of SGA babies who had PWT/BWT ratios above 90th percentile for each respective GA group ranged from 28% to 43%.

Conclusion: Placental measurements are powerful independent predictors of birth weight. An increased PWT/BWT ratio in SGA babies indicates that nutrient transfer, per gram placenta, is reduced, supporting rodents' studies.

P1-509

Significant height response to growth hormone treatment in subjects with Wiedemann Steinert syndrome

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Background: Wiedemann Steinert Syndrome (WSS) is characterized by distinctive facial features (hypertelorism, thick eyebrows, long philtrum, broad nasal bridge), growth retardation, and intellectual disability of varying degrees. Affected individuals are often born small for their gestational age and have generalized hypertrichosis. Some have growth hormone deficiency, usually partial with normal pituitary MRI. The disease is caused by autosomal dominant variations in the KMT2A gene. The prevalence is estimated at 1/25,000 - 40,000 but may be underestimated. Differential diagnoses include Cornelia de Lange syndrome, Coffin-Siris Syndrome, Kabuki syndrome…

The height response to growth hormone treatment in this syndromic cause of short stature is unknown.

Objectives: We report the height response to growth hormone treatment in 6 subjects with molecularly proven WSS.

Results

Values are median (Lower limit; upper limit)	WSS
Birth height (SDS)	-1.5 (-2.5; -1)
Birth weight (SDS)	-0,5 (-2; 1)
Target height (SDS)	-0,5 (-2; 1)
Gestational age (WA)	36 (30; 40)
Gender (M/F)	F
GH peak to insulin induced hypoglycemia (μg/L)	14,1 (1,5; 105)
IGF-1 (ng/mL)	34,5 (4; 424)
Indication for GH treatment	SGA, GHD
Mean GH dose (μg/kg/d)	60 (60; 75)
Age at GH treatment (yr)	2,5 (1,5; 13,3)
Height at GH treatment onset (SDS)	-3,8 (-6,5; -2,5)
Height at 1 yr (SDS)	-2 (-5,5; -1)
Height at 2 yrs (SDS)	-0,85 (-5; -0,5)
Mean TT duration (yrs)	6 (1,5; 13)
Height at last measurement (SDS)	-1,8 (-2,2; -0,5)
Adult height if available (n)	152 (147; 160)
Adult height if available (SDS)	-1,8 (-2,8; -0,5)

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Conclusion: WSS subjects showed a remarkable response to growth hormone which is unusual in both idiopathic GHD and SGA subjects (total height gain from the literature + 1.3 SDS), and close to what is seen in deep organic GHD.

We believe that a trial of GH treatment can be offered to affected subjects.

P1-510

Tuberous sclerosis complex 1 (TSC1) deficiency leads to increased proliferation of adipose progenitor cells – case report and in vitro studies

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Introduction&Aim: Activation of mechanistic target of rapamycin (mTOR) as a major regulator of adipogenesis and lipid accumulation is controlled by upstream regulators hamartin/tuberous sclerosis complex (TSC) 1 and tuberin/TSC2. Hamartin and tuberin form a protein complex that inhibits signal transduction to mTOR. The impact of TSC1 deficiency is not clearly defined in human adipose tissue. We identified a likely pathogenic TSC1 splicing variant in a lipoma of a 10year-old boy with developmental delay and potential tuberous sclerosis. We aim to assess the effect of this TSC1 variant on adipogenesis and proliferation of adipose precursors and we will establish a cell model to test potential therapeutic options.

Methods: To establish an in vitro model we used siRNA knockdown of TSC1 in SGBS and LipPD1 lipoma cells. We examined proliferation and adipocyte differentiation of TSC1 KD vs. control cells using Hoechst stain for cell nuclei and Nile Red as well as Oil Red O stain for lipid accumulation. Gene expression of adipogenesis markers was measured by qPCR, activation of mTOR and downstream effectors was assessed via Western blotting with phosphospecific antibodies.

Results: The boy presented with a large lipoma within the right gluteal muscle. To our knowledge, lipomas located elsewhere than in the renal region have not yet been described as part of the phenotypic spectrum of tuberous sclerosis. In the lipoma tissue we identified a loss of heterozygosity on chromosome 9 starting in the region 9q32 to 9q34.3 including TSC1. An mRNA analysis conducted in blood and lipoma showed that in lipoma tissue only the alternative, truncated transcript was expressed. Preliminary in vitro analyses in preadipocytes with TSC1 knockdown suggested a higher proliferation of TSC1 KD cells compared to control cells. There was no significant effect on lipid accumulation and expression of adipogenesis markers PPARγ, adiponectin and FASN. We detected an increased phosphorylation of ribosomal protein S6 in TSC1 KD cells, phosphorylation of other mTOR targets was not altered.

Conclusion: We conclude that the variant in TSC1 is probably causative for increased proliferation of preadipocytes leading to lipoma formation and a therapy with mTOR inhibitors may be beneficial.

P1-511

Pathway to assess severe primary IGF-1 deficiency diagnosis by using the IGF-1 generation test in a real-life setting: data from the Global Increlex® Registry

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Background/Objective: Severe primary insulin-like growth factor-1 deficiency (SPIGFD) is a rare growth disorder, for which insulin-like growth factor-1 (IGF-1) generation test (IGFGT) is debated as a complementary diagnostic analysis. Diagnostic workup for SPIGFD varies geographically and diagnosis is delayed by the rarity of the condition (<1/10,000). Evaluation of real-world practices of IGFGT could help facilitate diagnosis and test use.

Objective: to describe real-life IGFGT results from patients with SPIGFD in the Global Increlex® Registry.

Methods: The ongoing Global Increlex® Registry is a multicentre, open-label, observational study (in 10 European countries and the USA) monitoring the long-term safety and effectiveness of recombinant human IGF-1 (rhIGF-1; Increlex® [mecasermin]) in children and adolescents with SPIGFD (NCT00903110). Eligible patients: aged 2–18 years of age, received rhIGF-1 for growth failure due to SPIGFD.

Results: At data cut-off (03 October 2022), 85.4% (n=263/308) of enrolled patients had a SPIGFD diagnosis; 14.6% (n=45/308) had Laron syndrome (LS) and 62.0% (n=191/308) were naïve patients with SPIGFD. IGFGT was reported in 42.4% (n=128/302) of enrolled patients; 44.7% (n=115/257) of patients with SPIGFD, 63.6% (n=28/44) of patients with LS and 45.5% (n=85/187) of naïve patients with SPIGFD. Between countries, IGFGT ranged from 100% (n=22/22) in Poland to 22.5% (n=18/80) in France. In naïve patients with SPIGFD, ΔIGF-1 (ng/mL) was <15 in 64.2% (n=52/81) and ≥15 in 35.8% (n=29/81). ΔIGF-1 (ng/mL) was <15 in all naïve patients with SPIGFD with LS. **Table 1** presents ΔIGF-1 (ng/mL) <15 and ≥15 subgroup results for naïve patients with SPIGFD; multivariate analysis demonstrated age at rhIGF-1 initiation (rII) was predictive of IGF-1 stimulation response.

Table 1.

		ΔIGF-1 (ng/mL)		
		<15 (n=52)	**≥15 (n=29)**	**Univariate analyses (p-value)***
Pubertal at rII	n (%)	4 (7.7%)	2 (6.9%)	-
Age at rII (years)	Mean (SD) 95%CI	6.8 (4.0) 5.7;7.9	10.3 (3.3) 9.0;11.5	<0.001**
Basal IGF-1 (ng/mL)	Mean (SD) 95%CI	39.0 (36.9) 28.8;49.3	65.7 (33.8) 52.9;78.6	0.005
Height SDS at rII	n Mean (SD) 95%CI	43 -4.2 (1.9) -4.7;-3.6	25 -3.2 (0.9) -3.6;-2.8	0.029

*Significance level of 0.05; **Significant in the multivariate analysis. CI: confidence interval; SD(S): standard deviation (score)

Conclusions: In patients diagnosed with SPIGFD, IGFGT was performed in >40.0%. However, there is geographic heterogeneity. ΔIGF-1 (ng/mL) ≤15 was reported in >60.0% of naïve patients with SPIGFD; ΔIGF-1 (ng/mL) increased with age at rhIGF-1 initiation. All naïve patients with SPIGFD with LS had ΔIGF-1 (ng/mL) <15.

P1-512

Growth and final height of adolescents with systemic juvenile idiopathic arthritis in the transitional age: a monocentric case series

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Introduction: Systemic Juvenile Idiopathic Arthritis (sJIA) is an autoinflammatory disease, characterized by the association of arthritis with fever, often accompanied by rash, generalized lymphadenopathy, hepatosplenomegaly, and serositis. The diagnosis requires adequate exclusion of infectious, autoimmune, autoinflammatory, and oncologic diseases. These patients need to be treated with glucocorticoids plus biologic drugs, anti-IL-1 or anti-IL-6 monoclonal antibodies. The glucocorticoids dose sparing is useful to permit a better growth and pubertal development.

However, chronic inflammation, chronic stress, malnutrition are additional factors that contribute to growth and pubertal impairment.

Materials and Methods: We evaluated a case series of 14 patients (7 M; 7 F; age at the diagnosis: 8-14 years), with an evolution of the disease monocyclic (4/12); polycyclic (7/12); persistent (1/12). All the patients reached the final height.

Results: All the patients were treated with glucocorticoids for a variable period, plus biological drugs (tocilizumab: 21%; anakinra: 7%; canakinumab: 72%). All the patients reached the final height, and their stature was in the target height. Puberty was reached in the physiological time in 12/14 patients (86%); 2/14 males showed a pubertal delay, secondary to prolonged glucocorticoid treatment, maintained during the pubertal age. However, they completed puberty, after the glucocorticoid discontinuation. None of the females showed oligomenorrhea or amenorrhea.

Conclusions: Adolescents with sJIA have a growth delay and/or impairment secondary to chronic inflammation, glucocorticoids, malnutrition, chronic stress. Long-term treatment with glucocorticoids compromises growth velocity and pubertal development.

Most of our patients, started biological drugs in an early window of treatment opportunity, with a significant improvement of growth prognosis. Growth and pubertal delay were associated with a worsen response to treatment and a late start of biological drugs. We highlight the role of the early introduction of anti-IL-1 or anti-IL-6 treatment, as glucocorticoids dose sparing and the winning strategy to reach target height.

P1-513

Efficacy of Once-Weekly Treatment for Paediatric Growth Hormone Deficiency: A Systematic Literature Review and Indirect Treatment Comparison

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Introduction: Paediatric growth hormone deficiency (pGHD) is a rare disorder characterised by inadequate secretion of growth hormone (GH). Daily injections of somatropin, a recombinant human GH, is the standard of care. Once-weekly GH treatments have been recently developed, but no direct comparisons have been published. This study examined the clinical efficacy of the available once-weekly treatments vs. daily treatment for pGHD via a systematic literature review (SLR) and indirect treatment comparison (ITC).

Methods: An SLR aimed to identify phase three trials of weekly treatment for pGHD. Results were used to conduct an ITC of available treatments. The base case employed Bucher ITC methods to estimate, at 12 months, annualised height velocity (HV), change in height standard deviation score (SDS), and change in bone maturation (BM). Frequentist random-effects meta-analysis was used in the sensitivity analyses. An established and a prespecified non-inferiority margin of -1.8 cm/year was used in follow-up analyses for annualised HV.

Results: The SLR identified four relevant trials of three once weekly GH interventions: somatrogon, lonapegsomatropin, and somapacitan. In the base case analysis, somatrogon was non-inferior to lonapegsomatropin (mean difference [MD]: -0.57; 95% confidence interval (CI): -1.43, 0.29) and somapacitan (MD: 0.83, 95% CI: -0.03, 1.69) in annualised HV. No statistically significant differences were found for changes in BM or height SDS between somatrogon versus lonapegsomatropin or somapacitan. Results of sensitivity analyses were consistent with the base case.

Conclusion: This research demonstrated that once weekly somatrogon was as efficacious as once weekly lonapegsomatropin and somapacitan for pGHD in the evaluations HV, BM and height SDS. Further, weekly treatment is as efficacious as daily treatment as reported in primary trial results. Studies on patient preferences and adherence between weekly and daily treatment would be beneficial to further demonstrate the benefits of weekly treatment for pGHD.

P1-514

Addition of genetic workup in children with isolated short stature to improve the diagnostic yield for growth hormone treatment

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Introduction: Short stature is a common finding that affects per definition about 3% of the population. Isolated, severe short stature may be treated successfully with recombinant human growth hormone (rhGH). Currently, rhGH is offered to short children with specific disorders or biochemically proven growth hormone deficiency (GHD). However, biochemical testing for GHD is artificial and therefore controversial. Adding genetic testing may improve the diagnostic workup.

In this pilot study, we performed whole exome sequencing (WES) in children with isolated short stature with biochemically proven GHD or severe idiopathic short stature (ISS) with a normal growth hormone stimulation test to evaluate the added value of a molecular diagnosis.

Methods: Individuals were divided into groups: A) patients with isolated GHD and GH test peak <7ng/dl (13/30, 43.3%); B) isolated GHD and GH test peak 7-10ng/dl (10/30, 33.3%), and C) ISS with GH test peak >10 ng/dl (7/30, 23.3%). WES was performed and analysed with a specific, in-house data filtering algorithm tailored for growth disorders. We used several in silico tools to predict the impact of gene variants and searched for disease-causing variants in literature and in HGMD and ClinVar. Variants were classified according ACMG guidelines.

Results: So far, we studied 30 children with isolated GHD or ISS that are part of a larger study from the University Children's Hospital Bern. We identified 17 disease causing or candidate gene variants in 13 of 30 patients (43.3%). These were from group A (6/13, 46.1%), followed by group B (5/10, 50.0%) and group C (2/7, 28.6%). Three variants were found in genes that are involved in the GH/IGF axis (GH2, POU1F1, STAT5B), four in components of cartilage extracellular matrix (ACAN, HSPG2, PRG4), five in components of fundamental cellular processes (ARID1B, OCRL, PTCH1, SH3BP2, TP63), four in genes involved in intracellular pathways (PTPN11, RAF1) and one variant in other genes related to syndromic SS (RUNX2).

Conclusions: We identified disease-causing or candidate variants in almost half of the children with isolated, severe short stature in a broad range of genes. These were found in children with isolated GHD and ISS, thus correlation with biochemical testing seems poor. No genotype-phenotype correlation was observed.

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The high diagnostic yield of WES in the workup of short children demonstrates the added value of a molecular diagnosis. Genetic testing, together with auxiological and biochemical methods may improve the current clinical routine care of patients with short stature and rhGH.

P1-515

Two novel cases of CHOPS syndrome support the evidence of a highly homogeneous phenotype including short stature with skeletal abnormalities and obesity

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CHOPS syndrome is a rare monogenic disorder caused by heterozygous gain-of-function variants in AFF4. The 13 patients reported to date share a highly recognizable phenotype: Coarse face, Cognitive impairment, Heart defects, Obesity, Pulmonary involvement, Short stature and Skeletal dysplasia. AFF4 encodes a scaffold protein involved in transcriptional elongation and critical for gene expression regulation during embryogenesis. Notably, it appears to regulate adipogenic differentiation via autophagy; his overexpression enhances adipogenesis in mice models.

We report two additional cases of CHOPS syndrome.

Patient 1 is 13 years old. During pregnancy, IUGR, polyhydramnios, and rhizomelic shortening were reported. At birth, weight was adequate (-0.92 SD); he showed patent ductus arteriosus, mild dilatation of ascending aorta, recurrent pulmonary infections, conductive hearing loss, strabismus and cataracts. He has moderate intellectual disability with speech impairment; mild, nonspecific anomalies were found at brain MRI.

From the first months of life, he has displayed severe short stature (-4 SD) with adequate bone age; GH deficiency was ruled out. He underwent progressive weight gain due to hyperphagia; currently he shows severe obesity (BMI 32 kg/m2) and has been on liraglutide from the age of 12. Spine X-ray revealed decreased height and ovoidal shape of dorsal vertebral bodies.

Patient 2 is 2 years old. Prenatal ultrasounds showed short femur length. Birth weight was 2700g (- 1.68 SD), length was 47 cm (-1.75 SD), OFC 32.5 cm (-1.72 SD). At birth, distal hypospadias, sensorineural hearing loss and cataracts were observed. He was diagnosed with multiple ventricular septal defects and underwent two heart surgeries. After the second surgery he developed chronic lung disease, probably multifactorial. He shows severely delayed neurodevelopment.

At the last auxological evaluation at 2 years, short stature (-3.9 SD) and overweight (BMI 90th centile) were evident.

Both patients share peculiar dysmorphic features: brachycephaly, thick and arched eyebrows with synophrys, long and curved eyelashes, anteverted nares, long philtrum, brachydactyly.

In patient 1, WGS identified the AFF4 most recurrent variant c.772C>T (p. Arg258Trp). In patient 2 we performed targeted sequencing of AFF4 mutational hotspot, detecting another recurrent variant c.760A>G (p. Thr254Ala). Both mutations occurred de novo.

Our patients share highly similar features to previously reported cases, confirming the presence of a core phenotype. Despite a partial overlap with CdLS, some distinct features (obesity, pulmonary involvement and skeletal findings) can lead to a targeted diagnosis. This condition should be kept in mind in differential diagnosis of syndromic obesity with hyperphagia.

P1-516

Analysis of Pubertal Height Gain after Menarchal girls in Korea

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Purpose: Both timing of menarche and growth patterns have changed with time. Menarche is supposed to important role in pediatric linear growth. This study is aimed to investigate the relationship between the timing of menarche and pubertal growth, specifically to analyze when menarche occurs related to the pubertal growth spurt, and how the pubertal height gain is related to the timing of menarche.

Method: From January 2022 to June 2022, 44 girls aged 12 to 16 years who visited the pediatrics outpatient clinics for adolescent developmental evaluation were included. Pubertal growth and predicted adult height (PAH) were analyzed before and after the timing of menarche. Eight patients were excluded by using recombinant growth hormone. The patients were divided into two groups by use of GnRH agonist or not. Among 35 patients, 27 girls (77.1%) was treated by GnRH agonist. The differences in the auxological data, menarche onset and predicted final adult height were compared using Mann-Whitney U test. Bone age was determined by the method of Greulich and Pyle. Predicted adult height was analysed by BoneXpert version 3.1 (https://bonexpert.com)

Results: Among 35 patients, adult height was reported in 6 children (17.1%) which defined as height at age ≥18 years, bone age ≥16 years, and/or a height velocity <1 cm/year. The mean menarche age with GnRH agonist was delayed (11.5 ± 1.0 vs. 12.1 ± 1.7, respectively). The mean PAH were 156.7 ± 1.8 in normal group and 160.0 ± 1.8 in GnRH agonist group before menarche. After menarche, mean PAH were 157.0 ± 0.7 in normal group and 160.5 ± 0.9 in GnRH agonist group. The pubertal height gains were more achieved in normal group 6.6 ± 3.9 vs. 4.9 ± 3.0 cm ($p < 0.05$).

Conclusion: The mean menarche age with GnRH agonist was delayed and predicted final adult height was higher than normal group. However, the later the age of menarche, the less pubertal height gains were achieved. There is a broad variation in pubertal growth, where menarche is one important factor for different growth patterns around puberty in girls.

P1-517

Bridging the gap between short stature and metabolic alterations in children born small for gestational age: an exploratory study

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Introduction: Children born small for gestational age (SGA) represent a heterogeneous population, displaying different phenotypes for both growth and metabolic status. Low birth length and/or weight increases the risks for not only growth impairment but also for metabolic derangements (cardiovascular disease, hypertension and type 2 diabetes), the latter with an even amplified risk in children with rapid postnatal weight gain. Variability in metabolic parameters, catch-up growth and different GH treatment responses are still poorly understood.

Aims: We investigated a possible association between anthropometric/metabolic parameters in SGA children.

Methods: This cross-sectional observational study evaluated a series of 32 children aged between 4 to15.7 years, with birth weight and/or length<-2.0SDS according to INeS Growth Charts. All patients with chronic conditions, GH deficiency, other endocrinopathies and genetic syndromes were excluded. Anthropometric (height-HT, Mid-parental height-MPH, weight, Body Mass Index-BMI, Tanner stage, body composition by Body Structure Analyzer BC-420MA TANITA) and metabolic (fasting glycemia and insulin, glycosylated haemoglobin-HbA1c) parameters were collected. Insulin resistance (HOMA-IR) and sensitivity (QUICKI) were calculated.

Results: Thirty-two SGA patients (F16/32,50%), with a mean age of 9.1±3.0 years were consecutively enrolled. In 18.7% of patients HT was below -2.0SDS. Mean HT was 126.5±15.2 cm, -1.09±1.13SDS according to WHO Growth Charts with a MPH distance (MPH SDS-HT SDS) of 0.62±1.10SDS. As far as glycemic profile was concerned, glycemia was in the normal range in all study patients apart from one with impaired fasting glucose (glycemia 107 mg/dL), mean glycemia was 83.3±8.5 mg/dL, mean HbA1c 34±3.1 mmol/mol, with a median HOMA-IR of 1.6 (IQR 0.9-3.1) and QUICKI of 0.35 (IQR 0.32-0.39). At multiple regression, HbA1c was positively associated with HT SDS (P=0.001) and negatively with MPH distance (P=0.017).

Conclusions: Our results suggest a relationship between postnatal catch-up growth and metabolic impairment, as underlined by the association found between HT and HbA1c, even after correction for MPH. This is only an explorative analysis; we would like to confirm our results on a larger scale. Moreover, considering that Fibroblast Growth Factor-21 (FGF-21), acting with its cofactor β-klotho, has recently emerged as a "starvation hormone" with a key role in the glucose metabolism regulation but also, interacting with GH/IGF-I axis, in longitudinal growth and growth hormone resistance, we ought to investigate FGF-21/β-Klotho system in our cohort in order to eventually bridge the gap between height gain and metabolic impairment in children born SGA.

P1-518

Outcomes of growth hormone treatment in children with Prader Willi Syndrome over a 30-year period at the Children's Hospital at Westmead, New South Wales Australia

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Background: Prader-Willi syndrome (PWS) is a rare genetic obesity syndrome associated with relative growth hormone deficiency. Scoliosis is a known association of both PWS and growth hormone therapy (GH), although its role in causation remains uncertain. In the literature, short-term and long-term data revealed no adverse effects of GH on scoliosis. As the metabolic and clinical benefit of growth hormone therapy is established in the management of PWS, it is difficult to conduct a randomized controlled trial of the effect of growth hormone therapy in PWS. However, the potential adverse effects of growth hormone therapy remain an important consideration. This study aims to determine whether growth hormone therapy increases the risk of scoliosis in children with PWS.

Design and Method: This is a retrospective, descriptive study evaluating data of patients aged 0-18 years with PWS, who received growth hormone therapy between March 1992- December 2022. Scoliosis was defined as Cobb's angle of more than 10 degrees; with severity based on Cobb's angle categorized as mild 11-20; moderate 21-40; severe >40 degrees.

Results: This cohort comprised of 73 patients aged 0-18 years (female 53%) from 1992-2022. Scoliosis was detected in 34% of patients (a total of 25; 14 females: 11 males). Mild scoliosis was diagnosed in 3 patients, moderate scoliosis in 10 patients, and severe scoliosis in 12 patients. The mean age at which scoliosis was first diagnosed was 9.12 years. Out of the 25 patients, 9 required braces to minimize the progression of scoliosis and 11 patients underwent spine surgery. There was no statistical difference in the median maximum growth hormone dose among the patients with scoliosis was 7.6mg/m2/week [IQR 7.45- 7.77] vs. patients without scoliosis 7.4 mg/m2/week [IQR 6.74-8.06] (p=0.17). In generalized estimating equations, sex, age, initial height, weight and maximum growth hormone dose per body surface area were not significant predictors of scoliosis.

Conclusion: In this single-center study spanning 3 decades, there were no significant clinical predictors identified in the presence of scoliosis in children with PWS. Our results suggest that the presence of scoliosis should not limit the routine dose of GH therapy in PWS. As described previously, our findings confirm the high prevalence of scoliosis in PWS and thus the need for close surveillance.

P1-519

Evaluation of Cognitive Profiles in a cohort of patients with Turner Syndrome

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Background: Turner Syndrome (TS) is a chromosomopathy affecting 1 out of 2000-2500 live births. Although short stature, heart disease and ovarian dysgenesis are the best-known features, patients have variable cognitive impairments. Aim of this study is to analyze the cognitive profile of a cohort of patients enrolled between February 2018-March 2023.

Methods: 49 TS patients [Group A: 45, X0 (n=13); Group B: mosaicism (n=14); Group C, X-ring chromosome (n=5); Group D, miscellaneous karyotypes (n=17)] were assessed using Wechsler Scales: WISC IV (6-16.11 years), WAIS-IV (≥ 16 years) and WPPSI-IV (2.6-3.11 years). The parameters measured for each scale were the intellectual quotient (IQ), the Verbal comprehension index (VCI), the Perceptual Reasoning Index (PRI), the Working Memory Index (WMI), and Processing Speed Index (PSI). Information's about pubertal development and growth hormone (rhGH) therapy were collected.

Results: Mean age at cognitive evaluation was 15,02 ± 7,69 (range 3,03-34,08, median 15,04). Regarding puberty, 13 patients (26%) were prepubertal, 28 patients (57%) were under hormone replacement therapy (HRT) at the time of evaluation; 8 patients (16%, 7 Group B and 1 Group A) have spontaneous puberty. Regarding GH treatment, 9 patients (18%) were GH naïve (awaiting treatment), 22 patients (48%) were under treatment and 18 patients (36%) have reached adult height discontinuing rhGH.

The median overall IQ score was (73,12 ± 17,59 SDS; range 34-103) significantly lower in group C (52,4 ±12,13; 34-65) compared to other patient's groups (p=0,03 to Group A, p=0,057 to Group B, and p=0,007 to Group D). Twenty-one patients (42%) had overall IQ score lower than normative data (42% of Group A, 28% of Group B, 100% of Group C and 35% of Group D). No differences were found in IQ scores in patient with spontaneous puberty vs patients under HRT.

VCI, PRI, and PSI were significantly lower in patients of Group C compared to the patients of Groups B and D: although the VCI, PRI and PSI values were lower, no statistical differences were found between Groups C and A.

Conclusions: Distinct cognitive functioning is affected in TS and should be assessed during follow-up to avoid undiagnosed school/academic difficulties. Patients with X-ring chromosome have worse cognitive profiles than patients with different karyotypes. Cognitive assessments and interventions are warranted from an early age and should be part of healthcare assessment in order to enable these girls to develop their full potential.

P1-520

Does cervical medullary decompression have an impact on growth in children with achondroplasia?

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Background: Foramen magnum stenosis (FMS) is a life-threatening complication in children with achondroplasia (ACH) which may require cervicomedullary decompression (CMD). There is no evidence if FMS and CMD affects growth in children with ACH.

Aim: To evaluate the impact of FSM and CMD surgery on anthropometric measurements in children with ACH.

Methods: Sixty-five patients with ACH (32 females -F-, 33 males-M-) were evaluated between 4-6 yrs of age. Height SDS (H-SDS), weight SDS (W-SDS) and body mass index (BMI) SDS (BMI-SDS) were calculated according to Merker et al.

Results: Thirty-nine children (60%; 21 F, 18 M) underwent CMD, n= 21 (32%; 13 F, 8 M) within the first yr (mean 0.62±0.20 yrs) and n= 18 after the age of 1 yr (mean 1.84±0.84 yrs). Mean age at anthropometric evaluation was 5.2± 0.4 yrs. H-SDS of patients with CMD was significantly lower (-0.55±0.99 vs 0.85±1.24, P=0.01) and even lowest when CMD occurred after 1 yr of age (-0.81±0.95 vs 0.07±1.04, P=0.006). Furthermore, H-SDS was more affected in M (-0.90±1.06 vs-0.10±1.22, P=0.01) than F. There were no significant differences in BMI-SDS, but in patients without FMS W-SDS was significantly higher than in patients underwent CMD after 1 yr of age (-0.07±1.22 vs -0.86±0.97, P=0.03).

Conclusions: H-SDS evaluated at the age of 5 years is more affected in children with ACH who underwent CMD. Furthermore, height and weight appear to be influenced by age at the time of surgery. Our data suggest that FMS and/or CMD may have a negative impact on growth in children with ACH, and that early initiation of medical therapy is desirable in these children.

P1-521

A variant of uncertain significance in *HMGA2* gene, in a 2-year-old child with Silver Russel syndrome like phenotype - a case report

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Introduction: Silver-Russell syndrome 5 (SRS5) is characterized by asymmetric intrauterine growth restriction (IUGR), poor postnatal growth, macrocephaly at birth and feeding difficulties. Other possible features include triangular shaped face, prominent forehead, hypertelorism, epicanthus, micrognathia, brachydactyly, clinodactyly of the 5th hand finger, and syndactyly of the 2nd and 3rd toe fingers. Pathogenic variants of the *HMGA2* gene, on chromosome 12q14, which regulates the transcription of the growth factor IGF2, have been recently associated with this syndrome.

Aim: Herein we present a 2.5-year-old boy with growth delay, SRS-like phenotype, and a variant of uncertain significance in the *HMGA2* gene, which hasn't been described yet in the medical literature.

Material and Methods: A 2.5-year-old boy was referred due to growth delay. From the perinatal history he was born at gestational age of 37 weeks. His birth weight was 2260gr and birth length 46cm (IUGR). The family history was unremarkable. The clinical examination showed a triangular face, hypertelorism, micrognathia and long eyelashes. Rest examination was normal. Furthermore, his weight (8kg) and height (75cm) were from birth, below the third percentile. Cardiac examination, renal ultrasound, hormonal and basic laboratory tests including celiac disease antibodies were found to be unremarkable. His bone age was delayed by 7 months. In view of his clinical features, a genetic consult was requested.

Results: In view of normal Array Comparative Genomic Hybridization (aCGH) and negative result for epimutation at chromosome 11p15 and maternal uniparental disomy of chromosome 7, a Whole Exome Sequence (WES) was revealed the variant c.111+5G>A in the *HMGA2* gene, which may cause a disruption in the splicing process and is being considered as a variant of uncertain significance (VUS). At last, our patient was commenced on replacement therapy with recombinant human growth hormone (HGH) with a good response.

Conclusion: SRS presents a large genetic heterogeneity. Genetic testing confirms the diagnosis in 60% of SRS cases. Except for the epimutation of the imprinting center region 1 (ICR1) on chromosome 11 or the maternal uniparental disomy of chromosome 7 (matUPD7), twenty-eight pathogenic variants in the *HMGA2* gene, in patients with clinical SRS phenotype have been recently reported. Therefore, *HMGA2* gene testing should be always checked in the SRS patients that are found negative for the typical 11p15 (epi) mutations and matUPD7, as well as be added to growth retardation disorder panels. To the best of our knowledge, the above-mentioned variant hasn't been described yet in the medical literature.

P1-522

ACAN gene mutation in a patient born small for gestational age with familial short stature

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Introduction: Aggrecan, encoded by the ACAN gene, is an important component in the cartilage extracellular matrix. Mutations in the ACAN gene have been associated with idiopathic and familial short stature in the recent years. Bone age (BA) is often advanced, although it can be delayed or normal. Patients can have dysmorphic features like broad forehead, midfacial hypoplasia, prognathism, posteriorly rotated ears, broad and short thumbs. Bone and joint problems can be present. Despite that the growth hormone-IGF-1 axis is usually normal, growth hormone (GH) has been successfully used for treatment with or without gonadotropin releasing hormone agonists (GnRHa). We report a patient with familial short stature due to ACAN gene mutation.

Case Report: A 4.3-year-old girl presented for the first time with short stature. She was the first child from an in vitro pregnancy. The mother had uncontrolled hypertension during pregnancy. At 4 months of gestation cerclage was performed and intrauterine growth retardation was established on ultrasound. Prenatal genetic testing was performed which was normal. Placental abruption led to emergency delivery at 34+5 g.w. The patient was born small for gestational age (SGA) with weight 1300 g (-2.6 SDS), length 38 cm (-2.63 SDS) and head circumference 28 cm (-2.19 SDS, Fenton charts). By 1 year of age her height reached the 3rd percentile but after 3 years it dropped below the 3rd percentile. Her father (152.9 cm) and mother (147.0 cm) are short while there are both very short and very tall relatives at father's side followed three generations back. At first presentation the patient's height was 93.3 cm (-2.62 SDS, https://www.cdc.gov/growthcharts/) and weight was 12.5 kg (-2.92 SDS). She had proportionate short stature, midfacial hypoplasia and short and broad thumbs. Her BA was 5.2 years (1.2 SDS, Greulich&Pyle by BoneXpert). Hormonal tests were unremarkable. On follow-up at 9.1 years her height was 117.5 cm (-2.9 SDS), weight was 21.5 kg (-2.21 SDS) and BA was 9.26 years (0.41 SDS). Hormonal tests were again normal. A brain MRI was performed which was unremarkable. Genetic analysis revealed a heterozygous mutation in the ACAN gene (c.6972G>A (pTrp2324)) inherited from the father. Due to her short stature the patient is indicated for GH treatment.

Conclusion: We describe a patient born SGA with familial short stature due to ACAN gene mutation. This is the first reported case in Bulgaria. Based on previous reports for treatment effectiveness, GH treatment is offered.

P1-523

A rare occurrence of non-classic congenital adrenal hyperplasia and type 1 diabetes mellitus in a girl with Prader-Willi Syndrome: Case report and review of the literature

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Prader–Willi syndrome (PWS) is a rare genetic disorder resulting from lack of expression of the paternally derived chromosome 15q11–13, associated with several complications, including pubertal disorders, short stature, hyperphagia, obesity, glucose metabolism abnormalities, scoliosis, obstructive sleep apnea syndrome (OSAS) and behavioral problems. We report the case of a girl affected by PWS who presented at the age of 5.9 with premature pubarche, accelerated linear growth and advanced bone age (BA). She was subsequently diagnosed with non-classic congenital adrenal hyperplasia (CAH) confirmed by genetic analysis. Considering the clinical, biochemical, and genetic findings, hydrocortisone therapy was started to prevent rapid BA acceleration and severe compromission of final height. During infancy, short stature and low levels of insulin-like growth factor-1 (IGF-1) for age and gender led to suspicion of growth hormone deficiency (GHD), confirmed by stimulation testing (arginine and clonidine). rhGH therapy was administered and continued until final height was reached. During endocrinological follow up she developed impaired glucose tolerance with positive markers of b-cell autoimmunity (anti-glutamic acid decarboxylase antibodies, GAD Ab), which evolved over time into type 1 diabetes mellitus and insulin therapy with a basal-bolus scheme and an appropriate diet were needed.

Years	2.4[Δ]	5.9	6.3[¤]	7.7*	8.4	9.0[#]	15.7^
	-	-	-	-	-	-	-
Auxological parameters							
Height (SDS)	-2.16	-1.04	-0.57	+0.14	-0.2	-0.36	-1.75
Weight (SDS)	-1.73	-1.35	-0.68	+0.06	+0.33	+0.35	-1.13
BMI (SDS)	+0.04	-1.0	-0.45	+0.16	+0.7	+0.8	-0.15
HV (SDS)	-2.3	+0.33	+4.7	+5.2	-0.63	-1.9	<2.0 cm/yr
Pubertal stage							
Breast	1	1	1	2	2	2	3
Pubic hair	1	2	2	3	3	3	5

*[Δ] rhGH was started (0,33mg/Kg·d); [¤] Patient and her parents were referred for genetic testing for non-classic CAH; *Hydrocortisone was started (20 mg/m^2); [#] Hydrocortisone was reduced (11.5 mg/m^2) and rhGH was increased; ^Hydrocortisone and rhGH were gradually reduced and stopped at the ages of 11.8 and 14.7 years, respectively.*

BMI, body mass index; CAH, congenital adrenal hyperplasia; HV, height velocity; SDS, standard deviation score.

P1-524

Two male siblings with extremely tall stature, moderate mental retardation and a deletion of ASH1L at chromosome 1q22

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Background: Several symmetric monogenic overgrowth syndromes with tall stature have been described, which is why children with syndromic tall stature should undergo comprehensive diagnostics. Tall stature has not been associated with chromosome 1.

Objective: To present height growth and diagnostics in two male siblings with extreme tall stature and moderate mental retardation. Both had a deletion of *ASH1L* at chromosome 1q22.

Case report: The siblings were born at term, with birth weight and length of 5220 g, 58 cm and 4820 g, 60 cm, respectively. Father's, mother's and sister's height were 193, 168 and 177 cm, respectively. Sibling 1 was referred 10.3year old with height of 173 cm (+ 5SD), and sibling 2 was referred 6.3year old with height of 138 cm (+ 4SD). The children were not disproportionate, but they had discrete dysmorphic features with epicanthus and slight swan neck deformity of their fingers. Both were moderately mental retarded. Both had a male 46XY karyotype, normal hormonal axes, and a normal magnetic resonance imaging of the brain including normal hypothalamus and pituitary anatomy. Sibling 1 was treated with testosterone injections to accelerate closure of the growth zones -final height was 215 cm. Sibling 2 refrained from testosterone treatment and refrained also from epiphysiodesis -final height was 223 cm. An array comparative genomic hybridization (BAC array CGH) and analysis for fragile X were normal (year 2010). Using next generation sequencing, whole exome sequencing was carried out on both siblings and parents. The siblings were analyzed for causal variants in genes known to be associated with tall stature (human phenotype ontology 28/03/2019) without identification of pathogenic variants, but confirmed paternity. An 180K array CGH conducted in 2021 revealed a 68 kb deletion of chromosome 1q22 including *ASH1L* in both siblings, but not in their parents and sister.

Conclusion: The two extremely tall male siblings with moderate mental retardation both had a large deletion at chromosome 1q22, including *ASH1L* known to code for a histone methyl transferase involved in epigenetic modification of chromatin. Variants in *ASH1L* have previously been associated with mental retardation. Pathogenic variants in genes coding for methyl transferases have been associated with symmetric overgrowth syndromes – e.g

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variants in *EXH2* at chromosome 7 causes Weavers syndrome and variants in *NSDL1* at chromosome 5 causes Sotos syndrome. Therefore, the deletion of the *ASH1L* at chromosome 1 in the siblings may explain both their mental retardation and their extremely tall stature.

P1-525

Human milk insulin-like growth factor-1 (HMIGF1) and its effects on Infantile and Childhood Growth

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Introduction: Accumulating evidence indicates various but significant effects of human breast milk IGF1 (HMIGF1) on infantile linear growth and weight gain.

Objectives and Methods: We performed electronic literature systematic review using PubMed, Google Scholar, and Web of Sciences with the aim to provide an update on various effects of HMIGF1 on infantile and childhood growth. We reviewed 12 studies (n = 941 infants) fitting the search criteria.

Results: Breast milk IGF1 was significantly higher in Obese and overweight infants (n= 40) versus normal-weight infant. A study on 103 mother-infant pairs (for 3 months) showed that the breast milk consumed by the infants with high weight gain contained higher levels of IGF-1 than that consumed by those with low weight gain at all periods studied (p = 0.032 at 3 months of lactation). In obese infants, HMIGF1 levels were correlated with infant's weight for length z-score at 2 months (r -0·476; P = 0·034).

Breast milk from mothers of moderate-late Preterm Infants (169 mothers of 191 preterm infants) showed that higher HMIGF1 concentrations on day 5 after birth was associated with greater infant fat-free mass at 4 months' corrected age. HMIGF1 concentrations at 4 months were positively associated with both fat mass and fat-free mass at 4 months in boys but not girls.

A study on 60 LBW infants discharged from NICU (35 infants (AGA) and 25 (SGA) showed that serum IGF-1 was positively correlated with HMIGF-I (r=0.5, p= 0.003). Both serum and breast milk levels of IGF-1 were correlated positively with various parameters of growth. Milk levels of IGF-1 were higher in mothers whose infants attained catch up growth compared to those who didn't attain catch up growth. In a large cohort study (501 mothers and the respective 507 infants) higher HMIGF-1 was associated with higher infant weight at 13 months (p = 0.004) but lower weight at 3 (p = 0.011) and 5 years of age (p = 0.049). Higher cyclic glycine-proline (cGP),(a metabolite of IGF-1) in milk, was associated with lower weight across the 5 years (p = 0.019) but with higher BMI at 5 years (p = 0.021).

Conclusion: These data provide evidence that the ingested milk-borne IGF-1 can affect the postnatal growth of infants and influence catch-up growth of LBW. Future work should expand on these findings and further explore the link between hormonal profiles in human milk and infant outcomes.

P1-526

The first description of neonatal progeroid syndrome (Wiedemann-Rautenstrauch syndrome)in the Russian Federation

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Introduction: Wiedemann-Rautenstrauch syndrome (WRS). or neonatal progeroid syndrome, is an orphan hereditary disease associated predominantly with bi-allelic mutations in the POLR3A, POLR3B, and POLR3GL genes and characterized by congenital lipodystrophy, progeroid facial features, and premature aging. Unlike Hutchinson-Gilford progeria, the clinical features of the syndrome are evident at birth. The prevalence of the disease is unknown; 19 proven clinical cases are described in the literature. The average life expectancy of patients is 7 months – 2 years. Patients most often die from sepsis caused by aspiration or bacterial pneumonia. There is no pathogenic treatment for the syndrome.

Materials and Methods: A 6-years-4-months-old girl with WRS, observed in the pediatric endocrinology department of the Sechenov Center for Maternity and Childhood, Moscow. The diagnosis was confirmed by full-exome sequencing.

Results: A girl from healthy unrelated parents, born from the 1st pregnancy, complicated with delayed intrauterine development, meningocele, and fetoplacental insufficiency from the 30th week of gestation. Delivery by Caesarean section at 37 weeks. Birth length 46 cm (SDS -2.20), birth weight 1840 g (SDS -4.27); born with noticeable absence of subcutaneous fat, hydrocephalic skull with prominent venous network in all regions, micrognathia, neonatal incisor of maxilla which fell out on its own on the second day of life.

At 2 years, she was first examined by geneticist, progeria was suspected.

At 6 years 4 months she was examined at the pediatric endocrinology department: height 99 cm (SDS -3.14), weight 10 kg (BMI 10.20 kg/m2, SDS -5.49); progeroid facial features; hypotrichosis of the scalp; generalized lipodystrophy with preserved isolated areas of subcutaneous fat in the neck, external genitalia, coccygeal region and foot area; limited mobility of the hip joints and interphalangeal joints of the hands.

Multisystemic lesions were revealed: endocrine (stunting, body weight deficiency, lack of subcutaneous fat); sceletal (scoliotic posture disorder, flexion contractures of hip and knee joints, osteoporosis; macrocrania, Arnold-Chiari type 1 anomaly, spina bifida C1); dermatological (irritant dermatitis of hands); cardiovascular (sinus tachycardia); pulmonological (bronchoobstructive syndrome); gastroenterological (chronic constipation); psycho-neurological (dysarthria); ophthalmological (retinal angiopathy, mild degree hyperopia, astigmatism).

Based on the history and phenotype data, WRS was diagnosed; compound heterozygous mutation c.3337-11T>C/c.3677T>C in the POLR3A gene was detected.

Conclusions: The presented clinical case expands our knowledge of premature aging syndromes. Early diagnostics of the disease allows differential diagnosis with other progeroid syndromes and determination of the optimal management plan for patients by a multidisciplinary team.

P1-527

Application of next-generation sequencing in patients suspected of having skeletal dysplasia

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Background: Skeletal dysplasias (SD) are a heterogeneous group of heritable conditions with generalized bone and cartilage impairment caused by pathogenic variants in genes primarily affecting skeletogenesis and/or bone homeostasis. In this study, we conducted a next-generation sequencing (NGS) in patients with a suspected SD to reveal the underlying etiologies of skeletal dysplasia.

Methods: Thirty-four pediatric patients with skeletal dysplasia were subjected to targeted exome sequencing study or NGS-based gene panel sequencing.

Results: The clinical and genetic diagnoses were confirmed in 27 out of the 34 patients, and the diagnostic yield was 79.4%. At the time of diagnosis, the average age was 5.93±8.5 years and the average height SDS was -1.84±2.12. In these patients, 34 variants were identified, of which, 14 (41.1%) pathogenic or likely pathogenic variants were found in 12 genes (NPR2, GORAB, LMX1B, ALPL, NBAS, MATN3, SHOX, SMAD3, COL1A1, COL1A2, COL2A1, FKBP10), and 16 were novel variants. In patients with skeletal involvement and other clinical manifestations including dysmorphisms or multiple congenital anomalies, and developmental delay, the diagnosis rate was much higher (11 out of 12, 91.7%) than in those who had isolated skeletal involvement only (16 out of 22, 72.7%).

Conclusions: NGS-based approaches can be useful for diagnosing SD which has clinical and genetic heterogeneity. In particular, considering the high diagnosis rate of patients with skeletal dysplasia and accompanying abnormalities, active genetic evaluation is necessary for them.

P1-528

Seasonality in growth of preschool children in Palestine ,a pilot study

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Introduction: Genetics, diet, and physical activity are just a few of the variables that determine child growth rates, but seasonal variations in these variables can also have an impact on growth patterns. Among kids aged four and five, we looked at the seasonality of changes in height, body weight, and BMI.

Methods: This was a pilot study carried out in Palestine at a private school where psychological factors could be ruled out and where all participants had a common background. Data was gathered every season's start for a year, from September 2021 to September 2022. Five readings were taken in all, the first in September 2021 at the beginning of autumn and the other four in 2022 at the beginning of December, March and June. The change in height, weight, and BMI throughout the year was examined using the Friedman test. For pairwise comparisons in post-hoc analysis, Dunn's test was applied if the Friedman test was significant ($p \leq 0.05$).

Results: Of 64 children approached, 60 children completed the needed measures throw-out the year and were included in the analysis. 53.3% (32) children aged 4 years and 46.6% (28) aged 5 years. 51% (31) of them were females.

Weight increment was statistically significant and was better during Autumn compared to all other seasons and was most significant compared to spring. However, weight change wasn't significant comparing other seasons. When compared to spring and summer, weight change among males was statistically significant in autumn. While females' weight changes were not significant.

In comparison to winter, height change was statistically significant and was better in the autumn and summer. Males' height change was better in autumn than it was in the winter, but it wasn't statistically significant elsewhere or in females.

Body mass index (BMI) was significantly different and was higher in Autumn compared to Spring, however no significant change found among other seasons. Alongside with weight and height change, males showed significant increment in BMI during Autumn compared to spring.

Conclusion: In terms of height, weight, and BMI, both the overall participant population and the male participants showed significant changes in the fall; however, the female participants did not exhibit any significant seasonal variations.

P1-529

A Rare Cause of Pathological Tall Stature: Luscan Lumish Syndrome

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Introduction: Luscan-Lumish syndrome (LLS) is a postnatal overgrowth syndrome characterized by macrocephaly, mental retardation, seizures, postnatal overgrowth, and developmental delay, caused by a heterozygous mutation in the SETD2 gene on chromosome 3p21, which exhibits autosomal dominant inheritance.

Case Report: A ten-year-old girl presented with menarche. She was born to healthy non-consanguineous parents at 37 weeks, 3100g (0.6SD), 56cm (4.5SD) and head circumference 38cm (3.78SD). She had a voracious appetite since infancy, walked at 18 months, spoke at two years, and her motor development lagged behind her peers. However, after the age of three, her growth increased compared to her peers. She was having tantrums. At admission, physical examination showed weight 59.2kg (+2.76SD), height 157.6cm (3.04SD), mid-parental height 163.8cm (0.11SD), body amss index 23.8 (+1.91 SD) and macrocephaly, short neck, long and dull face, prominent forehead, cubitus valgus, abdominal obesity, cafe-au-lait spot and scoliosis. She was Tanner stage 5, and bone age was two years advanced. Cranial and pituitary imaging were normal. Insulin-like growth factor levels were normal and GnRH analogue treatment was started with the diagnosis of central precocious puberty. On oral glucose tolerance test, impaired glucose tolerance and hyperinsulinism were detected while growth hormone was suppressed, and metformin was started. Mccune-Albright syndrome was excluded as no mutation was found in the GNAS gene. Luscan Lumish Syndrome was diagnosed after detection of the c.1322G>C (p.Arg441Pro) heterozygous missense novel pathogenic variant in the SETD2 gene on whole-exome sequencing (WES). On child psychiatry examination, it was reported that intellectual development was normal, but she had behavioral problems.

Discussion and Conclusion: LLS is characterized by overgrowth, mental retardation, speech delay, and behavioral problems; obesity, advanced bone age, autism, and seizures occur with variable frequencies. While seizures, autism, and mental retardation are observed in frameshift or nonsense mutations in SETD2, the mild clinical presentation in this case may be explained by the missense mutation. Rapid growth in children may be perceived as "healthy growth" by parents and may cause late presentation. When evaluating the pathological cause of tall stature, even if there is precocious puberty, in the presence of dysmorphic findings, genetic diagnosis and WES may be advisable, for optimal diagnosis and subsequent management of patients.

Multisystem endocrine disorders

P1-134

Molecular and Phenotypic Expansion of Bardet-biedl Syndrome in Chinese Patients

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Background: Bardet Biedl syndrome(BBS) is a type of non-motile ciliopathy primarily characterized by retinal dystrophy, obesity, polydactyly, cognitive impairment, urogenital anomalies and renal abnormalities. To date, 26 genes have been reported to be associated with BBS: *BBS1-BBS21*, *IFT74*, *SCLT1*, *SCAPER* and *NPHP1*. BBS is genetically heterogeneous with significant clinical overlap with other ciliopathies, further complicate the diagnosis of this syndrome. There are a few case reports of BBS patients in China, but no clinical data has been analyzed in detail. Thus, our study aims to describe the genotypic and phenotypic spectra of BBS in China, and elucidate genotype-phenotype correlation.

Methods: 20 Chinese patients diagnosed with BBS were enrolled, the clinical manifestations were documented and exome sequencing were performed. We compared the phenotypes between Chinese BBS patients and those with BBS in Spain, Germany and India to analyze the phenotype differences across patients worldwide. We also summarized all previously reported cases of Chinese BBS patients (94 patients) and identified common and specific variants in the Chinese population.Besides, genotype-phenotype correlation were described in our cohort.

Results: 20 BBS patients from 18 unrelated families were included in this study, aged from 5-34 years old, and 28 BBS variants, of which 15 are novel, in 5 different BBS-associated genes were confirmed. Mutations were predominant in *BBS2*(21.28%) and *BBS7*(17.02%), and the most commonly variants were *BBS2*:c.534+1G>T(10 alleles) and *BBS7*:c.1002delT(7 alleles), which were different from the genotypic spectra of BBS abroad. Comparing BBSome genes(*BBS2*,*7*,*9*) versus chaperonin-like genes(*BBS10*,*12*) phenotypes, we found that patients with chaperonin-like genes had an earlier age of onset($p < .01$) and diagnosis($p < .01$), while patients with BBSome genes BMI were higher($p < .05$) and more vision problems($p < .05$).

Conclusion: We recruited 20 Chinese BBS patients for genetic and phenotypic analyses, identified common clinical manifestations, pathogenic genes and variants in Chinese BBS patients. We also described the phenotypic differences across patients worldwide and different BBS-associated genes. This is the largest cohort of Chinese BBS patients, expanding the spectrum of the genotypes and phenotypes associated with this condition.

P1-135

A novel heterozygous variant of *FOXJ1* in a Chinese female with primary ciliary dyskinesia and hydrocephalus: A case report and literature review

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Background: Primary ciliary dyskinesia (PCD) is a type of ciliary dyskinesia that is usually caused by autosomal recessive inheritance and can manifest as recurrent respiratory infections, bronchiectasis, infertility, laterality defects, and chronic otolaryngological disease. Although ependymal cilia, which affect the flow of cerebrospinal fluid in the central nervous system, have much in common with respiratory cilia in terms of structure and function, hydrocephalus is rarely associated with PCD. Recently, variants of Forkhead box J1 (*FOXJ1*) have been found to cause PCD combined with hydrocephalus in a de novo, autosomal dominant inheritance pattern.

Methods: We performed DNA extraction, whole-exome sequencing analysis, and mutation analysis of *FOXJ1* to obtain genetic data on the patient. We subsequently analyzed the patient's clinical and genetic data.

Results: The proband was a four-year-old female exhibiting normal growth and development. At the age of 3 years and 2 months, the patient experienced hand shaking and weakness in the lower limbs. Cardiac ultrasonography showed a right-sided heart, and the cranial Magnetic Resonance Imaging (MRI) showed obstructive hydrocephalus. Whole-exome sequencing indicated a de novo, heterozygous variant of *FOXJ1*, c.734-735 ins20. This variant was identified to be novel, not included in the Human Gene Mutation Datebase (HGMD) and Genome Aggregation Database (gnomAD), and was likely pathogenic according to the American College of Medical Genetics and Genomics (ACMG), causing earlier termination of amino acid translation.

Conclusion: This is the first report of a de novo, autosomal dominant pattern of *FOXJ1* causing PCD combined with hydrocephalus in China. The patient's clinical symptoms were similar to those previously reported. Whole-exome sequencing confirmed that a novel variant of *FOXJ1* was the cause of the PCD combined with hydrocephalus, expanding the spectrum of the genotypes associated with this condition.

P1-136

Endocrinopathies in Congenital Disorder of Glycosylation (CDG): Short stature and hypergonadotropic hypogonadism are the main endocrinological manifestations in two unrelated cases of PMM2-CDG

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Introduction: PMM2-CDG is the most common congenital disorder of glycosylation (CDG). Since glycoproteins are involved in every endocrine axis, PMM2-CDG patients have a high risk of developing endocrinopathies.

Case Report: We describe two 12 years-old female PMM2-CDG patients with severe short stature and no clinical sign of puberty. One patient showed low serum levels of insulin-like growth factor-1 (IGF-1) and IGF binding protein 3 (IGF-BP-3), associated to normal somatotropic response to the stimulation test and delayed bone age. The other patient had normal IGF-1 and IGF-BP-3 serum levels, deficient somatotropic response to the stimulation test and slightly delayed bone age. Both patients had hypergonadotropic hypogonadism with increased levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) and very low levels of 17-beta-estradiol and anti-mullerian hormone (AMH). Abdominal ultrasound showed infantile uterus and small ovaries. Thyroid function, adrenal function, prolactin, glucidic and lipidic metabolism were normal in both patients.

Discussion: Short stature and hypergonadotropic hypogonadism were the main endocrine manifestations observed in our PMM2-CDG patients. Significant postnatal growth decline and final short stature are reported in PMM2-CDG and can be associated with low serum levels of IGF-1 and IGF-BP-3, as shown in one of our patients. Recent literature describes that abnormal glycosylation prevents correct processing of IGF-1 and its receptor (IGF-1R) impairing the GH-IGF1 signalling pathway. Puberal abnormalities, such as delayed, incomplete, or absent puberty, can also be part of the PMM2-CDG phenotype, especially in females. A dysfunction in the FSH cascade seems to be the main cause of hypergonadotropic hypogonadism since glycosylation is required to allow high binding affinity between FSH and its receptor (FSH-R). They did not show signs of other endocrinopathies related to PMM2-CDG, including thyroid abnormalities (high thyrotropin and low thyroxin-binding globulin are common findings while hypothyroidism is infrequent), hypoglycemia and hyperinsulinemia, adrenal insufficiency, hyperprolactinemia and hypolipidemia.

Conclusion: Endocrinopathies are frequently part of the clinical phenotype of PMM2-CDG, therefore the pediatric

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endocrinologist is an important figure for both diagnosis and subsequent management of this disorder. In presence of multiple endocrinological abnormalities, particularly severe short stature and absence of puberty, differential diagnosis should include PMM2-CDG. The involvement of the endocrine system in CDGs should be further investigated in light of recent discoveries on the biochemical mechanisms underlying CDGs and of the new treatments available in the field of pediatric endocrinology.

P1-137

Hypercalcitoninaemia in girl with pseudohypoparathyroidism type 1A

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Background: Pseudohypoparathypoidism (PHP) type 1A is a rare endocrine disorders caused by *GNAS* mutation. Patients phenotype with PHP type 1A include obesity, round facies, brachydactyly, subcutaneous ossifications, short stature. The resistance of action of parathyroid hormone (PTH) leads to hyperphosphatemia, hypocalcaemia and secondary hyperparathyroidism. Hypercalcitoninaemia has been described in limited patients with PHP without thyroid pathology, but pathogenetic mechanism remain unknown. Hypercalcitoninaemia is considered an associated resistance to calcitonin.

Results: A 2,7 years girl presented to our clinic primarily with complaints of high level of calcitonin and obesity. She was born at 38 week gestational age with a normal birth length (52 cm, SDS +1,71) and weight (3250 g, SDS +0,36). She had excessive weight gain in the first two years of life. Hypothyroidism was diagnosed at 2 years (TSH 12,45 mIU/L (reference range: 0,35-4,0), free T4 0,63 ng/dl (reference range: 0,6-1,12), anti-TPO ab was normal). Levothyroxine was started with a dose 12,5 mkg once a day. Ultrasound didn't not excluded focal change in the left thyroid lobe, of approximately 0.5 cm. Calcitonin level was 60,1pg/ml (reference range: 0-7,0). The girl was referred to our department due to suspicion of medullary thyroid carcinoma

On physical examination in our clinic: height 95 cm (SDS = +1,03), weight 25,6 kg, BMI 28,4 kg/m^2 (SDS = +4,6). Family history was without endocrine conditions.

We found no changes in biochemical and hormonal parameters, excluding calcitonine and thyroid hormone. Fasting glucose, insulin, cortisol and adrenocorticotropic hormone levels were within normal range. Also laboratory showed normal level calcium and PTH (ionized calcium 1,14 mmol/l (1,03-1,29), phosphorus 1,9 mmol/l (1,45-1,78), PTH 50,86 pg/ml (15-65) and high level calcitonin – 90,7pg/ml and 79,9pg/ml on re-analysis. Subclinical hypothyroidism (TSH 7,014 mIU/L, free T4 10,98pmol/l) persisted on therapy, the dose of levothyroxine was increased to 25 mkg once a day. Ultrasound showed normal thyroid gland without nodules. Abdomen ultrasound and MRI examination demonstrated no tumors.

Molecular genetic study of the *RET* gene did not reveal any anomalies.

Due to the presence of obesity from early age, hypothyroidism and hypercalcitoninaemia Albright's syndrome was suspected. The molecular genetic study of the *GNAS* gene was carried out and revealed a heterozygous pathogenic variant c. 493C>T (p. Arg165Cys) affecting *GNAS* exon 6, described in literature before.

Conclusions: The present case represents patient with PHP1A and hypercalcitoninaemia without thyroid nodules that could be related to resistance to calcitonin.

P1-138

An isolated hyperchlorhidrosis in a a patient with CA12 mutation

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Hyponatremia is a common electrolytes disorder in children. It can result from sodium chloride losses through GI, the kidneys, or in the sweat. Sodium chloride loss in the sweat can be caused by many different etiologies as cystic fibrosis, malnutrition, metabolic diseases, dermatological diseases and endocrine diseases.

We are reporting a 6 months old boy, medically free, who had recurrent admissions to the PICU as a case of hyponatremic dehydration, with a sodium level of 117-116. Both of his parents are healthy, no consanguinity, with one healthy older brother. Investigations ruled out adrenal insufficiency, renal and GI losses of NACL, and pseudohypoaldosteronism. Additionally, a sweat chloride test was performed and came back positive with a result of 70 mEq/L, thus the diagnosis of cystic fibrosis was considered. However, he did not have frequent respiratory infections, no history of chronic cough or foul-smelling loose stools, and with no family history of cystic fibrosis.

Due to the uncertainty of the diagnosis, WES was sent and came back positive for heterozygous pathogenic variant (c.601G>A) with a heterozygous risk factor (c.1210-11T>G) was identified in the CFTR gene, with the genetic diagnosis of AR cystic fibrosis, also a homozygous variant of uncertain significance was identified in the CA12 gene (c.668G>C) with the genetic diagnosis of AR isolated hyperchlorhidrosis is possible. Further genetic testing was done to the family to determine the pathogenicity.

	CFTR pathogenic variant (c.601G>A)	**CFTR risk factor(c.1210-11T>G)**	**CA12 gene (c.668G>C)**
Index case.	Heterozygous	Heterozygous	Homozygous
Mother.	Wild type	Heterozygous	Heterozygous
Father.	Heterozygous	Wild type	Heterozygous
Brother.	Heterozygous	Wild type	Heterozygous

Based on the family sanger testing, we concluded that the patients presentation is due to hyperchlorhidrosis, as a result of Carbonic anhydrase XII (CA12) gene mutation. CA12 mutation causes an isolated chloride losses in the sweat. Furthermore, literature review showed that patients having mutation in CA12 can present with CF- like phenotype (FTT, Recurrent respiratory infections). However our patient did not develop any other cystic fibrosis manifestations.

P1-139

Endocrine disorders in Inborn Errors of Immunity

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Inborn Errors of Immunity (IEI) include more than 400 disorders representing aberrant function or development of the immune system. Recently, more attention has been paid to the interaction between the immune and endocrine systems. In this study, we aimed to investigate endocrine disorders in a cohort of IEI. We investigated the prevalence, clinical, and laboratory features of endocrine disorders in patients who were diagnosed with IEI from 1994 to 2022 in Samsung Medical Center, Seoul, Korea. IEI was classified according to the International Union of Immunological Societies classification. Of the 170 patients with IEI, endocrine evaluation was performed in 125 (73.5%). Among 125 patients, 35 (28%) had endocrine disorders. The median age of the 35 patients with endocrine disorders was 14.0 years (IQR, 11.0 – 20.0, range, 1-79) and twelve patients were male. The most common type of IEI with endocrine disorders was "Combined immunodeficiencies" (40%) followed by "Predominantly antibody deficiencies" (20%), "Immune dysregulation" (14.2%). Among 35 patients, ten patients (28.6%) underwent hematopoietic stem cell transplantation, and seven patients (20%) were treated with long-term steroid therapy. One patient received both HCT and long-term steroid therapy. Thyroid involvement was most commonly observed; non-autoimmune hypothyroidism (n=12), and Hashimoto's thyroiditis (n=3). Hypogonadotrophic hypogonadism was observed in five females and three males, and all of them received hormonal replacement therapy. The adrenal insufficiency was noted in seven patients, five of whom were due to long-term steroid use. Growth hormone (GH) deficiency was found in six patients, five of whom were treated with GH and the response was good without side effects. Hypoparathyroidism was found in three patients, and all of them were diagnosed with DiGeorge syndrome. Type 2 diabetes mellitus was noted in two patients. This is the first study to describe endocrine disorders in IEI patients in Korea. As these endocrine disorders may cause health burden, endocrine evaluation should be carefully considered in IEI patients.

P1-140

Childhood cancer survivors endocrine late effects: one year retrospective observational study

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Objectives: Childhood cancer survivors (CCS) are a growing population group. Current oncology treatments have led to improved patient survival rates and an increase in late effects of treatment. Endocrine disturbances, such as pituitary insufficiency, thyroid dysfunction and obesity are the most common late endocrine effects of oncology treatments. The purpose of the study was to investigate the endocrine health of CCS and to record the prevalence of late endocrine effects.

Methods: Over a period of 12 months (3/2022-3/2023), sixty CCS (32 boys), aged 10.92±4.7 years, were studied. Patients were followed-up every 3-6 months after the first endocrinological assessment.

Results: The CCS had presented with: 56.8% hematologic malignancy (46.7% acute lymphoblastic leukemia, 5% acute myeloid leukemia, 1.7% chronic myeloid leukemia, 1.7% myelodysplastic syndrome, 1.7% chronic congenital neutropenia), 18.3% solid tumors of central nervous system (3.3% pituitary germinoma, 3.3% brain glioma, 8.3% medulloblastoma, 1.7% neuroblastoma, 1.7% squamous cell carcinoma) and 24.9% other tumor (11.7% lymphoma, 3.4% ovarian germinoma, 1.7% rhabdomyosarcoma, 1.7% Ewing sarcoma, 1.7% hepatoblastoma, 1.7% Langerhanshistiocytosis, 1.7% intestinal carcinoma, 1.3% other). The mean age at diagnosis of malignancy was 7.07±4.68 years. All patients received chemotherapy, 35.0% received radiotherapy and 16.7% bone marrow transplantation while relapse occurred in 18.3%. Late endocrine effects were recorded as disturbances of: 35% thyroid, 10% pituitary, 8.3% puberty,1.7% adrenals, 18.3% glucose metabolism, 28.3% bone mass and 23.3% body weight.

Conclusion: The increased endocrine morbidity in CCS emphasizes the need for continued and thorough endocrinological follow-up of these patients as well as the importance of a structured transition to adult endocrinology care.

P1-141

Bilateral adrenalectomy for Cushings syndrome in Infantile McCune Albright Syndrome(MAS)-A Case Report

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McCune Albright Syndrome is a rare disease characterized by classic triad of polyostotic fibrous dysplasia, café-au-lait spots and endocrine dysfunction and out of them cushings syndrome is a fatal manifestation which might need bilateral adrenalectomy.

We report a 6 months old baby who presented to Paediatric Endocrinology Unit due to elevated alkaline phosphatase levels while investigating for failure to thrive, hypotonia and global developmental delay. This child was born to non conasanguinous parents at POA of 36+5, weighing 1.78kg. Interestingly on examination he had irregular pigmentary patches in his body. He was cushinoid and had hirsutism. Systemic examination revealed tachycardia, hypertension and hepatosplenomegaly. Investigation results showed normal serum calcium 2.72mg/dl(2-2.2-2.7), low phosphate 0.87mg/dl(1.4-2.1), high ALP 553 U/L and deranged liver function tests with high ALT, AST and gamma GT. Overnight dexamethasone suppression test revealed unsuppressed serum cortisol of 750 nmol/l with normal ACTH 11.31 (4.7-48.8) confirming ACTH independent cushings syndrome. FT4 level was 24.95pmol/l which was high. X-ray right side humerus showed fibrous dysplasia and 2D echo revealed left ventricular hypertrophy.

These clinical findings led us to the diagnosis of MAS with multiorgan involvement.

Thyrotoxicosis was treated medically with carbimazole, propranolol and potassium iodide. With these FT4 level was kept within normal range. 1 alpha calcidol and phosphate supplements were started for hypophosphatemic rickets. Hypertension was difficult to control even with three antihypertensives, prazocin, amlodipine and propanolol.

After the multiprofessional meeting decision with Paediatric surgical team bilateral adrenalectomy was done after which baby was started on IV hydrocortisone infusion initially followed by oral hydrocortisone. Then he developed hyponatremia with hyperkalemia and fludrocotisone was started with oral 3% saline. He did not develop any hypoglycemic episodes in the post operative period.

During the hospital stay he sustained a fracture in his left lower femur, which caused pain and needed analgesics with Orthopaedic intervention with casting.

Unfortunately 2 weeks after the surgery he developed a severe lower respiratory tract infection complicated with sepsis and despite giving intensive care treatment baby succumbed to death.

Cushing syndrome and thyrotoxicosis in infancy with MAS is challenging. Bilateral adrenalectomy would be helpful to ameliorate the hypercortisolism in cushings syndrome with liver derangement and to prevent life threatening sepsis. After bilateral adrenalectomy patient needs lifelong steroid therapy. However the option of undergoing surgical treatment itself is not without morbidity even with the best care.

P1-331

A patient with multi-locus imprinting disturbance and 46, XY hypovirilization

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Hypomethylation of the ICR1 in 11p15 is the epigenetic alteration causing Silver Russel Syndrome (SRS) in over 50% of the patients. It is reported that 7-38% of SRS patients have multi-locus imprinting disturbance (MLID). MLID has been suggested to result from maternal mutations affecting the acquisition or maintenance of imprints

We report on a patient with MLID who presented with features of SRS and Temple syndrome in addition to severe 46 XY hypovirilisation, pseudohypoparathyroidism, hypertension, in a consanguineous family.

Genetic analysis showed massive multilocus hypomethylation including loss of methylation of the telomeric region 11p15 (ICR1) confirming the diagnosis of Silver- Russel syndrome.

Loss of methylation of the centromeric region 11p15.5 (ICR2) and other 12 regions were also found.

Discussion: We report on a patient with clinical features of SRS, Temple syndrome, PHP1B and 46 XY hypovirilization in the context of a massive multilocus hypomethylation.

There are currently 10 reported imprinting disorders in humans. Hypospadias and/or cryptorchidism have occasionally been described in SRS patients. The reported patient has a mixed picture of gonadal dysgenesis (low AMH) and partial androgen insensitivity (high Testosterone, absent mullerian remnants). Modifications in the methylation pattern contribute to random transcriptional modifications that may give rise to either testicular dysgenesis or partial androgen insensitivity (androgen

Clinical features
Full SRS features (Netchine criteria 5/6) BW 1450 (-4.8 SD), BL 37 cm (-6,3SD), BHC 34 cm (+0,05 SD)
Ambiguous genitalia (46 XY hypovirilization without mullerian remnant)
Temple Syndrome features: obesity, precocious puberty, intellectual deficit
Type 1B pseudohypoparathyroidism
Hypertension, Hypokalemia
Alopecia

insensitivity has been associated to aberrant methylation of the Androgen Receptor promoter). Another possible explanation would be a distinct autosomal recessive condition causing to 46XY VSD in the context of consanguinity.

This observation leads us to hypothesize that imprinting may influence the genital phenotype by modifying tissue-specific gene transcription.

P1-332

Results from learner's feedback on the use of free, globally accessible CME-accredited e-learning modules in Paediatric Endocrinology and Diabetes

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Introduction: The ESPE e-Learning web portal is a free, globally accessible online tool to enhance learning in Paediatric Endocrinology and Diabetes. Since August 2022, the e-learning content includes 30 accredited hours of ESPE/ISPAD e-learning Continuing Medical Education (CME) courses with ten core modules each in Paediatric Endocrinology, Paediatric Endocrinology in Resource Limited Setting (RLS) and Paediatric Diabetes. The CME modules were created by world-leading experts in Paediatric Endocrinology and Diabetes and are typically based on consensus guidelines.

Aims and Objectives: To assess learner's demographics and feedback from mandatory surveys after completion of the CME e-learning courses and to identify areas for improvement.

Methods: The survey was created by the ESPE e-learning committee and was mandatory on completion of each CME module. The survey consists of 14 questions and included learner's professional background and country of residence; feedback on the quality of the learning content, presentation, accessibility, and the anticipated impact on clinical practice was assessed by defined questions with a five-level Likert scale, ranging from strongly agree (positive response; 1) to strongly disagree (negative response; 5). The provision of general feedback was encouraged with an open question.

Results: From August 2022 until April 2023, a total of 155 CME modules were completed, 68 (44%) in Paediatric Endocrinology, 63 (41%) in Paediatric Diabetes and 24 (15%) in RLS modules. There was global participation with most learners practicing in Europe (65%), followed by the Americas (14.7%), Asia (12.3%) and Africa (7.7%). 43% of users were medical experts, followed by fellows/residents (21%), medical students and nurses (both 12.9%, respectively); 9.6% of learners practice in resource-limited countries. Overall, the learning content was well received for all modules with regards to accessibility, organisation, level of interest, improvement of individual clinical practice, appropriateness of content for individual learning level and provision of feedback following self-assessment (Likert scale 1-2/5). Some learner's free-text feedback identified some areas of improvement, mainly to reduce text-heavy content and include more graphics and interactive case reports, which the e-learning team has already addressed in the revised diabetes/ISPAD CME modules.

Summary and Conclusion: The ESPE CME-accredited e-learning modules are well received and accessed globally to provide free CME education in Paediatric Endocrinology and Diabetes.

P1-333

Case Report: Carney Complex presenting as Bilateral Large Cell Calcifying Sertoli Cell Tumours Treated with Anastrozole

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We present a 13-year old boy, who presented with acute testicular pain. Examination revealed bulky, nodular testicular enlargement. Testicular ultrasound showed multifocal, hyperechoic, calcified masses in both testes, characteristic of large cell calcifying Sertoli cell tumours (LCCSCTs), following which he was referred to endocrinology.

He had a history of benign skin tags and a previous chest wall tumour, confirmed as a lipoblastoma on histology. Physical examination showed no dysmorphic features, but he had multiple small lentigines over his face. He had grade 2 gynecomastia and was in mid-puberty. Initial investigations showed advanced bone age, and high Estradiol and Anti-Mullerian hormone. Carney Complex (CC) was considered the likely diagnosis.

LCCSCTs are seen exclusively in CC and Peutz-Jeghers syndrome. Both are rare genetic disorders, that predispose to tumour development. In CC, tumours arise in heart, skin, and endocrine glands. It is caused by mutations in several genes, notably PRKAR1A. Genetic testing confirmed a previously unreported de novo pathogenic mutation (c.503-1G>A) in PRKAR1A, confirming the diagnosis.

As part of his evaluation, he underwent an MRI of Chest & Abdomen, which showed enlarged para-aortic lymph nodes, for which he underwent laparascopic resection to exclude another tumour or metastasis. Histology showed reactive lymphoid follicular hyperplasia. Following the lymph node biopsy result, the patient started anastrozole. LCCSCTs overexpress the enzyme aromatase, resulting in elevated estrogen with gynecomastia, and advanced bone age, as in our case. Anastrozole blocks the aromatization of testosterone to estradiol and has been shown to be beneficial in several reported cases of LCCSCT, resulting in reduced tumour size and preserving fertility.

This complex case highlights the challenge of timely diagnosis and management of CC. His treatment required a multidisciplinary approach involving key medical specialties – notably endocrinology, radiology, surgery, plastic surgery, cardiology, histopathology, genetics and oncology. We had to proceed with investigations on the basis of the likely diagnosis, pending genetic results, which are vital for confirmation of the diagnosis. LCCSCTs are rare – even more so in association with CC – with just a handful of reported pediatric cases. Presentation with pre- or peripubertal gynecomastia and testicular enlargement should point to the diagnosis. In the past, orchidectomy was commonly performed, but LCCSCTs are overwhelmingly benign and respond well to aromatase inhibitors. He will remain under long-term endocrine and oncology follow-up.

P1-334

Gut microbiota, a potential cause of higher insulin sensitivity in children with Prader-Willi syndrome

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Keywords: Prader-Willi syndrome; Gut microbiota; Insulin sensitivity; Metagenomics sequencing; Obesity.

Aim: Obesity is the main driving factor for comorbidities in Prader-Willi syndrome (PWS) patients due to overeating behaviors. The gut microbiota has been implicated in the aetiology of obesity and associated comorbidities. The purpose of the present study is to characterize the fecal microbiota in Chinese patients with PWS and compare it to that of patients with obesity as well as healthy controls.

Materials and Methods: We conducted a cross-sectional study with 35 PWS patients (PWS), 35 patients with obesity (OB), and 35 healthy controls (HC). Metagenomics sequencing were performed in stool samples.

Results: The compositions of fecal microbiota in PWS patients differed from that of participants in OB and HC group. It was characterized by increased Akkermansia Eubacterium, Eubacterium rectale, Roseburia intestinalis, and decreased Parabacteroides, Phascolarctobacterium. Additionally, homeostatic model assessment of insulin resistance (HOMA-IR) were lower in PWS patients compared to patients with obesity. The Spearman rank correlation analysis showed that Achromobacter, Acidiphilium, Xylophilus, and Frisingicoccus were significantly negatively correlated with HOMA-IR.

Conclusion: The compositions of gut microbiota in Chinese PWS patients differed from that of patients with obesity, which might contribute to higher insulin sensitivity in PWS patients.

P1-335

High yield of genetic testing in various endocrine disorders

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Background: A specialized endo-genetic service was established in our clinic in January 2018. The service is multi-disciplinary and includes not only endocrinologists but also other physicians from different fields (e.g urology, orthopedics, imaging), nursing staff, psychologists, social workers, dieticians, genetic laboratories and bioinformaticians. The service is now run by a board-certified physician in both pediatric endocrinology and medical genetics.

Object: Genetic consultation and testing of patients and families with different endocrine disorders and a high suspicion of monogenic etiology.

Methods: Most patients are referred to by their endocrinologists and more rarely by other specialists. The first step of evaluation includes a thorough anamnesis, family history, meticulous physical examination, and an explanation to the family about possible genetic etiologies and the options for genetic testing. The second step is genetic work-up which can include different genetic tests, according to the specific phenotype. The third step is analyzing the results and the fourth step is explaining the results to the family, including the possible effect on treatment and follow-up, the need to test other family members, recurrence risk and further family planning. The final step includes long term follow-up and care.

Results: Over 200 genetic pediatric consultations were performed until today. Out of all cases, a genetic diagnosis was made in 33% of all cases, but 32% of patients did not complete the genetic testing that was recommended. Out of the patients who did complete the work-up, a genetic diagnosis was made in 50%. Variants of uncertain significance were found in 6%. The most common reason for referral was short stature (34% of consultations), in which a genetic diagnosis was made in 35% of patients who completed the work-up. The second most common referral was monogenic diabetes (14%) with a monogenic etiology established in 60% of patients. The third was calcium and bone metabolism abnormalities (10% of patients), with a similar high yield of 60% positive diagnoses. Other reasons for referral included differences in sex development (7.5% of patients), recurrent hypoglycemia (7%), obesity (6.5%), adrenal disorders (4.5%) and more rare cases of hypogonadotropic hypogonadism, multiple pituitary hormone deficiency, premature ovarian failure etc.

Conclusions: The experience and knowledge of an endogenetic specialized service yields a high rate of positive genetic diagnoses. In many cases, the diagnosis influences endocrine recommendations, treatment, follow-up, and prenatal consultation. The multi-disciplinary team enables a holistic approach and a better care frame for the patients and their families.

P1-336

Clinical presentation and incidence trends of paediatric endocrine conditions at a tertiary referral and teaching hospital, Nairobi, Kenya. a 14 year retrospective study from 2008 to 2021

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Background: There is significant disparity in pediatric endocrinology and diabetes care between developed countries and developing countries. Over the years nevertheless, the diagnosis and management of pediatric endocrine conditions has improved. However, there is paucity of data on clinical presentation and incidence trend amongst pediatric endocrine conditions in sub-Saharan Africa.

Methods: A hospital-based retrospective, descriptive study was carried out at Kenyatta National Hospital between 2008 to 2021 to determine the clinical presentation and incidence trend of pediatric endocrine conditions among patients aged 25 years and below. Data was analyzed using Statistical Package for Social Science version 23.0.

Results: A total of 2238 cases were seen in the 14-year period. Calcium and phosphate disorders were the leading at 35.2% (n=788) followed by glucose and lipid metabolism disorders, growth disorders, testes and male reproductive tract conditions and thyroid disorders at 17.02% (n=381), 14.3% (n=321), 11.2% (n=252) and 7.55% (n=169) respectively. There was a decline in rickets and growth disorders with an increasing trend in type 1 diabetes and thyroid conditions. Diabetic ketoacidosis (DKA) was the most common clinical presentation at diagnosis of type 1 diabetes at 90.2%. Approximately 35.7% of those who presented with DKA reported concomitant weight loss. Fever from various infections including pneumonia, vaginal candidiasis, urinary tract and ear infections formed 16% of all the presenting complaints. A few patients presented with polyphagia and secondary enuresis at 2.7% and 2% respectively while just 2% of the patients presented with classical symptoms of polyuria, polydipsia and hyperglycemia. Amongst disorders of the testes, 50% and 43% of patients presented with unilateral and bilateral undescended testes correspondingly whereas 88.4% of patients with disorders of the penis presented with hypospadias. Disorders of Sexual Differentiation (DSD) commonly presented with ambiguous genitalia at 84.6%. Congestive cardiac failure was the mostly occurring initial presentation amongst cases of hypothyroidism followed by poor growth at 56.3% and 33% sequentially. Patients with rickets commonly presented with pneumonia, delayed milestones and fever at frequencies of 36.3%, 34% and 30% correspondingly.

Conclusion: An increasing trend in type 1 diabetes and thyroid conditions mirrors several studies hence the need to allocate more resources towards these conditions. Most children presented with symptoms suggesting longstanding effects of the disease and this poses an increased risk of mortality and reduced quality of life. There is need to sensitize primary care physicians and the general public on early identification of pediatric endocrine conditions and appropriate referral.

P1-337

Occurrence of central hypothyroidism in children with isolated growth hormone deficiency

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Background: A small subgroup of children with isolated growth hormone deficiency (IGHD) develop central hypothyroidism (CH) during GH treatment. Prognostic parameters are still unclear.

Objective and Hypothesis: Long-term evaluation of children with initial diagnosis of IGHD to identify those with an unmasking CH under GH treatment. IGHD was diagnosed in children with short stature, low height velocity, retarded bone age, pathological low IGF-1 and two GH stimulation tests with a GH peak < 8 ng/ml.

Methods: Retrospective analysis of all patients with IGHD diagnosed between 1995 and 2022 in our center. Patients with septo-optic dysplasia, neurosecretory dysfunction and CH at start of GH treatment were excluded.

fT4- and TSH-levels were measured by chemiluminescent immunoassay (CLIA). CH was defined by fT4 < 11 pmol/l in two independent consecutive measurements. Brain MRI was evaluated for the presence of pituitary malformation.

Patients: 200 children (141 males) with initial diagnosis of IGHD were identified. At onset of GH treatment, mean age was 5.9 years (+/- 2.2), mean height -3.2 SDS (+/- 0.9) and mean weight -2.2 SDS (+/- 0.7). 56 patients (28 %) showed a pituitary malformation. Median follow up time after onset of GH treatment was 13.4 years (0.4 – 25.5).

Results: In 4 % of the patients (n=8) a CH was unmasked during GH treatment. The lowest fT4 level before L-T4 treatment was median 10 pmol/l (7.8 – 10.4). Median time period to diagnosis of CH after initiation of GH treatment was 9 months (6 – 38).

CH was associated with a significant pituitary malformation in 5 patients. The likelihood of the occurrence of CH in the presence of a pituitary malformation was 8.9 % (5/56) vs. 2.1 % (3/144) in its absence (P= 0.027).

Conclusion: Central hypothyroidism occurred in 4 % of children with initial diagnosis of IGHD under GH treatment; in presence of a pituitary malformation occurrence of CH was significantly more likely.

Our data emphasize the need for regular measurement of fT4 and TSH over the course of GH treatment, especially in patients with pituitary malformations.

P1-338

Long-term endocrine sequelae after hematopoietic stem cell transplantation in children and adolescents

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Purpose: As the survival rate for pediatric cancers increases significantly with advances in treatment modalities, long-term endocrine complications have also risen. This study investigated the frequencies and risks of endocrine sequelae of childhood cancer survivors after hematopoietic stem cell transplantation (HSCT).

Methods: This study included 200 pediatric patients who underwent HSCT. Clinical and endocrinological findings were collected retrospectively. Median follow-up duration after HSCT was 14 years.

Results: Endocrine complications occurred in 135 patients (67.5%). Children who underwent HSCT at pubertal age (n = 100) were at higher risk of endocrine complications than prepubertal age (79% vs. 56%, P = 0.001). The most common complication was hypogonadism (40%), followed by dyslipidemia (22%). Short stature and diabetes mellitus were more prevalent in the prepubertal group, whereas hypogonadism and osteoporosis were more common in the pubertal group. Female, pubertal age at HSCT, and glucocorticoid use were predictors of increased risk for any complication. Radiation exposure increased the risk of short stature and hypothyroidism. Hypogonadism was significantly associated with female, pubertal age at HSCT, and high-dose radiation. Pubertal age at HSCT also increased the risks of osteoporosis and dyslipidemia.

Conclusions: This study demonstrated that long-term endocrine complications are common after HSCT in children and adolescents. Age at HSCT is a critical factor for endocrine complications after HSCT. These findings suggest that surveillance strategies for endocrine complications in childhood cancer survivors should be specified according to age at HSCT.

P1-339

Gastroenterological pathology in 7 patients with autoimmune polyglandular syndrome type 1

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Background: APS type 1 is known to be associated with autoimmune gastroenterological pathology, which could be the very first and the worst-controlled manifestation of APS type 1. Treating these conditions in APS type 1 is debatable at present.

Objective and Hypotheses: We describe gastroenterological pathology in7 patients with APS type 1: clinical specifics, therapy, outcomes.

Methods: 7 patients (male, n=6, female, n=1) with APS type 1 were treated in the gastroenterology department of our clinic in 2013-2022. In 6 cases, the diagnosis of APS type 1 is confirmed molecular genetically, in 1 case antibodies to interferon ω were detected. In AIH patients, LKM-1 and SMA antibodies were controlled.

Results: AIH was diagnosed in 6 patients. The mean age of onset is 3 years 11 months. In 3 patients AIH was the first identified manifestation of APS1. At diagnosis, hepatitis activity ranged from minimal to high, outcomes vary from absence of fibrosis to cirrhosis (from F0 to F4 METAVIR). LKM-1 AB detected in 1 case, SMA was not detected.

4 children received prednisolone + azathioprine combination with an outcome in stable remission, 1 child received immunosuppression simultaneously for AIE and AIH, a combination of Prednisone with Tacrolimus was chosen, stable remission for hepatitis achieved, in one case immunosuppression is not needed today.

Malabsorbtion was performed in 4 patients, requiring immunosuppressive therapy in 2 patients. Combination of Prednisone with Tacrolimus was performed in one case with complete response, in the second case Prednisone whith Azathioprine combination provided a partial response.

In 2 patients, severe B12 deficiency was detected. In one case, it led to severe anemia and leukopenia, GPA positive, biopsy showed atrophic gastritis. The second patient hasn't undergo examination yet.

5 patients were found to have a homozygous mutation R257X in the *AIRE* gene, 1 patient had a heterozygous mutation R257X/C434X, *AIRE* sequencing was not performed in one child, R257X mutation was not detected by PCR (ethnic Tajik).

Conclusions: in our group, hepatitis characterized by an early onset and atypical course (absence of typical antibodies for AIH 1 and 2, nonspecific biopsy pattern), high sensitivity to standard immunosuppressive therapy. Enteropathy characterized by an undulating course, high infusion dependence in exacerbations. In one case combination of corticosteroids with tacrolimus was used successfully. Immune atrophic gastritis is rare in childhood; in our department it was noted only in APS 1.

We didn't find out the genotype specifics in our group.

P1-340

Long-Term Endocrine Complications of Medulloblastoma and The Effect of Growth Hormone Therapy on Final Height

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Introduction: Medulloblastoma is the most common central nervous system tumour in children representing, approximately 20% of childhood brain tumours. Cure can be achieved with surgery, chemotherapy and radiotherapy. However, disease survivors encounter long term endocrine complications including short stature due to growth hormone (GH) deficiency and spinal radiotherapy.

Patients and Methods: We aimed to investigate long-term endocrine complications of childhood Medulloblastoma by reviewing charts of 18 patients treated for medulloblastoma and reached final height in our center.

Results: The mean follow-up period was 6.60 years (1.34-11.42). All patients had GH deficiency in whom 10 patients received GH treatment. Hypothyroidism was detected in 15 patients (83.3%), Hypergonadotropic hypogonadism was detected in 14 patients (77.7%), seven of them were in the GH treated group. Additionally, one patient developed precocious puberty and was treated with GnRHa. No recurrence/secondary malignancy was observed in any patient during the follow-up.

The mean age of the patients at presentation in GH treated group (5M/5F) was 9.4 years (±3.1), and the mean age of onset of GH treatment was 11.41 years (±3.59). The mean pre-treatment IGF1 and IGFBP-3 SDS values were -1.65 and 0,98, respectively. The mean peak GH value was 3.15 (±1.15), (0.72-6.09) mcg/L.

The mean age at presentation of untreated patients (4M/4F) was 11.39 (±3.1) years. At admission, the mean SDS values of IGF1 and IGFBP-3 were -1.54 and -0,92, respectively. The mean IH SDS and FH-SDS were -1.55 (±1.38) and -3.90 (±1.37), respectively.

While there was no significant difference between IGF-1 and IGFBP-3 SDSs and IH-SDSs between the groups ($p=0.877$, $p=0.44$, $p=0.928$, respectively), The loss of FH SDS from IH SDS was lesser in GH treated group than the untreated group (the difference between treated and untreated groups FHSDS was 1.6 SDS and significant, $p=0.0012$).

Conclusion: GH deficiency is uniformly seen in addition to hypothyroidism and hypogonadism which are seen approximately 80% in survivors of medulloblastoma treatment in our cohort. Although there is a decrease in the height SDS of the patients from diagnosis to the final height, FH loss were partially compensated in the patients who received GH treatment.

P1-530

Anthropometric, clinical, and molecular genetic characteristics of 42 patients with RASopathies

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Background: RASopathies are a group of diseases with common clinical features that occur as a result of pathogenic variants in genes encoding components of the RAS/MAPK pathway. The aim of this study was to evaluate the clinical and molecular features of RASopathy cases in our pediatric endocrinology unit.

Subjects and Methods: The clinical and molecular data of 42 patients (18 girls) from 39 families were evaluated, retrospectively. All cases with clinical and/or molecular genetic diagnoses of RASopathy were included in the study.

Results: The median age at admission was 3.8 years (range: 18 days – 15.1 years). Birth weight standard deviation scores (SDS) were 0.2±1.4. The ratio of consanguinity was 17.7% and the ratio of similar cases in the family was 20.0%. The reason for referral was short stature in 67.5% of the cohort. At admission, the mean±SD of height was -2.2±1.6 (target height SDS -1.2±1.1), body mass index was -0.6±1.4 SD, and 87.5% were prepubertal. Cryptorchidism was detected in 47.8% of the boys. Pulmonary stenosis and hypertrophic cardiomyopathy were detected in 27.5% and 12.5% of cases, respectively. Echocardiography was normal in 45%. The rate of intellectual disability was 47.5% when mild cases were also included. The molecular genetic analyses were performed in 34 (80.9%) of the cases, and the diagnosis was supported molecularly in 88.2% (n=30) of them. Pathogenic variants were detected more frequently in the PTPN11 (n=11, 32.3%) followed by NF1 (n=4), MAP2K2 (n=3), KRAS (n=3), RIT1 (n=2), RAF1 (n=2), MAP2K1 (n=1), HRAS (n=2), BRAF (n=1) and LZTR1 (n=1).

For the patients followed for one year or longer, the median follow-up period was 7.5 years (range 1.9-18.1 years). Growth hormone (GH) deficiency (peak GH<7 ng/ml) was detected in 28.9%. GH treatment was commenced in 14 cases (33.3%). The duration of GH treatment was 4.9±2.7 years. The median final height was -1.9 SD in patients who received GH treatment (n=8), and -2.9 SD in patients who did not receive GH treatment (n=8) ($p=0.083$).

Conclusion: Similar to the previous reports, the ratio of PTPN11 gene variants in our RASopathy cohort was 39.0% and the diagnostic yield of our molecular genetic evaluation was 88.0%. Our approach to GH treatment in selected cases with RASopaties showed a +1 SD contribution to final height.

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P1-531

Clinical analysis of 193 patients with McCune-Albright syndrome in China based on literature review

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Objective: Summarizing and analysing the clinical characteristics of 193 patients with McCune-Albright syndrome (MAS) in China to improve the understanding of MAS for early detection, diagnosis and management. Methods All MAS-themed case-report or case-series studies published by the Chinese between January 1990 and November 2022 were retrieved from the Wanfang Full Text, CNKI, China Science and Technology Journal, PubMed and Embase databases, and clinical data were collected. Intergroup comparison was performed using the t-test, Mann-Whitney U test, $\chi 2$ test and Fisher's exact probability methods. Results 1. A total of 927 articles were retrieved from the database, and 108 studies were finally included in the statistics, including 193 patients with MAS (42 males and 151 females). The onset age of females was earlier than males. The typical triad group accounted for 46.1%(89/193) of patients, and the first-visit and diagnosis age was earlier than the atypical group. 2. Fibrous dysplasia (FD), mainly polyostotic, occurred in 84.5%(163/193) of patients, with an average onset age of 6.1 (3.5, 10.0) years old and 90%≤16 years of age. Pathological fractures, mainly femoral, happened in 46.9%(53/113) of patients with FD, with an average onset age of 8.0 (4.0, 13.0) years old and 92.2% ≤ 18 years of age. 3. Endocrine hyperfunction happened in 79.3% of patients, with a higher proportion of females than males. Peripheral precocious puberty occurred earlier in females than males and earlier in females with ovarian cysts than without. Pituitary involvement accounted for 21.8% of patients. The incidence of craniofacial FD and cranial nerve compression in patients with elevated growth hormone(GH) was significantly higher than in normal patients. 4. The Cafe-au-Lait Spots (CALMs) happened in 86.5% of patients, most of which exhibited a scattered distribution. 30.4% of CALMs were located on different sides from FD, and at least 8.8% of CALMs crossed the midline.

Conclusion: MAS, mainly atypical, has a multisystemic involvement, which is more common and occurs earlier in females than males. Most patients develop FD before age 18, as early diagnosis and evaluation are needed. Multiple endocrine glands can probably be involved, and regular imaging is recommended to detect potential glandular lesions. Patients with elevated GH should be aware of cranial nerve compression. CALMs are often irregularly distributed, as the extent of FD cannot only be determined by the distribution of CALMs.

P1-532

Prevalence of endocrinopathies in a cohort of patients with Rett syndrome: a double center observational study

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Objective: to assess the prevalence of endocrinopathies in a pediatric population of Rett syndrome (RTT) patients.

Design: retrospective observational double center study.

Methods: 51 caucasian patients (47 girls, 4 boy) with genetically confirmed diagnosis of RTT were enrolled (mean age: 9.65±5.9 years, range: 1-18 years). The patients were referred from the Rett Center of two Italian Hospitals for endocrinological evaluation. All the patients underwent clinical assessment (height, weight, BMI, pubertal staging) and hormonal workup. Thyroid ultrasonography (US) was routinely performed. Pelvic US and bone densitometry (DEXA) were performed in post pubertal girls. Midline defects were excluded by brain MRI.

Results: MeCP2 deletions were detected in 38 patients (74.5%) and CDKL5 deletions in 11 patients (21.6%). Only 2 patients exhibited mutations of FOXG1. Overall, 40 patients were treated with anticonvulsant drugs.

-Short stature: 24 patients (47%) had a height <-2 standard deviation score SDs (mean SDs -3.18, range: - 8.26/-2.0) and below targets height. Of these, 7 girls also had BMI<-2 SDs and 4 had thyroid dysfunction. Celiac disease and GH deficit were excluded.

-Malnutrition: 13 patients (25.5%) had severe underweight (mean BMI SDs -3.79, range: -2.54/-8.19 SDs), in absence of other chronic diseases.

-Obesity: 10 patients (19.6%) had BMI>2 SDs (mean BMI +2.35 SDs, range: +2.0/+2.98 SDs), 2 of them with basal hyperinsulinemia.

-Gonadal function: among the 26 post-pubertal girls, 4 had a history of precocious puberty and one premature isolated pubarche. 12/26 (46.1%) patients claimed menstrual cycle abnormalities (secondary amenorrhea and oligomenorrhea); all of them had concurrent weight disorders (7 were overweight or obese and 5 underweight).

-Thyroid abnormalities (5 patients, 9.8%): central hypothyroidism (1 patient), subclinical hypothyroidism (1 patient), Hashimoto's thyroiditis in euthyroidism (1 patient), and thyroid nodules (2 patients).

-Hyperprolactinemia: 7 patients (13.7%) exhibited high prolactin blood levels, with occurrence of galactorrhea in one case, during anticonvulsant therapy.

-Bone health: 11 patients (21.6%) had vitamin D deficiency. DEXA highlighted osteopenia in 4 patients and osteoporosis in 6 patients (two of them requiring bisphosphonates).

In the entire study population, endocrinopathies were significantly more frequent in patients with MECP2 deletions (p=0.0005).

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Conclusions: in our RTT pediatric population, short stature was the most frequent endocrinological report, followed by menstrual cycle abnormalities and weight disorders.

Interestingly, patients with MECP2 deletions seemed to be at higher risk for developing endocrinopathies.

Therefore, in the context of a multidisciplinary approach, endocrinological evaluation should be recommended in RTT patients.

P1-533

Utilizing ESPE e-learning to educate Pediatric Endocrinologists in Indonesia: Web-Series on Pediatric Endocrinology and Diabetes (WeSPED), an initiative of the European Society for Paediatric Endocrinology (ESPE) e-learning committee and the Indonesian Pediatric Society (Ikatan Dokter Anak Indonesia-IDAI)

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Introduction: The ESPE e-learning web-portal (www.espe-elearning.org) was developed to address gaps in education in pediatric endocrinology and diabetes and was first published online in 2012. Since then, it has been utilized in different settings and applications. Here, we present its utilization in a series of e-learning and e-consultation webinars in collaboration with the Indonesian Pediatric Society (IDAI- Ikatan Dokter Anak Indonesia).

Methods: A local moderator organized the webinars with assistance from the ESPE e-learning committee and facilitated tutor-participant interactions. Each session (lasting 1.5-2 hours) started with discussion of relevant sections of the e-learning web-portal (chapter and/or clinical cases) by an expert tutor on a given topic during which interactive polling kept participants engaged (e-learning component). Subsequently, selected participants presented 2-4 anonymized cases followed by questions for discussion with the tutor (e-consultation component). After the session, a survey was conducted for participants to provide feedback regarding the webinars. Furthermore, the tutor prepared a summary of key messages of the e-learning component and e-consultation discussion, and provided recent relevant review papers for further reading by the participants. The platform used was Zoom.

Results: From September 2021 to January 2023, 11 WeSPED sessions were conducted by 10 tutors. Topics included calcium and bone, diabetes mellitus, growth, precocious and delayed puberty, differences of sex development (DSD), congenital hyperinsulinism, pediatric and adolescent gynecology amongst others. Attendance ranged from 34 to 43 participants per session. Webinar participants were from Indonesia (from 17 out of 34 provinces) with the majority being pediatricians or pediatric endocrinologists, followed by trainees in pediatric endocrinology. Results from 286 survey responses from 11 sessions, revealed that most participants found the content of the sessions was most interesting (47% strongly agree, 48% agree) and that the objectives of the course were clearly identified and met (36 % strongly agree, 57% agree). Additionally, the majority found the e-consultation part of the webinar series to be very informative (41% strongly agree, 49% agree) and agreed (41% strongly agreed, 55% agreed) they plan on using information learned during the web-series in their clinical practice.

Conclusions: E-learning and e-consultation Web-series (WeSPED) demonstrates that the ESPE e-learning web-portal can be successfully utilized to provide interactive e-learning education and expert consultation in pediatric endocrinology and diabetes in Indonesia. Continuation of WeSPED to overcome inequalities in knowledge and skills along with similar initiatives in other resource limited settings provide opportunities to improve clinical knowledge and clinical practice at low cost.

P1-534

Endocrinal Disorders in Patients with Chronic Lung Diseases, Single-Center Experience

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Keywords: Endocrine, Non-cystic fibrosis bronchiectasis, Interstitial Lung Disease (ILD)

Introduction: Recent evidence shows that there is association between different endocrinal disorders and the pathogenesis of chronic lung diseases. These disorders have an impact on quality of life and management of these diseases.

Aim of Work: Assess the correlation between two chronic lung diseases (interstitial lung diseases (ILD) and non-cystic fibrosis bronchiectasis) and different endocrine disorders including diabetes, thyroid abnormalities, calcium disorders.

Patients and Methods: This study was conducted as a cross sectional analytic study and included 50 patients diagnosed with chronic lung disease (ILD and non-cystic fibrosis bronchiectasis) attending the Pediatric pulmonology outpatient clinic and Department. Each patient underwent: Full history taking, thorough clinical examination and laboratory investigations (Blood glucose: (Fasting and 2 hours post prandial blood glucose), HbA1c, thyroid profile, calcium profile:(calcium, phosphorus, alkaline phosphatase, parathormone, vitamin D), and basic laboratory investigations as (CBC, liver function tests, serum albumin…etc).

Results: Among the studied population 15(30%) of patients were prediabetic, (20% had impaired fasting glucose, 100% had impaired glucose tolerance). Twenty (40%) were diabetic (85% diagnosed as type 1 diabetes and 15% diagnosed as drug induced diabetes). Hypothyroidism was evident among 13(26%) of the study group. Vitamin-D insufficiency was evident among 8(16%) and was deficient among 17(34%) of the study group. Furthermore, 3(6%) had hypoparathyroidism, 1(2%) had hyperparathyroidism. By comparing the 2 subgroups, (ILD and non-cystic fibrosis bronchiectasis) regarding anthropometric measures (height and weight), ILD group has shown more stunted growth compared to bronchiectasis group with statistically significant difference with p values 0.013 and 0.008 respectively. Bronchiectasis group had more hypocalcemia, hypophosphatemia and more vitamin D deficiency compared to ILD group with statistically significant difference with p values 0.022, 0.007 and 0.035 respectively.

Conclusion: There is increasing evidence that several endocrinal and metabolic disorders were detected among children with chronic lung diseases. That's why screening for endocrinal disorders in those patients is mandatory for early diagnosis and treatment to ameliorate the clinical course of the disease and improve the outcome.

P1-535

An unusual case of secondary amenorrhea in an adolescent

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Our patient was a 19-year-old female who was referred for evaluation of secondary amenorrhea and underdeveloped secondary sexual characteristics, having undergone her first and only menstrual cycle at age 16. She had experienced four episodes of hypoglycemia during her childhood; two were associated with seizure activity. She was evaluated by endocrinology after her second episode of hypoglycemia at 3 years of age and no cause could be identified. She also had learning difficulties and delayed developmental milestones. Our exam showed diffuse hyperpigmentation over the entire body including her lips and tongue. She had no axillary hair; Tanner III breast development and Tanner II pubic hair distribution were evident. She had normal external female genitalia without clitoromegaly. Karyotype was reported as 46 XX. Current laboratory investigation revealed undetectable cortisol, ACTH level of 1493 pg/mL (normal 7.2-63.3 pg/mL), low circulating adrenal androgens (17-OHP, DHEA-S), pre-pubertal levels of estradiol and testosterone. However, she had a normal serum sodium, potassium, aldosterone levels and a normal plasma renin activity. Sixty minutes after a single 250 mcg dose of cosyntropin, an unmeasurable cortisol was observed, along with an undetectable 17-Hydroxypregnenolone, 17-Hydroxyprogesterone, DHEA, pregnenolone, a very low progesterone and androstenedione levels. Leuprolide stimulation resulted in a prepubertal response of LH and FSH. Clonidine-arginine stimulation test revealed growth hormone deficiency (peak value = 4.8 ng/mL), however the patient has in fact exceeded her mid-parental height. Other remarkable findings included persistently elevated TSH (9.7-11.2 uIU/ml), low normal free T4, a very low IGF-1 level (33-46 ng/mL) and mild elevations in AST/ALT, of unclear etiology. Pelvic ultrasound revealed a normal uterus with 6 mm endometrial stripe and normal ovaries bilaterally. MRI pituitary was normal. The biochemical profile suggested ACTH resistance due to receptor loss of function, and a pathogenic homozygous variant in exon 2 of MC2R (melanocortin-2 receptor) gene was identified on extended gene analysis [c.C409T: p.R137W] and explains the loss of signal transduction at the ACTH receptor. Familial glucocorticoid deficiency type 1 is a rare autosomal recessive disorder, characterized by MC2R mutation leading to primary adrenal insufficiency with intact mineralocorticoid function. Treatment with physiologic doses of hydrocortisone was initiated. This case illustrates a unique phenotype of MC2R loss of function, presenting later in adolescence. Unusual features include growth hormone deficiency with normal growth, transaminitis, subclinical hypothyroidism and hypogonadism. These observations suggest a partial dependence upon ACTH for normal functioning of other endocrine axes.

P1-536

Development and implementation of a Pediatric Endocrinology Education Program in Francophone Africa(In French: Programme de formation en Endocrinologie et Diabètologie pédiatrique pour l'Afrique subsaharienne Francophone [PEDAF])

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Introduction: Non-communicable diseases are recognized as a major cause of morbidity in low and middle-income countries (LMICs). There are 21 francophone countries (>100 million speak French) in Sub-Saharan Africa (FSSA). We identified only 19 pediatric endocrinologists in FSSA (37% in Cameroon and Senegal) mostly trained in France or through the successful anglophone "Paediatric Endocrine Training Centers for (West) Africa" (PETC[W]A) offered in Nairobi and Lagos by ASPAE, ISPAD, ESPE, as well as adult endocrinologists and several general practitioners and pediatricians with an interest in diabetes. 11/21 countries had no pediatric endocrinologist.

Objectives: To build capacity in pediatric endocrinology and diabetes in FSSA through a Master program.

Methods: African and International partners were involved in the design of the curriculum. Monthly meetings took place since

June 2020 to develop a program recognized by the "Conseil Africain et Malgache pour l'Enseignement Supérieur" (www.lecames.org), which offers international and mutual recognition of a medical specialty. We critically reviewed the PETC[W]A program. Funding proposals were successfully submitted to international foundations (EKFS, WDF) and organizations (LFAC, CDiC).

Results: We first organized a 2-month, introductory, free, virtual, "prerequisite program" for all health professionals, prior to the Master program. The first edition (May-June 2022) was attended by 95 physicians and allied health professionals from 17 countries. For the Master, we decided for a hybrid 50% virtual and 50% in person, 2-year program to increase flexibility, decrease travel/cost while offering appropriate clinical experience. A full curriculum was developed with emphasis of LMICs needs. Two francophone training centres (U Dakar, Senegal and U Yaoundé, Cameroun) were chosen based on safety and political stability and on the presence of a university hospital offering a pediatric clinic in endocrinology and diabetes. Master candidates were selected among pediatricians and adult endocrinologists based on the CV, results of the "prerequisite" test and plans to develop a pediatric diabetes and endocrinology centre at home following Master completion. Eight Master candidates from 8 countries were selected among 22 applications and started the first 6 months (virtual) of the Master program in October 2022. All topics are jointly taught by African and International colleagues. In-kind support for an IT platform was provided by the "Université Numérique Francophone Mondiale" (www.unfm.org).

Conclusions: Regional conceptualization and international collaborations are key to implementing post-graduate training programs in pediatric endocrinology. Outcome evaluation will assess the long-term sustainability and effect on regional and national pediatric endocrine capacity.

P1-537

Effects of seasonal variability of insolation and COVID-19 pandemic isolation on vitamin D concentrations in children

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Introduction: Vitamin D may be considered as a hormone of prohormone of pleiotropic effects. Seasonal variability of insolation affects its synthesis in humans. In our latitude, vitamin D deficiency is widespread. In 2018, updated recommendations for vitamin D supplementation were published in Poland by Rusińska et al. In 2020, SARS-CoV-2 pandemic lockdown was introduced, with suggestions of protective anti-viral vitamin D role.

Aims: to investigate the effects of:

1. seasonal variability of insolation,
2. updating guidelines of vitamin D supplementation
3. limited sun exposure during pandemic lockdown and recommendations to increase vitamin D supplementation on 25(OH)D concentrations in children.

Methods: Retrospective analysis of the long-term variability of 25(OH)D concentrations was performed in a group of 1440 children (879 boys, 561 girls) with short stature, aged 3.0-18.0 years. Concentrations of 25(OH)D were compared between the periods from mid-2014 to mid-2018 (Group A), from mid-2018 to mid-2020 (Group B) and from mid-2020 to mid-2022 (Group C). Vitamin D deficiency was defined as 25(OH)D <20 ng/ml, suboptimal supply 20-30 ng/ml. Due to the lack of normal distribution of 25(OH)D concentrations in Shapiro-Wilk test, nonparametric Kruskall-Wallis test was applied for comparisons between groups, followed by post-hoc Bonferroni-Dunn test. Next, time series regression model of seasonal variability of 25(OH)D concentrations was created.

Results: In the whole group median (25-75centile) 25(OH)D concentration was 24.0 (18.3-30.2) ng/ml, in Groups A, B and C it was 22.9 (17.3-28.7) ng/ml, 26.0 (20.0-30.7) ng/ml and 29.9 (21.3-34.3) ng/ml, respectively, with significant ($p<0.05$) differences between all Groups. Concentrations of 25(OH)D were normal in 26.1% children, suboptimal in 41.9%, deficient in 32.0%. Time series model including insolation in previous 3 months explained 80% of pre-pandemic seasonal variability of 25(OH)D concentrations, however during pandemy with overprediction for 1st while underprediction for 2nd year (that probably reflects reduced sun exposure during lockdown and increasing vitamin D supplementation).

Conclusions: Significant increase of 25(OH)D concentrations was observed both after the update of supplementation guidelines and during SARS-CoV-2 pandemic, however the scale of vitamin D deficiency and insufficiency is still too high. Seasonal vitamin D supplementation is necessary in paediatric population. Further efforts to improve the vitamin D supply in children should be taken, including updates of recommendations, as it has recently been done in Poland (Płudowski et al. 2023).

P1-538

Endocrine Late Effects In Survival Children With High-Risk Neuroblastoma From Italian Tertiary Hospital

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Background: The treatment of high-risk neuroblastoma still represents a clinical challenge in pediatric oncology. About 50% of children survive after a multimodal treatment based on

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conventional and high dose chemotherapy, surgery, radiotherapy, differentiating treatment and immunotherapy.

Aim: To evaluate endocrine long-term sequels in a pediatric cohort with high-risk neuroblastoma.

Patients qnd Methods: The medical records of long-term neuroblastoma survivors with at least 4 years follow-up from diagnosis were reviewed. All patients were treated during a 22 years period.

Results: Forty-seven patients, median age 12.5 years (range 7-27) are alive with 9.7 years median follow-up (range 4-23). We observed long-term complications in 46/47 patients (98%), with a median number of 4 second health events per patient (range 0-10). The most common sequelae are endocrine alterations observed in 66% of long-term survivors followed by cardiac toxicities 64%, hepatic focal nodular hyperplasia in 44%, chronic respiratory diseases in 45%, hearing deficiency in 36% and chronic kidney disease 32%. In particular thyroid toxicities in 83% of patients were observed. Among them, 44% had thyroid toxicities revealed by ultrasound screening: non-cancerous thyroid nodules (32%), papillary thyroid carcinoma (4%), Plummer's adenoma (4%) and autoimmune thyroiditis (4%) and 56% manifested other thyroid toxicities: hypothyroidism (28%) and isolated hyper-TSH (40%). All patients with hypothyroidism were treated through L-thyroxine therapy. Seven out of 30 patients (24%) developed gonadal toxicities, of which 6 females and 1 male. Among them we observed 6 patients with hypergonadotropic hypogonadism, only one patient with hypogonadotropic hypogonadims. A small percentage of patients (20%) showed other endocrinological manifestations including primary hyposurrenalism, central hyposurrenalism and GHD. Moreover, Six patients developed a second neoplasm: 1 ganglioneuroma, 1 osteosarcoma, 1 papillary thyroid carcinoma and 3 myelodysplasia syndrome.

Conclusion: A high proportion of long-term survivors is affected by treatment-associated chronic health conditions, most commonly endocrinological conditions. Further studies with large series are needed to clarify the impact of treatments and to underscore the importance of medical intervention and long-term monitoring of these at-risk subjects to increase overall quality-of-life. We recommend that during follow-up of neuroblastoma children, special attention should be paid to their endocrine function.

P1-539

Long Term Effects of Pediatric Hematopoietic Stem Cell Transplant on Endocrine Function

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Background: Advances in the treatment of childhood and adolescence cancer treatment have led to significant increase in survival rate. Current 5-survival rate of childhood cancer is nearly 80%. Hematopoietic stem cell transplant (HSCT) is treatment of choice in many clinical conditions including malignant and non-malignant hematological diseases, solid tumors and immunodeficiency diseases. Children receiving HSCT are prepared with different pre-transplant conditioning regimens. These regimens expose the recipients to potent cytotoxic chemotherapy and sometimes to fractionated or non-fractionated total body irradiation (TBI). Adverse effects on endocrine function and bone health are the most commonly found sequelae affecting 20%-50% subjects.

Method: We did a retrospective chart review of children age less than 18 years at the time of HSCT at King Faisal Specialist Hospital and research Centre Jeddah. They received conditioning regimen prior to HSCT either myeloablative (MAC) or reduced intensity (RIC) regimen and in few case no conditioning regimen was given. All participants were followed for a median period of 5 years. Endocrinology assessment carried out periodically including thyroid, adrenal, pituitary glands function and gonadal assessment upon expected physiological age of puberty.

Results: 141 children (75 males and 66 females) had HSCT at median age of 7 years. 128 patients had allogenic while13 patients had autologous HSCT. The conditioning regimen include MAC in 110 (78%), RIC in 28 (19.9%) and no condition in three (2.1%) children. Only 17 children received radiation; 13 had fractionated and four had non-fractionated. Nearly half of the patients (65/141, 46%) developed one of endocrine dysfunction. Girls are more effected than boys (48 vs 17). Growth hormone deficiency in 4 children (1 male and 3 females), adrenal insufficiency in 13 children (6 males and 7 females), thyroid deficiency in 23 children (13 males and 10 females) and gonadal failure in 36 children all females. Endocrine outcomes are compared against the primary disease and conditioning regimen. Gonadal failure has significant association with MAC (p-value 0.0002) however; other endocrine dysfunctions do not have any significant association with conditioning regimen or underlying disease.

Conclusion: Current treatment strategies for childhood cancers and hematological diseases have significantly improved long-term survival. However, this survival is associated with treatment associated adverse effects, which have an impact not only to physical health but also on psychosocial wellbeing of survivor. Our data suggests further improvement in conditioning regimens to avoid endocrine dysfunction.

Pituitary, neuroendocrinology and puberty

P1-142

Stimulated copeptin based diagnosis of central diabetes insipidus in children and adolescents

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Introduction: Diagnosis of central diabetes insipidus (CDI) remains challenging. Water deprivation test and hypertonic saline infusion, as established diagnostic tests, are mentally and physically demanding for patients. Copeptin response to arginine-stimulation and insulin tolerance test (ITT) has been shown to be a putative parameter in the diagnosis of CDI in adults, but data are lacking for children and adolescents.

Methods: In this single-centre retrospective study, we identified paediatric patients with suspected pituitary disorders who underwent standard arginine-testing or ITT. Patients with CDI, matched controls without CDI and primary polydipsia (PP) were identified. Diagnoses were confirmed retrospectively using comprehensive clinical and diagnostic characteristics. Serum copeptin concentrations were measured using a commercially available automated immunofluorescence assay (B.R.A.H.M.S CopeptinproAVP KRYPTOR®) in samples stored for a median of 4.0 years (1.3-10.8) and collected before and 60 minutes after arginine-infusion or subsequently in ITT. Cut-off analyses were performed using ROC curves.

Results: Serum samples from 32 patients with CDI, 32 matched controls and 5 patients with PP (n=69; 51 males, 18 females) and arginine test were available for analysis. Median copeptin concentrations increased from 4.47 pmol/l (IQR: 3.47-8.36) to 6.96 pmol/l (IQR: 4.51-12.89; p<0.001) in controls, from 1.46 pmol/l (IQR: 1.21-2.12) to 1.44 (IQR: 1.10-1.87; p=0.645, ns) in CDI and from 4.40 pmol/l (3.95-6.33) to 9.58 pmol/l (8.19-11.42; p<0.001) in PP. The published cut-off value of 3.8 pmol/l revealed a sensitivity of 100 % and a specificity of 86.5 % in confirming CDI. So far copeptin was measured in 7 patients with CDI and 3 controls at 0 and 60 minutes of ITT revealing a change from 1.48 pmol/l (IQR: 1.18-1.95) to 1.90 pmol/l (IQR: 1.43-4.12, p= 0.593, ns) and 4.87 pmol/l to 11.20 pmol/l (p=1.000), respectively.

Conclusion: Our results suggest that arginine-stimulated serum copeptin concentrations are a sensitive and specific diagnostic tool for CDI in paediatric patients, which may replace and simplify the conventional diagnostic pathway of water deprivation testing and hypertonic saline infusion. The copeptin response to ITT needs further evaluation.

P1-143

Comparison of the Test Accuracy of a Subcutaneous Gonadotropin-Releasing Hormone Agonist (Triptorelin Acetate) vs. Intravenous Gonadorelin in the Diagnosis of Central Precocious Puberty

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Purpose: In the diagnosis of central precocious puberty (CPP), the gonadotropin-releasing hormone (GnRH) stimulation test using intravenously injected gonadorelin is the gold standard. However, gonadorelin is not always readily available. In this study, the diagnostic accuracy of a test based on the GnRH agonist triptorelin acetate (triptorelin) was compared to that of the classical gonadorelin-based test in the diagnosis of CPP in girls.

Methods: A retrospective chart review was performed to compare the clinical outcome of patients who underwent a GnRH stimulation test performed using intravenous gonadorelin (n = 74) vs. a subcutaneous triptorelin acetate test (triptorelin) test (n = 74). Among the 148 patients, 74 had CPP and 74 had precocious thelarche (PT). Luteinizing hormone (LH) and follicle-stimulating hormone levels were measured 0, 30, 60, 120, and 180 min after triptorelin injection, and 0, 30, 45, 60, and 90 min after gonadorelin injection. CPP was defined as a peak LH concentration ≥ 5.0 IU/L and PT as a peak LH concentration < 5.0 IU/L. The peak LH time detected by each method was compared, and the diagnostic value of the triptorelin test for CPP was determined in a receiver operating characteristic analysis.

Results: Peak LH after gonadorelin injection was measured at 30 min in 48% of patients, at 45 min in 47%, and at 60 min in 5.0%. After triptorelin injection, LH levels peaked at 30 min in 8%, at 60 min in 49%, at 120 min in 8.5%, and at 180 min in 35%. In the triptorelin test for the diagnosis of CPP, the peak LH cutoff value of 5.02 IU/L provided a sensitivity of 100% and a specificity of 100%.

Conclusion: The triptorelin test has a high diagnostic accuracy in the differential diagnosis of CPP vs. PT in girls, thus providing an effective alternative to the classic gonadorelin-based GnRH test. It should be noted that the peak LH concentration after triptorelin stimulation is likely to be reached later than after gonadorelin stimulation.

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Idiopathic Central Precocious Puberty on the Rise: A Retrospective Study Before and During the COVID-19 Pandemic in a Portuguese Tertiary-Level Hospital

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Background and Aims: In light of the recent evidence suggesting an increase in idiopathic central precocious puberty (ICPP) cases during the COVID-19 pandemic, this study aimed to assess the proportion of patients referred for precocious puberty (PP) and, within this group, the number of ICPP cases diagnosed before and during the pandemic. Additionally, we compared the demographic, anthropometric, and clinical characteristics of ICPP patients between the two groups (group 1 – pre-pandemic / group 2 – during COVID-19 pandemic).

Methods: We conducted a retrospective study of patients referred to a pediatric endocrinology unit at a tertiary-level hospital in Portugal for suspected PP from January 2018 to March 2020 (group 1) and from April 2020 to June 2022 (group 2). We collected data on PP referrals and diagnosed cases of ICPP, and then compared demographic, clinical, and anthropometric characteristics from the first visits of ICPP patients in both groups.

Results: From 258 patients referred for PP we diagnosed 20 patients with ICPP (19 girls, 1 boy). Four patients were diagnosed in the pre-pandemic group, and 16 patients were diagnosed after the onset of COVID-19 pandemic. The number of patients diagnosed with ICPP during the pandemic period was significantly higher (16 vs 4; $p<0,05$). The pandemic group had significantly earlier thelarche onset (6,9 vs 7,3 years; $p<0,05$) and shorter time between treatment initiation and first visit (0,19 vs 0,79 years; $p<0,05$). The age at first visit, weight standard deviation score (SDS), height SDS, body mass index (BMI) SDS, Tanner stage at diagnosis, bone age at diagnosis, difference in bone and chronological ages, frequency of obesity or overweight, height SDS minus mid-parental height SDS, number of girls with menarche at diagnosis and number who required treatment were not significantly different between the two groups. Additionally, the number of referrals for PP (144 of 904 referrals) in the pandemic group was not significantly higher compared to the pre-pandemic group (114 of 758 referral; $p>0,05$).

Conclusion: This study revealed a fourfold increase in the diagnosis of ICPP among children, particularly girls, compared to the pre-pandemic period. Surprisingly, no significant increase in BMI was observed, suggesting that other factors may be involved. Larger-scale research is needed to validate these results and identify other potential contributing factors. Despite the pandemic, efficient work led to prompt treatment initiation without delays, unlike in other pathologies, as observed mainly in adults.

P1-145

Novel clinical and imaging tools to identify and grade hypothalamic disease in populations at risk

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Background: Hypothalamic dysfunction (HD) is life-threatening but precise diagnostic tools are lacking. Normal hypothalamic anatomy is difficult to delineate on MRI. Damage to the area is inferred from a visible lesion, but how widely it disturbs signalling connections or correlates with symptoms is unclear. Furthermore, in congenital/syndromic diseases the hypothalamus appears normal even in cases with clear HD. We aimed to develop novel clinical and radiological tools to quantify the spectrum of HD in populations at risk.

Patients and Methods: 62 children (28F,34M) followed for 8.0±4.0 years for hypothalamo-pituitary (H-P) disorders (34 congenital, 28 acquired), were recruited for study aged 12.5±2.9 years and prospectively screened for features of HD [disordered appetite, thirst, sleep, thermoregulation, and abnormal BMI SDS (<-2 or $>+2$)]. HD was considered "clinically likely" when there were either ≥3 features or ≥2 and a clear hypothalamic mass/syndrome. 3T high-resolution volumetric MR brain sequences (T1, T2) were prospectively acquired. A protocol to manually segment the hypothalamus was applied to children for the first time to identify and measure regions of interest. In patients with mass lesions, a novel injury score - ranging from 0 to 12 (no to total involvement) based on subsegmentagion of hypothalamic regions - was developed. Imaging data were compared with 25 age- and gender-matched controls (13F,12M, aged 13.6±3.1 years).

Results: The prevalence of "clinically likely HD" was similar in congenital vs acquired disorders (61.8%vs75.0%). 26 patients without visible hypothalamic lesions were subdivided into 13 with (Group1) and 13 without (Group2) "clinically likely HD". Group1 (6 congenital hypopituitarism, 3 ROHHAD(NET), 1 SRC1 variant, 3 SOD) had smaller hypothalami than Group2 (11 congenital hypopituitarism, 2 SOD) (759.2±130.6 vs 984.0±160.0 mm3, $p=0.046$) with Group2 being similar to controls (922.5±122.3 mm3). In 36 patients with mass lesions (13 OPGs, 12 craniopharyngiomas, 7 hamartomas, 3 germinomas, 1 arachnoid cyst) the hypothalamic injury score was higher in those with "clinically likely HD" than in those without (6.6±3.3 vs 3.6±2.8, $p=0.024$).

Conclusions: When prospectively assessed, HD is highly prevalent in both patients with congenital H-P disorders and hypothalamic tumours. We have for the first time to our knowledge manually segmented the hypothalamus to improve identification and quantification of hypothalamic injury on imaging. Our tools

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developed to assess congenital (reduced volumes) and acquired (hypothalamic score) injury appear discriminatory in defining severity of HD phenotype and may facilitate diagnostic accuracy and development of targeted therapies.

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Evaluation of pubertal suppression in adolescents with gender dysphoria in different Tanner stadia

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Background: Gonadotropin-releasing hormone agonists (GnRHa) are common treatment in adolescents with gender dysphoria to prevent development of unwanted physical changes. However, the safe use of GnRHa is debated in the media and objective literature is sparse. Specifically, there is a lack of literature comparing between different Tanner stadia, since it is debatable whether GnRHa treatment is effective in adolescents who have almost gone through puberty (Tanner stadia 4/5).

Aim: To gain more insight into the effects of GnRHa-treatment in adolescents with gender dysphoria in different Tanner stadia. This will help determine to what extent monitoring is useful and improve medical care.

Methods: A retrospective study was performed assessing the electronic medical files of adolescents treated with GnRHa in the Radboud Expert Centre Sex & Gender for 0,5-2 years with follow-up every three months. So far, 85 patients were included.

Outcomes: Population description, biometrics (age, pubertal development, height, weight, BMI, blood pressure, bone mineral density), biochemistry (hormones, renal/liver function, overall health parameters), and reported side-effects.

Preliminary Results: 57 trans males (TM), 26 trans females (TF), and 2 non-binary patients (NB) were included, of which 32,9% had psychiatric comorbidity and 41,2% were overweight/obese at start of treatment. Tanner stadia were reported for 65 of these patients; 36 patients had Tanner 2/3 and 29 patients had Tanner 4/5. 43,5% of TM reported menstruation at start of treatment and another 21,1% were treated with oral contraceptives. After start of treatment gonadotrophin levels were effectively suppressed in TM/NB, but not completely in TF. However, side-effects (flushes, local side-effects, mood swings, headaches, and sadness) were significantly more common in Tanner 4/5, while there was no significant effect on height velocity or pubertal development in this group. Effects were limited on overall health parameters.

Conclusion: Our study showed that GnRHa-treatment is effective and safe on the short term. No adverse effects on blood pressure, renal/liver function and blood count were found. However, side-effects are commonly reported, especially in patients with Tanner 4/5 at start of treatment, while the effectiveness on physical changes and pubertal development in this group is debatable. Furthermore, patients experience a high number of risk factors at start of treatment, such as obesity, insufficient dairy intake, low vitamin D levels and psychiatric comorbidities, for which additional support and monitoring is necessary.

P1-147

Quantification of overnight urinary gonadotropin excretion predicts imminent puberty in girls: a semi-longitudinal study

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Objectives: We explored the alternative of using overnight fold change in gonadotropin levels by comparing the last-night-voided and first-morning-voided urine concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) as a conceptual analogy to the invasive gonadotropin-releasing hormone (GnRH) stimulation test setting.

Methods: We investigated the nocturnal changes in the immunoreactivity levels of urinary gonadotropins between early and late prepubertal stages as well as between early and late pubertal stages in FMV and LNV urine samples from 30 girls, of whom the prepubertal ones were further investigated through follow-up visits within the one-year-period from the start of the study.

Results: ROC analysis revealed that the FMV total U-LH and FMV U-FSH concentrations at or above 0.3 IU/L and 2.5 IU/L, respectively were excellent predictors of a forthcoming onset of puberty within one year (100% sensitivity, 100% specificity, AUC: 1.00 and n=10, for both). FMV total U-LH concentration at or above 0.8 IU/L represented the cut-off for clinical signs of puberty. An overnight increase (FMV/LNV ratio) in total U-LH concentrations and in the U-LH/U-FSH ratio at or below 1.2-fold in pubertal girls was associated with the postmenarchal pubertal stage.

Conclusion: FMV total U-LH and U-FSH above 0.3 IU/L and 2.5 IU/L, respectively can be used as cut-off values to predict the manifestation of the clinical signs of puberty within one year. FMV total U-LH concentrations 0.3-0.8 IU/L and 0.6 IU/L may represent the range and the threshold, respectively, that reflect the loosening of the central brake on the GnRH pulse generator.

P1-148

Prevalence of brain alterations in boys with isolated central precocious puberty

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Introduction: Brain magnetic resonance imaging (MRI) is routinely performed to identify brain lesions in boys with central precocious puberty (CPP). In contrast to girls, in whom more than 90% of cases are idiopathic, it has been reported that 4 up to 75% of boys with CPP have pathological brain lesions.

Aim: to evaluate the prevalence of brain lesions in males with isolated CPP and to identify potential clinical and biochemical predictors of brain abnormalities.

Methods and Results: We conducted a retrospective cross-sectional study by retrieving clinical records of boys diagnosed with CPP from 2000 to 2022 diagnosed in a single tertiary center. Sixty-eight boys with CPP diagnosis were identified. All boys underwent a thorough endocrine assessment and brain MRI scan with a detailed examination of the hypothalamic-pituitary area. Patients with already known CNS abnormalities, associated endocrine disorders, previous hormonal therapies, malformations, neurofibromatosis, or other inherited conditions were excluded. The study population was subdivided into 3 groups according to the age at onset of pubertal signs: 48 patients with age > 8 years, 17 patients with age between 6-8 years, 3 patients with age< 6 years. The MRI findings were categorized into 3 groups: group 1, normal, boys with no CNS abnormalities or minor intracranial alterations not involving the hypothalamic pituitary region; group 2, mild abnormalities of the hypothalamic-pituitary region, considered incidental findings unrelated to central precocious puberty; and group 3, pathological and CNS abnormalities associated with precocious puberty. Brain MRI showed no alteration in 50 patients (73.7%), incidental findings of hypothalamic-pituitary area or other brain areas unrelated to CPP was found in 13 cases (19%), and pathological brain lesions were observed in 5 boys (7.3%). In group 3, 3 patients had tuber cinereum hamartoma (age 6-8 years) and 2 patients low-grade diencephalic ganglioneuroma (age older than > 8 years). Boys with normal MRI (aged 8.28 ± 1.52 years) were older than boys with pathological MRI (aged 7.66 ± 0.82 years, $p=0.08$). No significant differences in basal LH, LH peak after GnRH test, or testosterone level between MRI-groups were observed. Furthermore, no brain lesions in 7 adopted-boys was found and no history of precocious puberty was reported in boys with pathological-MRI group versus normal-MRI group (18 cases, 39%).

Conclusions: Our findings indicate that the prevalence of pathological brain lesions in boys with CPP, when accurately stratified, is considerably lower than previously reported thus making the diagnosis less alarming.

P1-149

Evaluation of new cutt-off points of the LHRH stimulation test in the diagnosis of central precocious puberty

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Introduction: Central precocious puberty (PPC) is defined by the appearance of sexual characters at a chronological age lower than -2.5DS of the average for the reference population. Diagnostic is clinical but the hormonal assessment is essential. Basal gonadotropin values are not enough for the diagnosis. Gonadotropin-releasing hormone (GnRH) stimulation tests evidence the activation of the hypothalamic-pituitary-gonadal axis, however there is controversy about the optimal cut-off points to define a progressive PPC.

Objectives: Due to method change, the objective were to evaluate the usefulness of the GnRH test for the diagnosis of PPC and to define the optimal cut-off point for a progressive PPC with the methodology used in our laboratory.

Methods: Descriptive, prospective study. 55 patients (52 women) visited for suspected precocious puberty during the years 2020-2022.

The evaluation included: anthropometric parameters, basal hormonal analysis, bone age, ultrasound of internal genitalia and GnRH test. According to clinical evaluation the cohort was divided in two groups: progressive puberty (PP) and non-progressive puberty (NPP).

The LHRH test was carried out with basal LH, FSH, Estradiol and testosterone determinations and LH and FSH at 15, 30, 60 and 90 minutes after the administration of 0.1mg of LHRH IV. Serum hormones were measured with Architect i200 immunoassay (Abbot diagnosis).

Data between both groups were compared with Mann-Whitney U and ROC curves are used to calculate the discriminatory cut-off points (MedCalc19.6).

Results: As expected, the determination of gonadotropins is the one that best discriminates a PP, being higher in this group. The other parameters did not obtain significant differences between groups.

Basal and stimulated LH, basal FSH and the basal and stimulated LH/FSH quotient were significantly higher in PP-Group ($p<0.05$).

A basal concentration of LH > 0.48mUI/L has 100% specificity for the diagnosis of progressive PPC, with a sensitivity of 50%.

The optimal cut-off points in the GnRH test to diagnose a PPC are LH at 30 minutes >5.1mUI/L (S84.62, E92.59. AUC 0.937) and LH/FSH at 60 minutes >0.35 (88.46, E96.3. AUC 0.946).

CONCLUSIONS: A basal LH of > 0.48mIU/L is 100% specific for progressive PPC, this would prevent the performance of a stimulation test in these cases.

The stimulated LH at 30 minutes and the LH/FSH quotient at 60 minutes are the optimal predictors of PPC in our cohort.

GnRH test could be simplified, intermediate or longer points do not contribute more sensibility according to our study.

P1-150

Comparative of serum estradiol levels in girls with different types of precocious puberty by liquid chromatography tandem-mass spectrometry and chemiluminescence immunoassay method

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Objectives: To compare the levels of E2 in girls measured by LC-MS/MS and CLIA, and to evaluate the correlations between E2 levels and bone age, uterine length, and uterine volume.

Methods: 133 newly diagnosed girls were selected. There were 80 girls in the ICPP group (44 in the Tanner II stage in the ICPP group, 36 in the Tanner III in the ICPP group), and 53 in the PT group, 40 healthy girls in the Tanner III group, bone age, and uterus and ovary ultrasound results were collected, and CLIA and LC-MS/MS methods detected essential serum E2.

Results: Among the 173 girls, 11 cases (6.4%) of E2 measured by CLIA were less than the lower limit of detection (43.31pmol/l), and two patients (1.2%) of E2 measured by LC-MS/MS were less than the lower limit of detection (3.70pmol/l).

Among the PT group, 5 cases (9.4%) of E2 measured by CLIA were less than the lower limit of detection, and 2 patients (3.8%) of E2 measured by LC-MS/MS were less than the lower limit of detection.

Among the Tanner II stage of the ICPP group, E2 measured by CLIA was less than the lower detection limit in 3 cases (6.8%), and E2 by LC-MS/MS was not less than the lower limit of detection.

Among the Tanner III stage of the ICPP group, 1 case (2.8%) of E2 measured by CLIA was less than the lower detection limit, and none of E2 by LC-MS/MS was less than the lower limit of detection.

In the normal puberty Tanner III group, 2 cases (5%) of E2 measured by CLIA were less than the lower limit of detection, and by LC-MS/MS was not less than the lower limit of detection.

In the PT, Tanner II of the ICPP, the Tanner III of the ICPP and the Tanner III of normal puberty group, the basal E2 level measured by CLIA was significantly higher than that measured by LC-MS/MS in the same group. From a clinical point of view, the difference between the results of the two detection methods is too significant. It can not be accepted in a clinic.

Conclusions: The E2 level detected by LC-MS/MS method differs from that seen by the CLIA method. LC-MS/MS method has higher sensitivity and lower E2 class, and LC-MS/MS method can quantitatively detect E2 in a lower concentration range.

P1-151

Clinical profile of children with central precocious puberty in a single tertiary centre

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Introduction: Our study aimed to describe the clinical profile of children with central precocious puberty (CPP) presenting to a single tertiary centre, and to determine the factors that would lead patients and families to pursue treatment with gonadotrophin releasing hormone (GnRH) agonist as well as the predictors of a more favourable final adult height in this cohort.

Methods: We conducted a retrospective medical chart review of all children (n = 203) with CPP at a single paediatric tertiary hospital from 1st January 2013 to 31st August 2021. Multivariable logistic and linear regressions were used to predict the use of GnRH-agonist treatment and determine predictors of final adult height respectively.

Results: A total of 203 patients confirmed to have CPP were included in this study, with a female predominance (96.1%). The mean chronological age at presentation was 7.54 ±1.31 years in girls (n = 195) and 9.86 ± 0.63 years in boys (n = 8). The mean bone age at diagnosis was 12.6 ± 0.71 years in girls and 9.62 ± 2.11 years in boys. Majority of the patients presented in Tanner Stage 3 of puberty. All of the children in the study were taller and heavier than their peers, with mean height SDS at presentation of 1.31 ± 1.12 and mean weight SDS at presentation of 1.05 ± 0.94. One-hundred and one patient received GnRH agonist treatment, with only 1 patient receiving combination therapy of GnRH agonist and growth hormone. At the end of the study period, only 41 patients with CPP completed their GnRH agonist treatment and had reached their final adult height. Compared to baseline, the mean gain of height standard deviation score (SDS) was 0.02 ± 0.87 suggesting that while GnRH agonist treatments did not significantly augment final adult height, it appeared at least to preserve the height SDS at final height. Predicted final adult height appeared to be a significant predictor of being on GnRH-agonist treatment with odds ratio 0.863 (95% CI 0.749 – 0.994, p-value=0.04). The strongest predictors for final adult height in those who had received GnRH-agonist treatment were age (beta-coefficient -3.63, 95% CI -6.10 – -1.17, p-value=0.006) and height at presentation (beta-coefficient of 0.894 (95% CI 0.465 – 1.324, p-value<0.005) respectively.

Conclusions: In our centre, while GnRH-agonist treatments did not significantly augment final adult height, it appeared at least to preserve the height SDS at final height. Age and height at presentation were significant predictors of final height in those who received treatment.

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P1-152

The awakening of the hypothalamic-pituitary-gonadal axis in the post-COVID era; the Greek experience

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Background: Puberty onset results from the interplay between genetic and environmental factors. During COVID-19 pandemic, children experienced epidemic-related changes, such as stress, sedentary lifestyle, excessive use of electronic devices, all leading to weight gain.

Objective: The aim of our study is to retrospectively evaluate the incidence of premature activation of the hypothalamic-pituitary-gonadal axis, as evidenced by positive GnRH (Gonadotropin-Releasing Hormone) stimulation tests, during and after the Greek lockdown for COVID-19 (4/2020-3/2023;COVID group), comparing with corresponding data from the previous two years (1/2018-3/2020;pre-COVID group).

Method: Children with suspected early puberty, who were referred to the Division of Endocrinology, were identified by electronic medical records. The children were referred due to ***(i)*** pubertal changes, at chronological ages < 8, and < 9 years for girls and boys, respectively, ***(ii)*** accelerated pubertal progression, and/or ***(iii)*** random basal luteinizing hormone (LH) > 0.3IU/L. GnRH analogue (GnRHa) was administered intravenously with subsequent blood samplings for FSH (Follicle-stimulation hormone) and LH at 30', and 60'. Samples at 0' were obtained for a full endocrinologic panel. A cut-off value of GnRHa-stimulated LH ≥ 5IU/L and a ratio of stimulated LH/FSH≥0.6 were considered diagnostic for pubertal response.

Results: Between April 2020-March 2023, 359 children (10.25 cases/month) were referred for suspected early puberty, compared to 163 subjects (6.27 cases/month) during January 2018-March 2020 (+63.48%). A significant increase of pubertal response was observed in the COVID group (53.7% *vs* 44.17%, in the COVID, and pre-COVID group, respectively;$p<0.001$), with the percentage of girls being significantly higher (176/193 *vs* 62/72 girls, equivalent to 91% *vs* 86,1%, in the COVID, and pre-COVID period, respectively; $p<0.05$) in both groups. The majority of cases was observed after the nationwide lockdown revocation (1-12/2021 with 81 cases, *vs* 38, 58, and 16 cases during 2020, 2022, and 1-3/2023, respectively). Interestingly, the age at diagnosis was 7.166±1.86 years in the pre-COVID-group, and 7.466±1.32 years during COVID-19 period, probably due to parental reluctancy for prompt consultation. Higher basal, and peak stimulated LH were observed in the COVID group.

Conclusion: The lockdowns during the pandemic, school closures, social distancing, and financial insecurity could have affected pubertal onset and course, due to severe emotional distress, sedentary lifestyle, and weight gain.

Hormones (IU/L)	Covid-Group, Mean±SD	pre-Covid Group, Mean±SD	*p*
Basal FSH	3.46 ± 2.51	3.29 ±2.56	<0.001
Basal LH	1.61 ± 1.66	1.31 ± 1.96	0.0087
Stimulated peak LH	11.35 ± 2.11	11.04 ±1.22	< 0.0001
Stimulated peak FSH	11.66 ± 6.32	11.51 ± 6.48	< 0.0001

P1-153

Precocious puberty: a new score to assist therapeutic management

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Context: Premature breast enlargement before the age of 8 in girls is caused by a broad spectrum from premature thelarche to central precocious puberty. Treatment with GnRH analogues aim to delay either early onset of menstruation with its psychological consequences and/or early epiphyseal fusion. The Indication of treatment is a challenge classically based on the result of the luteinizing hormone (LH)-releasing hormone (LHRH) stimulation test.

Objective: To examine the potential usefulness of unstimulated LH levels, in addition to age of onset of breast development and uterine length on pelvic ultrasound in treatment decision.

Method: Clinical, imaging and biological data were retrospectively analyzed in 115 girls with early breast development between 6 and 8 years of age, referred to our pediatric hospital between 2012 and 2021. 26 of them had breast development before the age of 7 (group 1: 22.6%), 24 between 7 and 7.5 years (group 2: 20.8%) and 65 between 7.5 and 8 years (group 3: 56.6%). LH was measured using an electrochemiluminescent immunoassay. Follow-up information was available for 85 patients.

Results: LHRH stimulation test showed LH response levels > 5 U/l in 63 girls (54.7%): 10 in group 1 (38%), 11 in group 2 (45.8%) and 42 in group 3 (64.6%). Only 73.3% of girls demonstrated LH peak > 5 U/l received GnRHa treatment and 20% received treatment while the simulated LH peak was <5 U/l. The analysis of age at breast development, unstimulated LH levels and uterine length in our cohort allowed us to determine a predictive score in 104 of the 115 girls, that was correlated to the LHRH stimulation test results in 83.6% of cases (n=82). Discrepancies were noted for 16 girls, 10 showing stimulated LH peak >5 U/l and negative score and 6 showing LH peak <5 U/l and positive score. For them, predictive score results fit better with the treatment decision than the LHRH stimulation test result.

Conclusion: LHRH stimulation test showed activation of the gonadotropic axis in only half of the girls with premature breast enlargement between 6 and 8 years of age. A score based on unstimulated LH levels, age of onset of breast development and uterine length could be sufficient for treatment decision. Our new score could thus make it possible to dispense with the LHRH stimulation test. However, others studies including growth velocity and bone age may be relevant to support the predictive score.

P1-154

Central Precocious Puberty in Boys; Diagnosis, Treatment and Follow-up: A Nation-Wide Study

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Objective: The aim of this study was to evaluate demographic characteristics; clinical, laboratory, imaging features; and response to treatment of boys who were followed up and treated with the diagnosis of central precocious puberty (CPP) in Turkiye.

Materials and Methods: The study was planned as a multicenter, retrospective study. Cases with a diagnosis of CPP, whose follow-up data were available were included. Patients with diagnosis of congenital adrenal hyperplasia (CAH), or with any other chronic systemic diseases were excluded.

Results: 297 cases were registered into the study and 266 cases were included. Mean age at diagnosis was 7.96±2.2 years and bone age was 9.53±2.53 years. 18.8% of the cases were obese, 30% was overweight and 3.7% had malnutrition. At admission, median Tanner stage was stage II, mean basal LH level was 1.33±1.59 mIU/ml, and total testosterone level was 5.78±71.82 ng/ml. The mean peak LH level of 201 subjects who underwent LH-RH stimulation test was 11.58±8.0 (5-74) mIU/ml. Peak LH/FSH ratio was lower in obese cases than in non-obese cases ($p=0.005$). Intracranial pathological findings were present in 37.6% of 247 patients who underwent cranial imaging. Duration of treatment was 32.17±23.53 months. Mean age at cessation of treatment was 10.55±2.55 years, and bone age was 12.78±0.99 years. 4.5% of the patients reached final height. It was determined that there was no change in the height-SDS, and there was an increase in weight-SDS and body mass index (BMI)-SDS of the patients during the treatment process ($p<0.001$). Total testosterone and DHEAS levels were higher in cases with intracranial pathology ($p<0.05$). Among the cases with and without intracranial pathology; height-SDS change throughout treatment and final height difference from target height were similar. Factors affecting the final height were height-SDS and predicted heightat the beginning of the treatment, paternal height-SDS and target height-SDS.

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Conclusion: In this nation-wide study with a large number of male CPP patients, more than half of the cases were diagnosed as idiopathic CPP. The peak LH/FSH ratio found to be lower in obese children, and similar to the girls with CPP, there was an increase in weight-SDS and BMI-SDS of the boys during treatment. It was determined that the height SDS and predicted height at the beginning of the treatment, the father's height SDS and the target height SDS were the factors affecting the final height.

P1-155

The long-term efficacy of triptorelin 3-month depot in girls with central precocious puberty

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Purpose: The 3-month gonadotropin-releasing hormone analogs (GnRHa) are expected to achieve better compliance in central precocious puberty (CPP) patients, but the 1-month depot remains the dominant choice for conventional treatment worldwide. Our study aimed to investigate the long-term efficacy of 3-month GnRHa for the treatment of CPP.

Methods: In this retrospective study, 69 Korean girls diagnosed with CPP were included with either the triptorelin pamoate (TP) 3-month (n = 29) or triptorelin acetate (TA) 1-month (n = 40) GnRHa and were followed up to one year after the end of treatment. Auxological, radiological, and biochemical data were collected every 6 months.

Results: The baseline characteristics of the subjects were similar between the two groups. The 28/29 (96.6%) of patients in the 3-month TP group had suppressed LH levels (below 2.5IU/L) after 12[W사1] months of treatment, and this suppression level was[W사2] reserved until the final injection. The degree of bone age (BA) advancement in the 3-month TP group decreased from 1.8 ± 0.4 years at the start of treatment to 0.6 ± 0.5 years one-year post-treatment. The height gain in predicted adult height (PAH) at one year after the end of treatment was[W사3] similar between the 3-month and 1-month groups, with a gain of 5.2 ± 3.1 and 5.3 ± 2.4 cm, respectively (P = 0.875)

Conclusion: Our long-term follow-up study showed that the 3-month depot of triptorelin effectively inhibited gonadal and sex hormones, suppressed bone maturation, and increased PAH. We suggest that considering convenience of patients, 3-month GnRHa is promising as a CPP treatment option.

P1-156

A novel ROBO1 gene variant in a patient with pituitary stalk interruption and multiple congenital anomalies

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Background: Pituitary stalk interruption syndrome is a rare disorder characterized by an absent or ectopic posterior pituitary, anterior pituitary hypoplasia and an interrupted pituitary stalk. In some cases, a variety of additional congenital defects may be present. A genetic cause is identified in only around 5% of all cases.

Case Presentation: A 13-year-old male presented to the pediatric endocrinology clinic because of short stature. The patient was diagnosed as an infant with a bicuspid aortic valve and vascular ring, as well as right kidney dysplasia with severe vesicoureteral reflux for which he underwent nephrectomy. At presentation, he had a height of 139 cm (<3rd percentile), a weight of 41 kg (10th - 25th percentile), absence of pubic and axillary hair, with a testicular size between 8 and 10 ml. The patient underwent laboratory testing which revealed growth hormone deficiency (IGF-1 41ng/ml, abnormal clonidine, and glucagon stimulation test), and central hypothyroidism (FT4 0.88 ng/ml, TSH 3.64 μIU/ml). Bone age was consistent with 11 years. Pituitary MRI showed absence of the pituitary stalk with hypoplasia of its anterior lobe and ectopic neurohypophysis, findings consistent with pituitary stalk interruption syndrome (PSIS). Various morphological abnormalities of the cervical spine were also detected. Replacement therapy with growth hormone and thyroxine was initiated. As part of the investigation of the patient's multiple pathologies, whole exome sequencing (WES) study was performed, detecting a c.1343-56G>C mutation in intron 10 of the ROBO1 gene in heterozygosity. No other significant variants were detected.

Discussion: PSIS is a rare cause of hypopituitarism. Mutations of the ROBO1 gene have recently been associated with this condition, as well as with renal agenesis or dysgenesis and congenital heart defects. We report a previously undescribed variant of the ROBO1 gene in a patient that had PSIS, heart and renal defects, although pathogenicity of this intronic variant remains unknown.

P1-157

Girls born small for gestational age may have an earlier pubertal development comparing to girls born appropriate for gestational age

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Keywords: girls, small for gestational age, thelarche, pubarche, menarche.

Background: Small for gestational age (SGA) babies are more prone to have an earlier onset of pubertal development and menarche. We conducted a study comparing the first menarche of small for gestational age (SGA) to appropriate for gestational age (AGA) girl newborns.

Objective: The objective of the study is to determine whether born for gestational age (SGA) have an early or delayed menarche compared to girls born appropriate for gestational age (AGA).

Method: This is a descriptive case –control study based on born girls at Notre Dame Des Secours University Medical Center (NDS-UMC), Byblos, Lebanon between 2000 -2002. Of these girls, 49 were diagnosed as being born SGA using charts produced by I. Olsen et al in 2010. Of these 49 cases, 31 cases SGA were included in our study and 31 girls born appropriate for gestational age were considered as controls.

Results: We used 'Z test' to compare the average age at menarche in both group of girls. The results showed that the average age at menarche in girls born SGA was 11.99 years whereas the average age at menarche in girls born AGA was 12.3 years. The age of menarche of SGA group was earlier than AGA group but this difference was not statistically significant. The beginning of both pubarche and thelarche in SGA and AGA girls was studied and did not show any statistical significance. The average age of thelarche for SGA was 10.78 years comparing to 11.03 years for AGA girls whereas the average age for pubarche for SGA girls was 10.8 years comparing to 11.04 years for AGA.

Conclusion: Our study showed that there is no statistical difference in the average age at menarche between girls born SGA and girls born AGA even if the average age (11.99 years) was earlier in SGA comparing to AGA(12.3 years) girls. An earlier onset of thelarche and pubarche was seen also between the SGA and AGA girls without a statistical difference in the average age.

P1-158

Outcome of Children with Neurofibromatosis in the West of Scotland

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Background: Neurofibromatosis 1 (NF1) is a clinically heterogeneous genetic condition caused by the mutation of the NF1 gene. Individuals with NF1 have an increased risk of developing tumours, both benign and malignant. The most characteristic are plexiform neurofibromas, occurring in almost all patients. Other manifestations include café-au-lait macules, ocular involvement, intertriginous freckling, and learning disabilities or behavioural problems. There is an increased incidence of endocrine disorders such as precocious puberty or GH deficiency, commonly occurring as a complication of visual pathway glioma involving the hypothalamic region. Most signs are visible during infancy, but many symptoms occur as the person ages. Its severity varies widely.

Objective: Our aim was to record the incidence, presentation, characteristics and progression of Neurofibromatosis 1 in the West of Scotland, particularly focusing on predictive factors for incidence and outcomes.

Method: Children diagnosed with Neurofibromatosis 1 at The Royal Hospital for Children Glasgow, between January 2005 and October 2022 were selected. Clinical characteristics were collected through retrospective electronic case note review.

Results: Our pool includes 35 patients with a diagnosis of NF1. Of these, 40% (14/35) reported a positive family history for NF1. Half of the patients did not need treatment. Among those that did (19/35, 54%), 6/19 had a positive family history. Visual problems were present in most patients, with only 5/35 not reporting any visual disturbance. The most frequent tumor was by far visual pathway glioma, diagnosed in 26/35 patients. Other tumors diagnosed were pilocytic astrocytoma (6/35), plexiform neurofibroma (4/35), brainstem glioma (1/35), MPNST (1/35). Endocrine complications were seen in 11/35. The most common was precocious puberty, present in 26% of patients (9/35). Other endocrine conditions were GH deficiency and hypopituitarism. Of the 11 patients that presented with endocrine problems, 6 of them had also undergone treatment related to the tumour. Skeletal problems were seen in 11/35 patients.

Conclusion: Visual pathway glioma, which can lead to visual and endocrine dysfunction, remain the major issue in the children with NF-1. Whilst only half of the NF-1 patients in our cohort developed problems, it is important they are seen regularly, preferably in a designated multi-disciplinary clinic to ensure adequate screening and follow up, including endocrine input.

P1-159

Long-Term Effect of Gonadotropin-Releasing Hormone Analogue Therapy on Adult Height in Girls with Central Precocious Puberty Diagnosed before 4 Years of Age

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Background: Central precocious puberty (CPP) is uncommon before the age of 4 and treatment with GnRH analogues have shown unequivocal benefits. CPP during or near mini puberty entails differential clinical and biochemical features in the diagnosis and leads to longer treatment and follow-up. There are very limited studies with long-term outcomes about CPP girls exclusively < 4 years of age regarding growth, menarche, and adult height after GnRHa withdrawal.

Objective: We describe a long-term case series of girls diagnosed with CPP who started GnRH analogue treatment before the age of 4 years and reached adult height.

Methods: Retrospective descriptive study that included 8 girls with CPP diagnosed before the chronological age (CA) of 4 years that reached adult height. Inclusion criteria were progressive breast growth, advanced bone age, vulvar signs of estrogenic stimulation, LH after GnRH stimulation test >20 UI/L. All girls received Triptorelin one-month formulation and were followed-up in our center. Patients with neurogenic causes were excluded, except for hypothalamic hamartomas. Data are expressed in median (range).

Results: 6 out of 8 girls had idiopathic CPP and 2 presented hypothalamic hamartoma. The CA of treatment onset was 2.5 (0. 7-3.3) years and the difference between bone age (BA-CA) was 1.2 (0.3-3.3) years. 7 girls presented thelarche and pubarche at diagnosis and 2 of them had presented vaginal bleeding. At diagnosis, height was 3.2 (1.5 - 3.9) SDS and height for bone age (H-BA) was -0.1 (-2.4 - 1.3) SDS. GnRHa was discontinued after 8 (7.4-10.2) years. At this time, CA, BA-CA and H-BA were 10.6 (10.1 - 11.1) years, 1.3 (-0.1-2.2) years and 0.1 (-0.9-1.1) SDS, respectively. Growth velocity was 7.2 (4.5-9.6) cm/year after 1 year of GnRHa cessation. Adult height was 161 (154-169) cm [0.0 (-1 – 1.4) SDS], in accordance with their mid-parental height [0.3 (-0.5 – 1.5) SDS]. Menarche occurs at a median CA of 11.6 years, within 1.2 years after therapy suspension The growth after discontinuation treatment to achieve AH was 12.9 (8.2-21) cm. The strongest correlation for AH was H-BA-SDS at the end of treatment ($r=0.93$, $p < 0.01$).

Conclusion: The outcome for adult height in patients with central precocious puberty diagnosed before the age of 4 was optimal. Long-term GnRHa treatment prevented progression of bone age, allowing girls to reach adult height according to their mid-parental height range. The most important predictor of adult height was H-BA-SDS at the end of treatment.

P1-160

COX deficiency: undescribed endocrinological features in three patients with SCO1 mutation

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Background: Cytochrome C oxidase (COX) is the fourth component of the respiratory chain. This protein is located within the internal membrane of mitochondria. COX deficiency is an inherited mitochondrial disease associated with considerable genetic and clinical variability(1).

In fact, four clinical subtypes of this condition have been identified, each one with several phenotypic and genetic variants.

Mitochondrial complex IV deficiency nuclear type 4 is a rare genetic disease caused by compound heterozygous/homozygous mutations of SCO1 gene. This condition is characterized by hypotonia, psychomotor regression, hepatic steatosis, lactate acidosis cardiomyopathy with early onset and poor prognosis(2–5).

Methods: A retrospective review of all cases of MC4DN4 identified at Meyer Children's Hospital was performed. Three cases with two different SCO1 missense mutations and previously undescribed endocrinologic features were identified. Two patients (aged 10 and 13) were siblings, while the third patient was 34 and unrelated to the former family. All of them were affected by hypopituitarism.

Pituitary dysfunction in these patients shows a progressive worsening and an unexpected hyper responsiveness to substitution therapy over time. A thorough genetic and metabolic characterization of each case was performed to exclude other possible mutations and metabolic disorders associated with panhypopituitarism.

Results: Our case series shows peculiar clinical features which consistently differ from previously described phenotype of MC4DN4: patients developed panhypopituitarism, were not affected by cardiomyopathy and had long term survival.

Conclusions: We propose panhypopituitarism as a new part of phenotypic spectrum of MC4DN4, moreover we propose a model to explain these findings and the other alterations in central nervous system found in these patients

References

1. Brischigliaro M et al. Cytochrome c oxidase deficiency. Biochimica et Biophysica Acta (BBA) - Bioenergetics. 2021;1862(1):148335.
2. Valnot I et al. Mutations of the SCO1 Gene in Mitochondrial Cytochrome c Oxidase Deficiency with Neonatal-Onset Hepatic Failure and Encephalopathy. Vol. 67, Am. J. Hum. Genet. 2000.
3. Stiburek L et al. Loss of function of Sco1 and its interaction with cytochrome c oxidase. American Journal of Physiology-Cell Physiology. 2009 May 1;296(5):C1218–26.
4. Leary SC, et al. Novel Mutations in SCO1 as a Cause of Fatal Infantile Encephalopathy and Lactic Acidosis. Hum Mutat. 2013 Oct 1;34(10):1366–70.
5. Brix N, et al. Mitochondrial Disease Caused by a Novel Homozygous Mutation (Gly106del) in the SCO1 Gene. Neonatology. 2019 Oct 1;116(3):290–4.

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P1-161

Quality of life domains changes in children with central precocious puberty

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Background: Precocious puberty is considered a stressful condition leading to psychosocial and behavioral problems in children. Many factors are involved in these changes such as early body changes which make them feeling strange and cause the sense of isolation from social groups. On the other hand, GnRHa treatment can affect psychological functioning of children with CPP through several pathways. There is controversy in the results of studies dealing with that issue, thus this study aimed at assessing the effect of CPP on quality of life among these children cohort.

Objectives: The main objective was to assess the quality of life in children with CPP. Moreover, the study aimed at determining the effect of GnRHa treatment on reversal of these psychological changes if they occurred.

Patients and Methods: It was a prospective case-control study conducted on children with CPP attending the pediatric endocrinology clinic of Alexandria University Children's Hospitals. The study included two groups. Group 1 included 30 patients with CPP and group 2 included 30 healthy controls. After approval of Ethics Committee, all patients were assessed on emphasis of detailed history taking, anthropometric measurement (height, weight, body mass index), and Tanner staging of pubertal signs. Furthermore, hormonal assay of patients was assessed including basal LH, FSH, testosterone/ estradiol, and GnRH stimulation test. Bone age, pelvic or testicular ultrasonography and magnetic resonance imaging of brain were done for all patients. Furthermore, The Arabic form of pediatric quality of life inventory TM 4.0 (PedsQLTM) generic core scale parent-report form was done by parents of patients.

Results: The age of patients ranged from 2.0 – 9.50 years. Besides, the age of controls ranged from 2.0 – 10.0 years. Twenty-nine patients (96.7%) were females. The most common presenting symptom was isolated thelarche in 15 patients (50%). Height SD of patients was significantly higher than that of controls. Twenty-five patients underwent GnRH stimulation test with pubertal response in all patients except one patient. According to MRI brain results, 73.3% of patients were idiopathic CPP and the remaining 8 patients were organic CPP. Children with CPP scored significantly lower than controls in all health-related quality of life (HRQoL) domains except school functioning. After one year of GnRHa treatment, Children with CPP had significantly higher scores in the quality of life domains.

Conclusion: Central precocious puberty has significant negative effect on children's quality of life. All pediatric quality of life domains showed significant improvement after GnRHa treatment.

P1-162

The Therapeutic Effect of Oral Desmopressin Lyophilisate Formulation in Children with Central Diabetes Insipidus

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Background: Experience with oral desamino-D-arginine-8-vasopressin lyophilisate (OLD) for central diabetes insipidus (CDI) in children with CNS malformations is limited.

Objective and Hypotheses: We aimed to assess the efficacy of oral use of OLD in children with CDI.

Methods: Clinical, laboratory, and imaging characteristics of twenty-five children with CDI treated with OLD were evaluated.

Results: Thirteen boys and eleven girls with a mean age of 23 months were evaluated. These children presented with failure to thrive, irritability, prolonged fever, polyuria and hypernatremia. Clinical and laboratory characteristics of twenty-five children are shown in Table 1. Oral administration of desmopressin lyophilisate (120 µg/tablet) was initiated at a dose of 5 µg/kg/day in two divided doses together with controlled water intake to avoid hyponatremia. Nine children were rehospitalization because of hypernatremia due to non-compliance with OLD and recurrent infections. Four episode of hyponatremia was encountered.

Conclusions: Administration of OLD was practical and safe in the treatment of CDI in children with CNS malformations in this small retrospective series.

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Table 1: Clinical and laboratory characteristics of twenty-five children with central diabetes insipidus treated with DDAVP lyophilised formulation through oral route

Age (months)	**52.37 ± 47.83**
Infants (age < 1 year)	**1**
Female	11
Gestational age (weeks)	35.46 ± 3.03
Birth weight (grams)	2463 ± 732
Weight at admission (kilograms)*	26.81± 14.8
Weight SDS at admission	-0.11 ± 1.8
Height at admission (cm)	92.52 ± 30
Height SDS at admission	-0.56± 1.4
Body mass index at admission	17.10± 12.14
Body mass index SDS at admission	0.27± 1.2
Urine output at admission (mL/kg/hour)	6.6 ± 1.4
Serum sodium level (mEq/L)	143.12± 8.6
Serum osmolality (mOsm/kg)	298.2 ± 18
Urine osmolality (mOsm/kg)	160.20 ± 8.7
Serum ADH level (pmol/L) **	<0.5
DDAVP lyophilisate dose at discharge (μg/kg/day)*	7.4 ± 14.2
Decline duration of serum sodium (hours)	15.2 ± 16.4
Decline rate of serum sodium (mEq/L/hour)	0.12 ± 0.04
Decline duration of urine output (hours)	48.6 ± 6.2
Decline rate of urine output (mL/kg/hour)	0.25 ± 0.14
Duration of follow up (months)*	37.79 ± 48.2
Weight at the last visit (kilogram)	31.48 ± 33
Weight SDS at the last visit	-0.29 ± 1.4
Height at the last visit (cm)	103.3 ± 44
Height SDS at the last visit	-0.97± 2.2
Body mass index at the last visit	19.03± 6.7
Body mass index SDS at the last visit	0.27± 1.2

Data are presented as mean ± std dev. unless specified.

P1-163

Identification of novel *NFKB2* mutation in a Korean boy presenting with muscle weakness

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Introduction: Deficient anterior pituitary with variable immune deficiency (DAVID) syndrome is a rare condition characterized by symptomatic ACTH deficiency and primary hypogammaglobulinemia, caused by a heterozygous mutation in the *NFKB2* gene (MIM#164012) on chromosome 10q24. We report the novel mutation of the *NFKB2* gene in a Korean boy presenting with gait disturbance, calf pain, and abnormal thyroid function test.

Case: An 11-year-old Korean boy was presented with limb weakness and an abnormal thyroid function test. The laboratory finding showed an elevated level of creatinine kinase (CK) activity and subclinical hypothyroidism. He complained of leg weakness and calf pain during long walks. The targeted exome panel for neuromuscular disorder was performed, and a novel variant in the *BAG3* gene, which is the causative gene for myopathy, myofibrillar 6 (MIM#612954), was identified. Segregation analysis showed that the subject's mother carried this BAG3 variant, but she had no myopathic symptoms or signs. Since persistent subclinical hypothyroism was noted in this subject, thyroxine was started and a thyroid function test showed a euthyroid state. Additional whole exome sequencing (WES) was done to identify the causative gene for muscular symptoms and CK elevation. During the analysis of WES, he was admited to our hospital for acute sinusitis, and an immunologic evaluation was done for his low albumin and protein levels and sinusitis. Hypogammaglobulinemia including low immuloglobulin G (135 mg/dL) was identified. The novel truncating mutation in *NFKB2* was found in this subject through WES. Segregation analysis for this *NFKB2* mutation revealed de novo mutation. A pituitary function test and sella magnetic resoning imagin showed ACTH deficiency and an empty sella. The hydrocortisone (12 mg/m2/d) and immunoglobulin (30 mg/kg every 3weeks) was started. After medication, the patient's symptoms, including muscle weakness, fatigue, and recurrent sinusitis were improving, and his growth velocity and pubertal progression were within the normal range until now.

Conclusion: In this study, we first report a case of DAVID syndrome caused by novel truncating *NFKB2* mutation in a Korean boy presenting with calf pain and gait disturbance. Since DAVID syndrome is a treatable condition and the onset of adrenal insufficiency is between childhood and adolescence, it is important to differentiate this condition in children who present with atypical muscle symptoms, despite its rarity.

P1-164

Insight into Gut Microbiota of Normal Body Mass Index Girls with Idiopathic Precocious Puberty

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Keywords: precocious puberty; idiopathic central precocious puberty; premature thelarche; gut microbiota; HPG axis

Background: The incidence of precocious puberty and obesity has increased significantly after the COVID-19 epidemic, and the specific cause is not clear. There seems to be a causal relationship between obesity and idiopathic central precocious puberty. A few studies have shown that the changes of gut microbiota (GM) in children with precocious puberty are similar to those in obese children, and there is no further exploration. It has not been reported whether there is the imbalance of GM in normal body mass index (BMI) girls with idiopathic central precocious puberty (ICPP) and the change of GM in ICPP children before and after gonadotropin-releasing hormone analog (GnRHa) treatment.

Method: The study subjects include 6-9 years old girls with normal BMI ,who were diagnosed and Follow- up in the Department of Endocrinology, Genetics and Metabolism of Children's Hospital Affiliated to Zhengzhou University from December 2021 to June 2022, and were divided into CPP group

(30 cases) and PT group (30 cases). 28 Age-matched healthy girls with normal BMI were control group. 10 Girls in the CPP group who received GnRHa treatment were selected, and divided into pre-treatment group and post -therapy group. All subjects collected their fresh fecal samples, and 16S rRNA gene sequencing was used to analyze gut microbiota .

Results: Alpha diversity of PT group was higher than that of HC group ,and there were significant differences in Beta diversity between CPP group and HC group, PT group and HC group ($P<0.05$).The CPP group and PT group both had significantly higher relative abundance of Alloprevotella ($P<0.05$). The GM of post-treatment girls were different with pre-treatment girls, and the GM of post-treatment girls were similar to that of healthy children. Luteinizing hormone and follicle stimulating hormone levels were negatively correlated with Veronococcus ($P<0.05$). Follicle stimulating hormone levels were positively correlated with rumen coccus ($P<0.05$). Estradiol was positively correlated with Chlorocurium, Bacillus and Acinetobacter ($P<0.05$), and negatively correlated with Clostridium ($P<0.05$).

Conclusion: Girls with normal BMI and precocious puberty also have intestinal flora disorder,

it was mainly manifested in the species difference of GM compared with the healthy control group. The changes of sex hormones have an impact on the structure of GM. There is a causal interaction between the hypothalamic-pituitary-gonadal axis (HPGA) and GM, which is worthy of further investigation.

P1-165

Pheochromocytoma and it's cardiovascular complications in children

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Intoduction: Pheochromocytoma is a neuroendocrine disease rarely encountered in childhood, and it's complications are even less frequent among children. Catecholamine-induced cardiomyopathy (CICMPs) is a rare complication of pheochromocytoma with a reported incidence of 8–11 % of all patients. Symptoms are often accompanied by hypertension, which is most common among children.

However, classical symptoms such as hypertension, paroxysmal headache, sweating, palpitation do not necessarily occur in all patients with CICMPs. In absence of clear signs of catecholamine excess, patients with non-ischemic and non-valvular cardiomyopathy should be considered as possible cases of CICMP.

Case Presentation: 14-year-old girl was admitted to the pediatric cardiology department with complaints of severe shortness of breath, excessive sweating, fatigue and weakness. According to outpatient records, EchoCG revealed a marked decrease in the contractility of the left ventricular myocardium with an ejection fraction of 17-19%.

Initial observation and tests were consistent with diagnosis of dilated cardiomyopathy and heart failure NYHA Class 3:

Observation and tests	Results
Subjective signs	Severe shortness of breath during minor physical activity, profuse sweat
Objective signs	Blood pressure 90/55mmHg, breath rate 25 per minute, heart rate 120 per minute
Fasting glucose	119.9 mg/dl
Insulin	10.94 mcU/mL
HOMA-IR	3.2
NT-proBNP	3858 pg/ml.
Cardiac MRI with contrast	Fibrous subendocardial and intramural changes in the myocardium of the left ventricle, dilation and dysfunction of the left ventricle
Thoracic CT	Hpertrophy of the left ventricle, limited pneumofibrosis of the lower lobe of the left lung
Abdominal ultrasound	Neoplasm (5,2x3,9cm) in the projection of the the right adrenal gland

Consequently, patient was consulted by endocrinologist. Secondary survey:

Tests	Results
Urine Metanephrines	21.21 mcg/day
Urine Normetanephrine	1447.20 mcg/day
Cortisol	929.50 nmol/l
ACTH	126.30 pg/ml
Aldosterone	810.34 pg/ml
NSE	13.58ng/ml
Abdominal MRI with contrast	Volumetric formation (3.8x4.0x4.3cm, adrenal incidentaloma?) of the right adrenal gland and hyperplasia of the left adrenal gland.

Therefore, patient was diagnosed with pheochromocytoma, catecholamine-induced cardiomyopathy, heart failure NYHA Class 3. Subsequently, laparoscopic tumoradrenalectomy was performed. Patient was later transferred back to pediatric cardiology department, for further heart failure and DCM treatment. Tertiary survey:

Tests	Results
Pathohistological examination of the neoplasm	corresponds to a pheochromocytoma.
Immunohistochemical examination	corresponds to a benign pheochromocytoma.

Discussion: This case shows necessity of alertness for early detection of pheochoromocytoma and it's complications in children.

Considering, the size of the tumor, and hyperplasia of the left adrenal gland, genetic study for MEN2 is necessary.

P1-341

Correlation Analysis of Genotypes and Phenotypes of 91 young male paediatric patients with congenital hypogonadotropic hypogonadism

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Background: Congenital hypogonadotropic hypogonadism (CHH) is a rare disorder caused by the deficient production, secretion or action of gonadotropin-releasing hormone (GnRH), which is the master hormone regulating the reproductive axis. CHH can be divided into Kallmann syndrome (KS) with dysosmia and normosmic Congenital hypogonadotropic hypogonadism (nCHH) according to the presence or absence of an olfactory disorder.

Methods: We retrospectively evaluated 91 CHH patients (56 KS and 35 nCHH) aged 0 to 18 years who were diagnosed at the Department of Endocrinology of the Children's Hospital Affiliated to Zhengzhou University from 2016 to 2021. We analysed the patients' clinical data, including their hormone levels and gene sequences.

Results: In total, 81.3% of the patients had micropenis, including micropenis(24,26.4%), micropenis with cryptorchidism (38,41.8%), micropenis with hypospadias(9,9.9%), micropenis with hypospadias and cryptorchidism(3,3.3%); cryptorchidism(3,3.3%), and puberty absence(14,15.4%). A total of 51 patients with KS completed an MRI examination of the olfactory bulb. and 3.9% (2/51) reported hyposmia,However, no abnormal olfactory bulb, olfactory tract, or olfactory sulcus was found on the MRI. Olfactory bulb MRI showed 47(92.2%) cases of olfactory bulb dysplasia, 33 (64.7%) cases of olfactory bundle were not clearly displayed. A total of 68 patients(KS=46,nCHH=22) underwent genetic testing, 73.5% of cases(50/68) were found 19 CHH-related pathogenic genes. digenic mutations in 7.4% of cases (5/68), and trigenic mutations in 4.4% of cases (3/68). The most common mutations were PROKR2(10/68,14.7%),FGFR1 (10/68,14.7%), CHD7(9/68,13.2%), ANOS1(5/68,7.4%). The most common mutations no signifificant difference in the proportion between KS and nCHH (all P>0.05). Comparing several common genes in CHH, it was found that patients with PROKR2 mutation had a higher proportion of normal testicular function, while patients with TCF12 mutation had relatively poor testicular function.

Conclusion: The diagnosis of CHH should be considered in patients with undescended testis of micropenis. Molecular genetics is an important means to diagnose CHH in children. Abnormalities of ANOS1, PROKR2, PROK2, FGFR1, and CHD7 genes lead to CHH with or without non-reproductive manifestations. Oligogenetic inheritance accounts for 11.8% of all CHH, which may be due to autosomal recessive inheritance or incomplete gene extransion. Except for anosmia, there was no significant difference in clinical phenotype between KS and nCHH. These findings provide greater insight into the diagnosis of CHH and will contribute to its clinical evaluation.

P1-342

The relationship between the amount of ghrelin-positive cells in the stomach and the concentration of ghrelin and anti-ghrelin antibodies in the blood in short stature children, with additional analysis of the impact of H. pylori infection

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Introduction: The growth process in children depends on GH/IGF-1. Ghrelin is stimulator of GH synthesis. Ghrelin also stimulates the orexigenic center peptides responsible for appetite. It is synthesized in the stomach, thus its secretion may be alter by gastrointestinal tract deseases. Recently, high titers of antibodies against some neuropeptides (including anti-ghrelin) have been found in indyviduals with certain microflora components, e.g. Helicobacter pylori (HP) in the molecular mimicry phenomenon mechanism.

The aim of the study was to analyze the relationship between the amount of ghrelin-positive cells in the stomach and serum concentration of ghrelin and anti-ghrelin antibodies in idiopathic short stature (ISS) children, taking into account the impact of HP infection.

Material and Methods: The study group consisted of 77 children with ISS. In each child the endocrine diagnostics were performed, including two GH secretion stimulation tests as well as serum IGF-1, ghrelin and anti-ghrelin antibodies. Then, gastrological diagnostics were performed, including serum anti-HP antibodies, upper gastrointestinal tract endoscopy with urease test, the assessment of HP presence, the inflammatory process severity and the number of ghrelin-positive cells in the collected biopsies.

Results: A significant range of ghrelin-positive cells activity percentage in gastric mucosa has been demonstrated. Their distribution was left-skew, ranged from 1 to 92%, the average was 32.05%. Thus, the study group was divided into patients with lower activity of ghrelin-positive cells (1%-33%) - Group1 (n=47) and with higher activity of ghrelin-positive cells (34%-92%) - Group2 (n= 30).

Significantly lower serum ghrelin concentration was found in Group1 than Group2: 1257.51±604.13 pg/ml vs 1940.59±1524.35 pg/ml, and significantly higher level of anti-ghrelin antibodies in Group1 than in Group2: 0.127±0.036 vs 0.101±0.021, $p<0.01$.

Searching for the reasons for the reduced activity of ghrelin cells in the stomach, the possible impact of the HP presence was analyzed. Of the 21 cases of HP infection, 16 were found in Group1 (34.0%), while only 5 in Group2 (16.7%). It has been shown that in children with HP and a lower number of ghrelin-positive cells, the severity of short stature was greater, but there was no effect on the nutritional status.

Conclusion: In short stature children, gastritis associated with HP infection reduces the number of ghrelin-positive cells as well as the synthesis of ghrelin and increases production of anti-ghrelin antibodies. It seems that this may have an impact on the growth deficiency observed in ISS children.

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Facilitating Transition of Care Into Adulthood in Brain Cancer Survivors With Acquired Pediatric Growth Hormone Deficiency: Insights From an Advisory Board

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Childhood cancer survivors (CCS), particularly brain cancer survivors, are at risk of developing growth hormone deficiency (GHD) due to hypothalamic-pituitary damage from direct tumor mass effects or treatment. Optimization of testing, long-term treatment, and monitoring during care transition from pediatric to adult endocrinology providers remain challenging. A group of endocrinology experts convened to discuss these challenges, the risks and benefits of GH therapy in CCS with GHD, and the importance of increasing collaboration between pediatric and adult care teams to ensure seamless continuity of care during this period. A panel of pediatric and adult endocrinologists convened in May 2022 for an advisory board meeting (sponsored by Novo Nordisk Inc.) to discuss ongoing challenges and provide strategies for optimal management of CCS with GHD. The advisors believe that some oncologists and adult endocrinologists remain concerned about continuing long-term GH therapy in CCS into adulthood given the possibility that GH therapy may facilitate cancer regrowth/spread. Additionally, patients and their families may lack understanding of the metabolic benefits of GH treatment at all ages. Other barriers to managing the transition phase may include loss of insurance coverage as patients age out of their parents' plans and long waiting lists for endocrinology appointments leading to patient dropout. Advisors believe that daily GH treatment is well accepted by patients experiencing fatigue, weight gain, and neurocognitive issues, but patients with no discernible symptomatic improvement may have adherence issues. Advisors recommend creating a summary of research findings (tailored to different educational levels) regarding risks and benefits of GH treatment in cancer survivors to be dispensed to oncologists, endocrinologists, patients, and families. Increased collaboration between pediatric and adult care teams is key to facilitating transition of care. Advisors also suggested highlighting benefits and safety of GH treatment for insurance companies to potentially increase coverage. Lack of communication and understanding seem to be the greatest barriers in continuation of GH therapy during transition of CCS to adult care. Increased education for oncologists, endocrinologists, patients, families, and insurance companies may facilitate acceptance of GH treatment and better treatment decisions for patients.

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Neurobehavioural impairments in children with septo-optic dysplasia spectrum conditions: A systematic review

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Background: Septo-optic dysplasia (SOD) is a rare condition diagnosed in children with two or more of the following: hypopituitarism, midline brain abnormalities, and optic nerve hypoplasia (ONH). Children with SOD experience varied visual impairment and endocrine dysfunction. Autistic-like behaviours have been reported, however the nature and prevalence of these neurobehavioural impairments remain to be fully understood. The present systematic review aimed to explore the type and prevalence of neurobehavioural impairments in children with SOD spectrum conditions.

Methods: The search was conducted in PubMed, EMBASE, and PsycInfo. Hand-searching reference lists of included studies was conducted. All peer-reviewed, observational studies assessing neurobehavioural impairments or autism spectrum disorder (ASD) symptoms in children (<18 years) with SOD, ONH, and SOD-plus were included. Studies were excluded if they did not report standardised measures of neurobehavioural or ASD outcomes.

Results: From 2132 screened articles, 20 articles reporting data from a total of 479 children were included in prevalence estimates. Of 14 studies assessing cognitive-developmental outcomes, 175 of 336 (52%) children presented with intellectual disability or developmental delay. A diagnosis of ASD or clinical level of symptoms was observed in 65 of 187 (35%) children across five studies. Only five studies assessed for dysfunction across behavioural, emotional, or social domains and reported impairments in 88 of 184 (48%) of children assessed.

Conclusions: This systematic review found that there is a high prevalence of neurobehavioural impairments in children within the SOD spectrum. Clinicians should therefore consider formal neurobehavioural and ASD assessments alongside routine care. There is, additionally, a need for further research to define and validate a standardised battery of tools that accurately identify neurobehavioural dysfunction in SOD spectrum conditions, and for research to identify the likely causal mechanisms.

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45 mg Subcutaneous Leuprolide Acetate Suppressed Unstimulated Luteinizing Hormone (LH) to Prepubertal Concentrations

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Background: There is evidence that unstimulated LH concentrations may be appropriate to monitor hormone suppression in children with central precocious puberty (CPP) during treatment with gonadotropin-releasing hormone agonists (GnRHa). Literature suggests that unstimulated LH concentrations <0.3 and >0.8 IU/L are prepubertal and clearly pubertal, respectively. We present secondary analyses of unstimulated LH suppression data from the pivotal trial of the first small-volume, long-acting, subcutaneously administered GnRHa for CPP (FENSOLVI®), with the goal of assessing whether the study drug effectively suppressed unstimulated LH to prepubertal concentrations.

Methods: Sixty-two children (60 girls, 2 boys) with treatment-naïve CPP received 2 doses of 45mg subcutaneous leuprolide acetate at 24-week intervals. Blood samples used to assess unstimulated LH concentrations were taken at screening, baseline, and weeks 4, 12, 20, 24, 36, 44, and 48. LH concentrations were assessed using a validated central Cobas ECLIA assay with a lower limit of detection of 0.1 IU/L.

Results: Proportions of children who achieved unstimulated LH <0.3 and <0.8 IU/L and their mean estradiol (E2) concentrations are summarized in Table 1. Proportions of children with various target unstimulated LH at week 24 are summarized in Table 2.

Conclusions: Across 48 weeks, 77 to 81% of children maintained prepubertal unstimulated LH concentrations throughout treatment. These data indicate that 45mg subcutaneous leuprolide acetate effectively suppressed unstimulated LH to prepubertal concentrations. Additionally, 81% of children with pubertal suppression (stimulated LH <4 IU/L) had unstimulated LH <0.8 IU/L, suggesting that this cutoff may be suitable for monitoring treatment efficacy, especially if considered along with sex hormone levels.

Table 1. Proportions (%) of Children Who Achieved Unstimulated LH <0.3 and 0.8 IU/L and Mean E2 (pg/mL) Across 48 Weeks

	Unstimulated LH <0.3		Unstimulated LH <0.8	
Week	**% of Children**	**Mean E2**	**% of Children**	**Mean E2**
12	28	11.1	80	10.5
24	24	10.0	77	10.1
36	22	11.1	81	10.3
48	25	10.0	80	10.1

Table 2. Proportions (%) of Children Who Achieved Target Unstimulated LH at Week 24 in Each Children Subgroup

Target Unstimulated LH (IU/L)	All Children N=62	Children with Stimulated LH ≥4 IU/L N=8	Children with Stimulated LH <4 IU/L N=54
<0.3	24	0	28
<0.6	63	38	67
<0.8	77	50	81
<1.0	84	50	89

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Does premature adrenarche affect adult height in girls?

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Background: Premature adrenarche (PA) is characterized by an advanced bone age (BA) relative to chronological age (CA); nevertheless, clinical importance of this is not entirely understood. Literature contains few data on the impact of increased BA on adult height (AH) in PA. Objective of this study is to assess AH in girls with PA, and factors influencing AH.

Methods: Retrospective analysis was carried out on 477 girls who had been diagnosed with PA in the previous 10 years. Patients with precocious puberty, congenital adrenal hyperplasia and adrenal tumors were excluded. 118 girls, reaching AH were included. Age of onset of symptoms, CA, pubic hair stage, BA, DHEAS level, height, BMI at diagnosis, target height (TH) were acquired from medical files. Multiple regression and ROC curves were used to determine factors affecting AH.

Results: Age at onset of the complaints, CA and BA at diagnosis were 6.6±1.3, 7.3±1.4, and 9.1±1.1 years, respectively. Pubic hair was T2 in 60.2% (71/118) of patients, and T3 in 39.8% (47/118). Height-SDS and BMI-SDS at diagnosis were 1.3±1.0 and 1.0±0.7, respectively. BA advancement was ≥2SD in 50.9% of patients,1-2 SD in 36.4%, and <1SD in 12.7%. 38.1% of patients had normal weight, 38.1% were overweight and 23.8% were obese. DHEAS was ≥35μg/dl in all patients, with a mean of 81.6±33.9μg/dl. Mean ages of thelarche and menarche were 9.8±0.8 and 12.2±0.8 years, respectively. Mean TH-SDS was -0.2±0.9, predicted adult height (PAH)-SDS at diagnosis was -0.7±1.3, and AH-SDS was -0.1±0.9. AH-SDS of patients were similar to TH-SDS (p:0.582). Adult height of 70.3% (83/118) of patients reached target height (AH-SDS≥TH-SDS), however in 29.7% of patients adult height was shorter than target height (AH-SDS<TH-SDS). Age of onset of symptoms, age at diagnosis and TH-SDS were similar between those who reached TH and those who did not. Patients who did not reach TH had more advanced BA, higher height-SDS, BMI-SDS, DHEA-SO4 levels and lower PAH-SDS at diagnosis. Annual change in BA after diagnosis was greater in this group (p<0.001). Most important factors affecting AH-SDS were BA-SDS and BMI-SDS at diagnosis (standardized β coefficient -0.864 and 0.762, respectively;r2=0.828;p=0.001). Threshold values that differentiated patients who did not reach TH from those who reached TH were 1.9SD for BA-SDS (AUC=0.898,p<0.001), and 2.1SD for BMI-SDS (AUC=0.864,p<0.001).

Conclusion: Girls with PA generally reached their target heights. In this cohort, advanced BA (≥2SD) and BMI-SDS≥2 have the greatest impact on adult height.

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Treatment of Children with Central Precocious Puberty (CPP) with Gonadotropin-Releasing Hormone agonist (GnRHa): Evaluation of The Effectiveness of Treatment and Recovery of Gonadal Function

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Background: GnRHa is the treatment for CPP, it arrests puberty progression, slows bone age (BA) maturation, and increases pubertal height. In the last decades, the use of GnRHa has demonstrated its favorable effects on linear growth, although the net height gain and predictors of long-term outcomes remains debated. Concerns raised on thepotential negative effects of treatment on weight and reproductive function.

Methods: We reviewed EMR of children with idiopathic CPP treated with GnRHa at the Endocrine clinic (2014 – 2022). The study aimed to evaluate the effects of GnRHa on height preservation measured by improvement in height SDS, along with changes in BA an AH. We analyzed the effects on BMI and determined the time of menarche and the growth pattern after cessation of GnRHa treatment.

Results: A total of 91 subjects; 84.6% were females (n=77) and 15.4% (n=14) were males. For females, median chronological age (CA) at the start of GnRHa thrapy were 8.5 years (7.8-9.2). For males, median CA at the start of therapy were 11.1 years (9.7-11.9). Comparing to CA, BA at start of therapy was advanced by 1.2 years (0.0-1.8) in females and 1.35 years (0.0-2.17) for males. The mean durations of therapy were 20.5 months (±9.8) for females and 21 months (±4.6) for boys. At the end of the second year of treatment, the difference between BA and CA was 0.6 years (0.0-1.6) in females and 0.4 years (0.1-3.2) (P<0.001). Of those who acived AH, all girls (n=9) and boys (n=3) height fall within thier MPH 2SDS. AH was positively correlated with height SDS and negatively with CA and BA at the start of treatment. The mean CA at menarche was 10.9 year (± 1.5), and median time interval from the cessation of GnRHa to menarche was 12 months (9-16). BMI SDS increased significantly during treatment and persisted at the end of treatment.

Discussion and Conclusions: Mof our patients were females. Treatment with GnRHa resulted in a marked reduction in bone age advancements. BMI SDS increased. The majority of our patients achieved final heights close to the MPH. Our study showed that FAH was correlated negatively with CA, BA, and BA-CA at the start of treatment. The suppression of the HPG axis was recovered after the discontinuation of GnRHa. The average time from the end of treatment to menarche was 10.9 years, which is comparable to the general population.

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Clinical course and genetic analysis in patients with childhood-onset congenital combined pituitary hormone deficiency

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Background: Congenital combined pituitary hormone deficiency (CPHD) has various clinical presentations and can be caused by genetic defects related to pituitary development. We investigated the clinical features and genetic analysis in Korean patients with congenital CPHD.

Method: Among 444 patients diagnosed with CPHD between 1994 and 2021 from Seoul National University Children's Hospital, 43 patients with congenital CPHD were included, after excluding 401 with acquired causes. Data on birth history, anthropometrics, hormonal evaluation, brain magnetic resonance imaging(MRI) findings, extra-pituitary phenotypes, and adulthood outcomes were collected. Next generation sequencing(NGS) analysis was performed in 24 patients using targeted exome (n = 18) or whole exome sequencing (n = 6).

Result: Median age of diagnosis was 2.0 (range, 0-14) years, and 18 (41.9%) were diagnosed 1 year of age. Mean height z-score at diagnosis was -2.4±3.8. Initial presentation at diagnosis were neonatal features suggesting hypopituitarism such as jaundice, hypoglycemia, and micropenis/cryptorchidism in 18 (41.9%), and short stature in 16 (37.2%). Despite suspicious presentation in neonatal period, 8 were diagnosed at later age (range, 1-13 years). Extra-pituitary phenotypes were shown in 31 (72.1%); developmental delay in 15 (34.9%), visual disorder in 9 (20.9%), or others. Growth hormone deficiency was most common (42, 97.7%), followed by thyroid stimulating hormone, adrenocorticotropic hormone, gonadotropin, and anti-diuretic hormone deficit in order. Brain MRI was done in 41 patients, and 33 (80.5%) had abnormalities including pituitary gland ectopia/hypoplasia/aplasia and thin pituitary stalk/aplasia. Those with MRI abnormalities had higher number of hormone deficiencies (P for trend 0.049) than those without. Height and metabolic outcomes were evaluated in 17 adult patients, final height z-scores was -0.8±1.9, and 8 (47.1%) had dyslipidemia without other metabolic disturbances. Pathogenic or likely pathogenic variants were detected in 6 (25%) patients; 1 *POU1F1*, 1 *GLI2*, 1 *HESX1*, 1 *TBC1D32* and 2 *ROBO1*.

Conclusion: Considering high proportion of neonatal presentation, it is important to early identify suspicious symptoms related to hypopituitarism to early manage pituitary and extra-pituitary phenotypes. Detection rate of genetic variant using NGS was 25%, and genetic causes in congenital hypopituitarism remain to be further determined.

P1-349

Compound heterozygous variants in *ROBO1* gene cause CPHD and middle line defects

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Abstract: Combined Pituitary Hormone Deficiency (CPHD) is characterized by growth hormone and at least one other pituitary hormone deficiency. It is of varying etiology, extent and severity and it usually occurs sporadically with only 10% of cases being familial. Although pathogenic variants in more than 30 genes expressed during the development of the head, hypothalamus and/or pituitary have been identified so far to cause genetic forms of CPHD, the aetiology of around 85% of the cases remains unknown.

Patient and Methods: A full-term male (46,XY) newborn, with gestational age 37+6 weeks and birth weight 3220g, was admitted in the 2nd day of life for investigation of dysmorphic facial features and episodes of hypoglycemia. Clinical examination revealed cleft palate, cleft lip, micrognathia/retrognathia, hypotonia, micropenis (0.7cm), hypospadias with bilaterally palpable small testes (testicular volume <1mL). Hormonal assessment revealed central hypothyroidism, adrenal insufficiency, hypogonadotropic hypogonadism and growth hormone deficiency. The MRI showed hypoplastic anterior pituitary with normal posterior pituitary and pituitary stalk. The patient was immediately placed on replacement therapy with hydrocortisone and levothyroxine. Molecular genetic analysis was carried out employing Whole Exome Sequencing (WES) on an Illumina NextSeq 500. Sanger sequencing was undertaken in order to verify the mode of inheritance of the variants identified to be related to the patient's phenotype.

Results: WES revealed the presence of two *ROBO1* gene rare variants, p.Ala972Thr and p.Val1253Met, maternally and paternally inherited. Both were categorized as VUS according to the ACMG criteria. Variant p.Ala972Thr has been reported in a patient with developmental disorders and pontine hypoplasia, thinning of the anterior commissure and corpus callosum, and absence of the transverse pontine fibers. Two secondary findings, *GPR161* p.His373Tyr and *NOTCH3* p.Ser502Phe, were also identified, both of paternal inheritance and categorized as VUS.

Conclusion: To date mutations in *ROBO1* gene have been reported in a few cases of CPHD and PSIS, inherited in an autosomal dominant manner usually from unaffected parents, whereas our patient was found to be compound heterozygote for two rare ROBO1 gene variants. It is not clear whether both *ROBO1* variants are the cause of the phenotype or this is a case of recessive inheritance. Furthermore, it is possible that the secondary findings, particularly the *NOTCH3* gene variant, are pointing to a digenic defect. Correlating the phenotype of patients with CPHD and midline defects with novel genes enhances our understanding of pituitary development, and the genetic basis of the disorder.

P1-350

Onset of puberty and timing of menarche in Saudi schoolgirls: Riyadh Puberty Study II

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Objective: Puberty has a significant contribution to different psychosocial wellbeing aspects. Hence; it is crucial to understand the normal variations in onset and tempo of puberty in a specific population. In this study, we aimed to provide normative data on timing of onset of puberty and age of menarche in Saudi schoolgirls in Riyadh

Methods: This is a cross-sectional field study (2011-2013) including Saudi schoolgirls (grade 1-12; aged 6 to 17 years). Schools were chosen to represent population from urban and rural areas in Riyadh region compared to Phase I study in only urban areas. We assessed the onset of puberty by the age of reaching pubertal maturity breast Tanner stage 2. We also assessed the age of menarche in those who attended it. Means and standard deviations were calculated using SPSS analysis.

Results: We recruited 2001 schoolgirls of which, 1218 attained their menarche at a mean age of 12.38 +/- 1.324 years (25th - 75th centile = 12-13 years). The estimated mean age of pubertal onset at B2 was 11.76 (9-16 years) +/- 1.297 with a 25th centile at 11, 50th at 12 and 75th at 13 years of age. (95%CI 11.60-12.0) years. Compared to data from the same team in Puberty phase I study in 2006, the age of menarche has further declined in adolescent Saudi girls from 13.08+/-1.1 years. However, the age of onset of puberty in phase I study was 10 years.

Conclusion: Our data present the norms of age of onset of puberty in Saudi schoolgirls in Riyadh. Saudi adolescent females had further downward secular trend in the age of menarche from that observed in 2006 phase I study. The inclusion of girls from rural areas could also affect these differences. Saudi girls probably now spend a shorter period in puberty giving a later age of onset and earlier age of menarche.

P1-351

Kallmann syndrome as a manifestion of tubulinopathies - a boy with newly defined *TUBB3* R262H syndrome

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Background: Microtubules, polar polymers of αβ-tubulin heterodimers, constitute dynamic cytoskeletal structures implicated in the regulation of axonal activity along with neuronal proliferation and migration. Tubulinopathies, caused by pathogenic variants in genes encoding different isotypes of tubulin, lead to a wide and overlapping range of nervous system malformations and neurodevelopmental disorders. Namely, heterozygous missense and nonsense mutations in *TUBB3* gene, encoding the neuron-specific β-tubulin isotype III, cause a rare syndrome termed ocular motility disorder termed congenital fibrosis of the extraocular muscles type 3 (CFEOM3), in addition to other clinical findings such as facial paralysis, intellectual and behavioral impairment, and axonal sensorimotor polyneuropathy. Recent studies have managed to delineate different subtypes of the TUBB3 syndrome, drawing on distinct phenotype-genotype correlations for reference, including the most recently defined TUBB3 R262H syndrome. Apart from core features, these patients present with Kallmann syndrome and joint contractures.

Case Description: A 20-month-old boy with facial weakness, bilateral congenital ptosis, hypertelorism, left eye strabismus and nystagmus, poor right eye movements, low-set ears, psychomotor delay, sensorimotor polyneuropathy and hearing loss was referred to the endocrinologist because of suspected hypogonadism. On clinical examination, micropenis and bilateral cryptorchidism were observed. Low serum levels of inhibin B (26 pg/mL, normal range: 50 - 130) and anti-Müllerian hormone (14.2 ng/mL, normal range: 74.7 - 252.7) with normal gonadotropin raise in GnRH test were indicative of hypogonadotropic hypogonadism. MRI of the brain revealed hypoplasia of the corpus callosum and olfactory bulbs, deformation of the ventricular system, and moderate widening of the subarachnoid spaces. First-line genetic evaluation revealed a 46,XY karyotype and array comparative genomic hybridization did not report any microdeletions or microduplications. Whole exome sequencing identified a de novo heterozygous pathogenic variant c.785G>A (p.(Arg262His)) in the *TUBB3* gene (NM_006086.4), which was absent from controls (not reported in the Genome Aggregation Database).

Discussion: Until now, there have been 22 different pathogenic variants in the *TUBB3* gene reported along the protein with several hot spots. Phenotypic features of Kallmann syndrome have been associated with only two of them, R262H and E410K. It has been shown that TUBB3-R262 residue plays a critical role for mediating kinesin interactions, which in turn are required for normal growth of axons.

Conclusion: The newly described TUBB3 R262H syndrome constitutes the most severe form of syndromic CFEOM. Due to enhanced genetic testing and established phenotype-genotype correlation, more tailored multidisciplinary medical care and genetic counseling can be assured.

P1-352

The incidence of central precocious puberty in Korea between 2012 and 2020, population-based study

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Purpose: A decline in the age of pubertal onset and increases in the prevalence of central precocious puberty (CPP) have recently been widely reported throughout the world. Based on national population data, this study was conducted to analyze Korea's CPP incidence rate.

Methods: Between 2012 and 2020, data from the Korean national health insurance service for girls aged 8 years and younger and boys aged 9 years and younger were analyzed. CPP was defined as the gonadotropin-releasing hormone stimulation test (GnRHt) positive (peak luteinizing hormone ≥5 mIU/mL) at less than 8 years for girls and less than 9 years for boys. The inclusion criteria are the positivity of GnRHt and the use of therapeutic drugs for more than 6 months. The genetic, neuro-developmental, cancerous, metabolic diseases and prematurity, small for gestational age were excluded.

Results: The size of the population aged 0 to 8 included in the analysis ranged from 2.4 million in 2012 to 2.0 million in 2020 in boys and aged 0 to 7 included in the analysis ranged from 2.0 million in 2012 to 1.7 million in 2020 in girls. In boys, the overall incidence rate of CPP per 100,000 was 15.9 in 2012 and it increased to 99.6 in 2020, and in girls, 981.0 in 2012 and 1754.6 in 2020. In 2012,

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73.7% of boys diagnosed with CPP were 7 and 8 years old, in 2020 it increased to 96.2% in the same age group. In girls, 86.3% of CPP were diagnosed at 6 and 7 years old in 2012, compared to 96.8% in 2020 at the same age group.

Conclusion: Between 2012 to 2020, although the population was declining, the incidence rate of CPP per 100,000 was increasing in boys, from 15.9 in 2012 to 99.6 in 2020, and in girls, from 981.0 in 2012 to 1754.6 in 2020. Further research on the continuous and rapid increase in CPP is needed.

P1-353

Clinical features of hyperprolactinemia in children and adolescents

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Background/Purpose: Hyperprolactinemia is a rare endocrine disorder in childhood and there are limited etiological, clinical, and demographic data. The purpose of this study was to evaluate the clinical features and course of hyperprolactinemia in childhood and adolescents and to help diagnose and plan the management.

Methods: In this single-center retrospective study included 21 patients with hyperprolactinemia from Ajou University Division of Pediatric Endocrinology. Clinical symptoms, brain magnetic resonance imaging (MRI), serum prolactin (PRL) levels, associated diseases, medications, and post-treatment course were reviewed.

Results: Among 21 patients (male=10, female=11) with hyperprolactinemia, 5 females were diagnosed with prolactinomas (median age 16.1 years, range 15.2–17.0 years). 16 patients were diagnosed with idiopathic hyperprolactinemia (median age 10.9 years, range 6.3-16.2 years, 6 females, 10 males). The mean PRL level at diagnosis was higher in patients with prolactinoma (134.12±112.05 ng/mL) than in patients with idiopathic hyperprolactinemia (27.48±9.13 ng/mL) (p=0.008) Children with hyperprolactinemia presented variable clinical symptoms. The clinical manifestations of hyperprolactinemia at diagnosis were headache (7/11, 63.6%), menstrual irregularities (5/11, 45.5%), galactorrhea (3/11, 27.3%), visual field defect (1/11, 9.1%), obesity (1/11, 9.1%) in girls. In boys, gynecomastia (8/10, 80%) and obesity (6/10, 60%) were present. Headache and menstrual irregularities were more common in patients diagnosed with prolactinoma than in patients with idiopathic hyperprolactinemia. Cabergoline as medical treatment (n=2) decreased the tumor volume and normalized the PRL level.

Conclusion: In children and adolescents with irregular menstrual cycles and headache, hyperprolactinemia is suspected prolactinoma and cabergoline was effective for the treatment of prolactinoma.

P1-354

The effect of leuprolide acetate 11.25mg 3-month formulation in children with central precocious puberty: A systematic review and meta-analysis

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Background: Central precocious puberty (CPP) results from the premature pubertal activation of the hypothalamic-pituitary-gonadal axis before eight years for girls or nine years for boys. A systematic review and meta-analysis was conducted to evaluate the long-term efficacy and safety of leuprolide acetate (LA) 11.25mg 3-month formulation in children with CPP.

Methods: A systematic search in PubMed and Embase was conducted for eligible studies. Primary end points include mean stimulated or peak LH, FSH (≤4 IU/L), oestradiol (<20 pg/ml) and testosterone (≤30 ng/dL) level after treatment; proportion of children with a supressed LH, FSH, oestradiol, testosterone levels; Secondary endpoints include height, weight, BMI, bone age, bone age to chronological age (BA-CA) and growth velocity before and after treatment; proportion of children with clinical suppression of breast or genitals.

Results: A total of 11 articles were included in this study and consisted of 582 patients with CPP. After treatment, the mean stimulated LH levels decreased to 1.03 IU/L (95% CI: 0.56 – 1.49) at 6 months and remained low at 12 months (1.78 IU/L [95% CI: 1.19 – 2.37]). The proportion of children with a suppressed LH at 6 months was 89.0% (95% CI: 82–94). The mean stimulated FSH levels were decreased to 1.65 IU/L (95% CI: 0.62 – 2.68) by 6 months. The mean basal estradiol and testosterone levels were suppressed in 97% (95% CI: 81–100) and 91% (95% CI: 79–97). Compared to baseline, the mean change in BA-CA ratio decreased at 6, 12 months and 3 years to -0.04 (95% CI: -0.08 – -0.00), -0.30 (95% CI: -0.46 – -0.14) and -0.65 (95% CI: -1.50 – 0.20) respectively. The mean growth velocity was 6.07 cm/year (95% CI: 2.27 – 9.87) at 6 months and decreased to 4.45 cm/year (95% CI: 3.05 – 5.85) at 12 months. LA 3-month formulation was well tolerated and most observed adverse events (AEs) were moderate.

Conclusion: LA 11.25 mg 3-month formulation is efficacious in suppressing LH, FSH peak, other gonadal hormones and in slowing the bone age and growth velocity in children with CPP.

P1-355

Effects of probiotic supplementation during childhood on the gut microbiota when puberty onset in lactating female mice

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Background: The relationship between probiotic supplementation and puberty onset has not been explored.

Objective: To investigate the effects of probiotics oral intake during childhood on the gut microbiota when puberty onset in lactating female mice.

Method: Feeding female mice with probiotic suspension of Bifidobacterium longum, Lactobacillus bulgaricus and Streptococcus thermophilus from postnatal 21 days for 7 days, observed the time of Vulva opening. The mice were sacrificed on vaginal opening day. Fecal samples were collected from each mouse for the first 3 days of VO, mixed, and tested for 16s rDNA and short-chain fatty acids respectively.

Result: The alpha-diversity analysis showed the Simpson and Good's coverage index were higher in probiotic (Pro) group, and there was no difference in beta-diversity index. LEfSe analysis showed the Pro mice had members of the phylum Verrucomicrobia, genera Akkermansia and Klebsiella were significantly higher than Control mice. The Pro mice had members of the phylum Bacteroidetes, genus Prevotella, Bilophila, Sutterella, and Oscillospira, that were significantly lower than the Control mice ($p>0.05$). The level of caproic acid in Pro group was significantly lower than the Con group (0.008±0.002 vs 0.011 ±0.003 ug/mg, $p<0.05$).

Conclusion: The multi-strain probiotic intervention given to weaned female mice showed the ability to modulate the gut microbiota composition, leading to a significant reduction of potentially harmful bacteria and an increase of beneficial ones.

P1-356

Acquired Hypothalamic dysfunction in childhood: "What do patients need?" – an Endo-ERN survey

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Objective: Hypothalamic dysfunction is a rare condition and can be encountered in patients who have been diagnosed or treated for a suprasellar brain tumor. Due to its rarity, signs and symptoms of hypothalamic dysfunction may be difficult to recognize, leading to delayed diagnosis of the suprasellar brain tumor or to difficulties in finding the health care expertise for hypothalamic dysfunction after tumor treatment. To improve care and outcome of patients with acquired hypothalamic dysfunction, professionals are required to understand the patient needs.

Design: A world-wide online survey was distributed from April 2022 to October 2022 to patients with childhood onset hypothalamic dysfunction following a brain tumor.

Methods: Patients were notified upon the survey through patient advocacy groups, the SIOPe craniopharyngioma working group and the ENDO-ERN platform.

Results: In total, 353 patients with hypothalamic dysfunction following craniopharyngioma (82.2%), low grade glioma (3.1%) or a pituitary tumor (8.2%) responded to the survey. Sixty-two % had panhypopituitarism. Obesity (50.7%) and fatigue (48.2%) were considered the most important health problems. Unmet needs were reported for help with diet, exercise and psychosocial issues. Patients' suggestions for future research include new treatments for hypothalamic obesity and alternative ways for hormone administration.

Conclusions: According to the patient perspective, care for acquired hypothalamic dysfunction can be improved if delivered by experts with a holistic view of the patient in a multidisciplinary setting with focus on quality of life. Future care and research on hypothalamic dysfunction must integrate the patients' unmet needs.

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P1-357

Evaluation of the pituitary gland in patients with Fanconi Anemia

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Introduction: Fanconi anemia (FA) is a genomic instability syndrome associated with congenital abnormalities. Structural anomalies of the central nervous system (CNS), particularly a small pituitary gland, have been published in a few case series. This has been thought to be the cause of the short stature (SS) observed in FA.

Methods: A cross-sectional exploratory study was carried out in pediatric patients at the FA Spanish reference center. Magnetic resonance imaging (MRI) was performed in 21 patients (11=females) between 2017 and 2022. Pituitary volumme (PV) was determined by elipse formula and expressed in SD adjusted for sex and age. MRIs were independently assessed by two observers.

Results: The median age was 11.1 years (IQR:8.8-14.4). MRI abnormalities were found in 11 patients (52.4%;Table 1). The median value of PV was -1.03 SD (IQR:-1.31,-0.36) and pituitary-height was -0.16 SD (IQR:-1.12,0.68). The ICC for volume SD was 0.62 (95%[CI] 0.03-0.85) and pituitary-height 0.95 95%[CI] 0.87-0.98) with a good correlation between observers. In 52.4 % PV was ≤-1SD.The median height was -2.3 SD (IQR:-2.8,-1.5) and 66.7% had SS. All have normal values of IGF1 and IGFBP3, except on patient with GHD. No statistically significant attributable factors were found to be associated with small PV (mutation, sex, pubertal stage, radiotherapy, SS, hormones deficiencies, IGF1 and IGBP3 values).

Discussion: CNS abnormalities are frequent in FA, including a slightly small pituitary gland. These results indicate FA pathway could be involved in the development of CNS. The etiology of SS does not seem to be related to this.

Tanner	Age (years)	Height (SD)	Pituitary Volumme (SD)	Hormonal Deficiencies	Brain Abnormalities
1	6.76	-2.52	-1.31		
1	8.81	-2.63	-1.81		CHIARI 1
1	9.14	-2.28	-1.59		
1	11.30	-2.53	-1.21		THICKENING OF THE PITUITARY INFUNDIBULUM
1	10.73	-1.37	-1.30		THORNWALDT'S CYST
1	14.72	-2.96	-0,01	HH	CORTICOSUBCORTICAL CAVERNOMAS
3	13.77	-1.58	-1.97	HH	NON-SPECIFIC WHITE MATTER LESION
4	15.58	-0.26	0.89	HH	SUPRAVERMIAN CISTERNAL LIPOMA
5	17.16	-2.30	-0.36	HH	
1*	3.57	-1.04	-2.05		
1*	7.34	-2.07	-1.03		
1*	7.39	-2.50	-0.79		CHIARI 1
1*	8.57	-2.96	-0.17		
1*	9.59	-1.47	-1.27		CHIARI 1
2*	11.11	-3.62	0.45	HH	
3*	10.50	-2.20	-0.62		CORTICAL ATROPHY
5*	11.99	-0.63	-0.77	HH	
5*	13.82	-2.76	0.01		NEUROGLIAL CYST
5*	14.44	-1.19	-1.00		MILD PITUITARY STALK THICKENING
5*	16.03	-3.39	-1.17		CORPUS CALLOSUM HYPOPLASIA
5*	17.92	-4.90	-2.2	GHD	SMALL ADENOHYPOPHYSIS AND ECTOPIC NEUROHYPOPHYSIS

Table 1.*Females. HH:Hypergonadotropic Hypogonadism. GHD:growth hormone deficiency

P1-358

Do gonadotropin releasing hormone analogues increase the total body fat mass and body mass index in girls with idiopathic central precocious puberty?

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Aim: Gonadotropin-releasing hormone analogues (GnRHa) are widely used in the treatment of idiopathic central precocious puberty (ICPP) cases due to premature maturation of the hypothalamus-pituitary-gonad axis. The effect of GnRHa therapy on body weight and fat distribution is controversial in the literature. We aimed to examine the anthropometric measurements and body composition analysis of the girls with ICPP and to investigate the effect of related factors on the body mass index and total body fat ratio under the GnRHa therapy.

Method: The girls who were diagnosed with ICPP and treated with GnRHa in the pediatric endocrinology clinic of our hospital between 2020 and 2022 were included in to the study. Anthropometry and body composition analysis with a bioelectrical impedance device were performed at baseline, 6th month and 12th month of the GnRHa treatment.

Results: 50 girls were included in to study. The mean age was 6.89 ± 0.62 years at the diagnosis of ICCP and the GnRHa treatment's start. Body mass index (BMI) was mean 17.39 ± 2.84 kg/m^2 and BMI standard deviation score (SDS) was median 0.46 (1.52) while the BMI was mean 17.9 ± 2.73 kg/m^2, BMI SDS was median 0.76 (0.97) at 6th month and BMI was mean 18.3 ± 2.89 kg/m^2, BMI SDS was median 0.74 (0.74) at the 12th month of the GnRHa therapy. Increasing BMI was statistically significant during the therapy (P<0.001). The total body fat ratio was found to be increased when we compared the baseline, 6th month and 12th month (24.8 ± 5.2 %, 26.4 ± 5.3 %, 28.1 ± 5.5 %, respectively, P<0.001). On the other hand, the total lean mass ratio was found to be decreased during the therapy (71.3 ± 5.6 %, 69.3 ± 5.0 %, 68.2 ± 5.2 %, respectively, P<0.001).

Conclusion: An increase in BMI and fat mass, and a decrease in lean mass were observed during the GnRHa therapy. The decrease in lean mass observed in ICPP cases may be due to the shortening of the prepubertal growing period or the effect of the GnRHa treatment. Continued fat mass accumulation may be a consequence of the GnRHa therapy suggesting that body composition should be monitored during the therapy to prevent future obesity.

P1-359

An Evaluation of coping strategies in girls diagnosed of central precocious puberty before and after the COVID-19 lockdown, and in their mothers: preliminary study

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During the COVID-19 pandemic, a significant increase in Central Precocious Puberty(CPP) has been observed worldwide. The reasons for this phenomenon are yet unclear. In order to evaluate if fear, stress and coping strategies used by children and parents when dealing with negative emotional situations and health issues might have acted as triggers for this phenomenon, we administered specific questionnaires to girls who had a diagnosis of CPP before and after the COVID-19 related lockdown, and to their parents.

Sixty-two girls were included (CA at diagnosis:8.2 ±0.69yr; height:136.5±7.5cm; BMISDS:0,26±0,95). All underwent a GnRH test, an MRI of the brain and pituitary gland, a pelvic ultrasound, and bone age assessment. Complete auxological parameters, biochemical and hormonal data besides parents' height, BMIs, age at puberty, age at menarche of mothers were all taken into consideration. The subjects were divided into rapidly progressive, and non-rapidly progressive CPP. Fifty-one/62 were put on blocking treatment with a GnRH agonist. All completed the Children's Coping Strategies (CCS)questionnaire, aimed at evaluating the strategies used by children in order to cope with situations with a negative emotional impact. The parents completed the Coping Orientation to the Problems Experienced-(COPE-NVI-25) questionnaire, which evaluates problem-, emotion- and avoidant-focused coping when dealing with the health issues of their children. We asked all to answer the items contained in the questionnaires as they would have answered at the onset of CPP. Prior to analysis we carried out a Cronbach test to assess the validity of answers.

Biochemical, hormonal, and anthropometric data had no impact on the answers given in the questionnaires. The parents' auxological data did not influence the answers to the questionnaires. We did not observe any significant difference in the mean scores related to the single subitems in both questionnaires, before and after the lockdown. The answers provided by the patients correlated well with the answers given by their parents. Interestingly, foreigners(12% of this series) had significantly higher results in the religion items in the COPE questionnaire. There were no observed differences between adopted and non-adopted girls. The parents of girls presenting with menarche at diagnosis showed significantly higher results in the social support-related items in the COPE questionnaire.

These preliminary data showed no significant differences in coping strategies in relationship with the onset of precocious puberty before and after the lockdown, however, we cannot exclude that the retrospective evaluation could have biased the results.

P1-360

Management of central diabetes insipidus in disabled children with diluted oral desmopressin lyophilisate formulation administered through nasogastric tube

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Background: Experience with nasogastric administration of oral DDAVP [desamino-D-arginine-8-vasopressin] lyophilisate (ODL) for central diabetes insipidus (CDI) in disabled children with swallowing coordination difficulties is limited.

Objective: We aimed to assess the safety and efficacy of nasogastric use of ODL in disabled children with CDI.

Methods: Clinical, laboratory and neuroimaging characteristics of twelve disabled children with CDI treated with ODL through nasogastric tube between 2012 and 2022 were evaluated.

Results: Six boys and six girls with a mean (± sd) age of 43 (±40) months were evaluated (Table 1). These children [mean weight (± sd) 17 (±13) kg; mean height (±sd) 93 (±30) cm] presented with failure to thrive, irritability, prolonged fever, polyuria and hypernatremia [mean serum sodium 162 (± 3.6) mEq/L]. At the time of hypernatremia, mean serum and urine osmolality were 321 (± 14) mOsm/kg and 105 (± 7.8) mOsm/kg, respectively. ADH levels were undetectable (<0.5 pmol/L) at admission in all cases. Nasogastric tube administration of DDAVP lyophilisate (120 µg/tablet) dissolved in water (10 ml) was initiated at a dose of 1-5 µg/kg/day in two divided doses together with controlled water intake to avoid hyponatremia. The frequency and dose of DDAVP were adjusted based on urine output and serum sodium concentration. Serum sodium normalised in a mean duration of 122.4 ± 10.6 hours with a mean decline rate of 0.52 ± 0.14 mEq/L/hour. Three children needed rehospitalization because of hypernatremia due to unintentional DDAVP omission by caregivers. No episode of hyponatremia was observed. Weight gain and growth were normal during the median follow-up duration of 4.5 years.

Conclusions: Nasogastric administration of oral DDAVP lyophilised formulation was safe and effective in the treatment of CDI in disabled children in this small retrospective series.

This study is underreview process in Pediatric Drugs Journal.

Table 1. Patient Summary

Patient	Diagnosis	Comorbidities
1	Hypoxic Ischaemic Insult	Epilepsy, Left hemiparesis, GH deficiency, ACTH deficiency, TSH deficiency
2	Hypoxic Ischaemic Insult	Epilepsy, Microcephaly
3	Intracranial haemorrhage	Hydrocephalus, Ventriculo-peritoneal shunt
4	Hydrocephalus	Ventriculo-peritoneal shunt
5	Absence of Posterior Pituitary Bright Spot	TSH deficiency
6	Holoprosencephaly	None
7	Holoprosencephaly	None
8	Holoprosencephaly	TSH deficiency
9	Septo-optic dysplasia	Agenesis of Corpus Callosum, GH deficiency
10	Holoprosencephaly	None
11	Hypoxic Ischaemic Insult	Arnold Chiari type 2 malformation, Absent Septum Pellucidum,
12	Septo-optic dysplasia	Cleft Lip and Palate, ACTH deficiency

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P1-361

First interim analysis of the value of First Morning Voided (FMV) Urinary GnRH for the Diagnosis in China CPP Patients

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Background: The gold standard for CPP diagnosis is gonadotropin releasing hormone stimulation test (GnRHST). However, this test is expensive, invasive and inconvenient for screening.

Some recent studies have demonstrated that the FMV urinary luteinizing hormone (U-LH) has a strong correlation with LH peak value and serum basal LH, and a high consistency with Tanner staging results, but due to the lack of large-sample, multicenter clinical research data, a formal standard of FMV urinary Gn has not been established for CPP screening, diagnosis and treatment assessment yet.

Objective: To explore a reasonable cut-off value of FMV urinary Gn for CPP early screening, diagnosis and treatment assessment in China.

Patients and Methods: This is a multicenter, prospective and non-interventional study is being conducted across 10 sites in China to evaluate the value of FMV urinary Gn in screening, diagnosis and follow-up of CPP patients. This study comprises two cohorts: 6,000 healthy children (aged 6-12 years) are enrolled and classified at different Tanner stages to explore the ideal cut-off value of FMV U-LH, and U-LH/U-FSH as a screening indicator for clinically established puberty; 400 precocious puberty patients will also be enrolled to determine if FMV U-Gn correlates with GnRHST results, and the sensitivity and specificity of U-Gn for diagnosis of CPP at different cut-off values will be evaluated to determine the cut-off value. The CPP group will be followed up every three months for a year to evaluate the value of FMV U-Gn in follow-up assessment of CPP patients.

Results: Overall, 142 children diagnosed with CPP were included in this interim analysis; 92.3% female. FMV urinary LH(U-LH), basal serum LH were significantly positively correlated with GnRH-stimulated serum LH($r=0.2$, $P<0.01$; $r=0.39$, $P<0.001$,respectively). The diagnostic ability of FMV urinary gonadotropins was assessed by receiver operating characteristic (ROC) curve analysis. The optimal cutoff values for positive GnRHST result prediction were determined to be 1.68 IU/L for FMV urinary LH (sensitivity, 57.9%; specificity, 84.4%; and AUC 0.700 (0.639-0.757); $p < 0.0001$), and 0.16 for the FMV urinary LH:FSH ratio (sensitivity, 69.2%; specificity, 87%; and AUC 0.843 (0.791–0.886); $p< 0.0001$) .

Conclusion: The FMV urinary LH levels were significantly positively correlated with the pubertal response to the GnRHST. U-LH could be a potential biomarker for CPP auxiliary diagnosis and early screening.

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Case report: rare case of genetic neurohypophyseal diabetes insipidus associated with congenital hypopituitarism: when the fluid deprivation test does not make the diagnosis

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Six-year-old female, diagnosed with GH deficiency at another Center (H: -3.13SDS; GH peak with clonidine 5.7ng/mL, with insulin 1.2ng/mL). Brain MRI at diagnosis: small pituitary gland, ectopic neurohypophysis, normal stalk, right internal carotid artery aplasia. At 10 years onset of polyuria-polydipsia syndrome (PPS) (4L/day–154ml/kg/die); mood disorders and ADHD diagnosis were also reported. A fluid deprivation test was performed, lasting 22 hours (pre: S-Osm 275mOsm/L, U-Osm 346mOsm/kg, Na^+ 142.4mmol/L; post: S-Osm 277mOsm/L, U-Osm756 mOsm/kg, Na^+ 143.5mmol/L, weight loss <5%). Conclusions: primary polydipsia, water restriction recommended.

At 12 years worsening of PPS was reported (5L/day–138ml/kg/die). A fluid deprivation test was repeated (pre: S-Osm 285mOsm/L, U-Osm 409mOsm/kg, Na^+ 141.3mmol/L; post: S-Osm 285mOsm/L, U-Osm 750mOsm/kg, Na^+ 144mmol/L, weight loss <5%), overlapping with the previous one.

At 14 years of age the patient reached her final height (H: -0.29SDS, ΔH pre-post-therapy +2.84SDS, menarche at 13 years, bone age 15 years old). Retesting with insulin was pathological (GH peak 2.4ng/mL). IN-OUT water balances 6L/day–120ml/kg/day. (S-osm 289mOsm/L, U-Osm 155mOsm/kg, Na^+ 143.3mmol/L). Familiarity in the maternal line for PPS emerged during a visit, never previously reported nor investigated. Therefore, the patient underwent NGS for short stature, currently ongoing, and diabetes insipidus: a heterozygous mutation in exon 1 of the AVP gene (c. 55G>A p. /Ala19Thr) was found, associated with neurohypophyseal diabetes insipidus (DI).

Therapy with desmopressin was started, with expected clinical response.

Conclusions: the differential diagnosis between DI and primary polydipsia is complex, especially in adolescence when psychosocial problems are more common. Fluid deprivation test, the pediatric gold standard for the diagnosis of DI, can be falsely negative in partial forms, due to the persistence of vasopressin secretory capacity and the alteration of the renal osmolar gradient, especially in the chronic forms of PPS.

In particular, the aforementioned mutation is associated with a later onset of disease and may not show any frank biochemical alteration due to progressive loss of vasopressin neurons. This can mislead the diagnosis towards forms of primary polydipsia, as in our case.

In the diagnostic-therapeutic process it is therefore always necessary to investigate familiarity, which may not be mentioned, and to consider genetic analysis as well as neuroimaging.

The peculiarity of the reported case is the genetic origin of neurohypophyseal DI despite the presence of a concomitant picture of congenital hypopituitarism, delineated by the anatomical alteration of the hypothalamic-pituitary region and by the permanent GH deficiency.

P1-363

Xanthomatous hypophysitis: A rare cause of paediatric hypopituitarism

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Primary Xanthomatous Hypophysitis (XH) is the rarest histological subtype of hypophysitis. Here we describe the case of a young 9-year-old girl diagnosed with this condition.

The patient presented with a four-month history of an intermittent temporal-frontal headache that became gradually worse and constant for three days prior to admission. She did not have clinical signs or symptoms suggestive of increased intracranial pressure but had mild ataxia. On admission she was febrile, lethargic and had lost 5kg of weight over five months. Her parents had noticed a sudden increase in her fluid intake eight weeks prior to this as well as nocturia.

An MRI head showed a pituitary and infundibula mass extending into the suprasellar cistern and hypothalamus, measuring 23x11x17mm with compression of the optic chiasm. The patient underwent transphenoidal biopsy and partial debulking. Histology showed fragments of fibrous tissue and anterior pituitary gland, with a dense, mixed inflammatory infiltrate composed predominantly of foamy macrophages, in keeping with XH. There were no features on neoplasia.

The patient had a suboptimal response to dynamic testing with glucagon (peak GH 3.1 mcg/L, peak cortisol 435 nmol/L) and remains on hormonal replacement with desmopressin, hydrocortisone, levothyroxine and growth hormone (GH). Repeat MRI five months after initial presentation shows no evidence of reoccurrence.

Hypophysitis is inflammation of the pituitary gland and is thought to have an incidence of 1 in 9 million(1). XH is the rarest form of primary hypophysitis with a female predominance of 3:1. Mean age at presentation is 38 +/- 15 years for both sexes.

Symptoms and imaging of hypophysitis can mimic a pituitary neoplasm (usually adenoma or craniopharyngioma). The most common presenting symptoms of hypophysitis are persistent headache and visual field deficit. Although XH has been reported to have a predilection for the anterior pituitary, it is hypothesised that diabetes insipidus occurs due to compression on the infundibulo-neurohypophysis rather than direct infiltration of the tissue.

The pathogenesis of XH is poorly understood and theories relating to infectious and autoimmune causes have been described.

There is evidence to suggest that XH is less responsive to medical management with steroids then other subtypes of hypophysitis and therefore surgery is often the treatment of choice. Prognosis for XH is variable from complete recovery to no improvement and often hormone replacement is required long term due to on-going endocrine deficiencies.

P1-364

Transient diencephalic syndrome as a result of hypothalamic compression in a paediatric case of neurofibromatosis Type 1 (NF1)

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Introduction: Diencephalic syndrome (DS) is a rare condition characterised by weight loss despite adequate calorie intake in association with other signs and symptoms such as hyperalertness, hyperactivity, visual field defects, nystagmus and vomiting. DS occurs in the presence of hypothalamic lesions, but its exact mechanism remains unclear. The diagnosis is often delayed due to the absence of specific clinical and biochemical features.

Case Description: The index case is a boy diagnosed with NF1 at five years of age with a large neurofibroma of the optic chiasm. Despite first- and second-line chemotherapy sight deterioration proceeded to almost complete blindness; after two years a pilocytic astrocytoma developed in close proximity to the neurofibroma and was deemed unresectable. A wait-and-see approach was adopted due to the slow progression. From an endocrine point of view, he displayed early puberty, growth hormone deficiency and progressive weight gain leading to obesity and insulin resistance. Metformin treatment and lifestyle changes were started with good effect. After three years, at the age of 15, he started to complain of lethargy, dizziness, loss of appetite and absence-like episodes. MRI demonstrated only a slight increase of the cystic component of the tumour with a stable appearance of a previously reported mild ventriculomegaly. In the following months the lethargy increased as well as the weight loss (10.5 kilograms in 1 year). He attended the emergency department for rapid deterioration of his general condition, ongoing weight loss, vomiting and increased frequency of seizure-like episodes. An urgent CT was performed and evidence of a slight increase of the ventriculomegaly and signs of obstructive hydrocephalus were found. He therefore underwent urgent decompression with endoscopic septal fenestration and cyst and tumour fenestration. After surgery his appetite improved with a significant increase in weight (7 kilograms in 4 months).

Discussion: Sporadic DS is typically diagnosed in early childhood and only few cases, mainly in NF1 patients, were reported in older children. The identification of signs and symptoms associated with this condition is difficult, particularly in the presence of multiple confounding factors: in this case the boy was already registered blind, was previously obese and was asked to lose weight. He presented with lethargy and fatigue instead of the more typical hyperactivity. It is still argued if DS is a result of tumour hormonal production/imbalance or of compression on the hypothalamus; our case supports the latter since the sole fenestration led to the resolution of symptoms.

P1-540

Central precocious puberty in boys: clinical decision-making and secular trend

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Objective: Recent studies suggest that boys are undergoing puberty at a younger age. Further, the number of idiopathic male central precocious puberty (CPP) cases are increasing over time. Only a few studies have evaluated the etiological factors in boys with CPP. We describe the etiology of CPP. Further, we define key auxological and clinical cues indicative of organic CPP (OCPP) and characterize the incidence of CPP.

Methods: We reviewed the medical records of 43 boys who had been diagnosed with CPP at the Helsinki University Hospital between 1985 and 2014. Patients were categorized into two subgroups based on the imaging findings: idiopathic CPP (ICPP) (n=32) and OCPP (n=11).

Results: Patients with OCPP were diagnosed younger (median 8.1 years) than patients with ICPP (median 10.3 years) (p=0.006). At diagnosis, there were no differences in the Tanner genital (p=0.65) or pubic hair stages (p=0.50). Though basal serum testosterone levels were higher in OCPP than ICPP (medians 15.0 and 4.8 nmol/l respectively, p=0.038), basal FSH (p=0.78) and basal or stimulated LH (p=0.22 and p=0.19, respectively) did not differ significantly between groups. At diagnosis, patients with OCPP were shorter (mean 0.5SD) than patients with ICPP (1.8SD) (p=0.003). Further, BMI, height velocity, measures related to bone age, or predicted adult height did not differ between the two groups (all, p=0.19-0.74). Multivariate regression with height SDS (HSDS) and age at diagnosis differentiated between OCPP and ICPP with good overall performance, AUC 0.84, p<0.001. With the addition of basal laboratory values (serum testosterone and FSH, both p<0.05), the performance was excellent AUC 0.97, p<0.001. Between 2010-2014, the annual incidence of CPP in boys was 3.7 per 100000 (95%CI 1.2-11.8 per 100000). A significant increase in incidence between 1990-2014 was evident in ICPP (p<0.001), whereas the incidence of OCPP appeared constant (p=0.45). The corresponding incidence rate ratios (IRR) were 1.11 (95%CI 1.05 to 1.19) in ICPP and 1.03 (95%CI 0.95 to 1.14) in OCPP.

Conclusions: In boys, age, HSDS, and serum testosterone values differentiated between OCPP and ICPP. Our analysis suggests that these cues, supplemented with serum FSH, showed good to excellent performance, and could be utilized in the diagnostic decision-making. The incidence of CPP was approximately 3.7 per 100000. The incidence of ICPP increased approximately 11% annually between 1990-2014, whereas the incidence of OCPP appeared constant. The increase in the incidence of ICPP seems too high to be explained only by secular trend.

P1-541

Prediction of Adult Height Based on Automated Bone Age Estimation in Early Puberty: A Single-Center Prospective Study

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Introduction: In cases of precocious puberty, an important factor in making treatment decisions is when adult height estimates based on bone age (BA) determination are behind midparental height. In Turkey, clinicians often use the Greulich Pyle (GP) atlas to determine BA, which can lead to significant differences between assessors. The aim of this study was to compare estimated adult height (EAH) calculations based on BA determined by the automated BoneXpert method with other methods.

Method: This study included 44 girls who were diagnosed with constitutional precocious puberty and admitted to the outpatient clinic between June 2016 and November 2018. BoneXpert was used for the determination of bone age, and the patients were followed up until they reached 'near-final height' (NFH). Three different methods were used for BA determination, including the GP atlas read by a pediatric endocrinologist (Clinician-GP), the GP atlas read by BoneXpert (BoneXpert-GP), and the Tanner-Whitehouse atlas read by BoneXpert (BoneXpert-TW). Seven different EAH calculations were performed using three different estimated height calculation methods, including Bayley Pineau-BP, Roche-Wainer-Thissen-RWT, and BoneXpert adult height predictor (AHP). The study compared the EAH-SDS values and NFH-SDS values of the patients.

Results: The chronological age of the patients at presentation was 9.09±0.89 years, the mean BA was 10.4±1.2 years according to Clinician-GP, 10.3±1.3 years according to BoneXpert-GP, 10.0±1.3 years according to BoneXpert-TW3; the mean height SDS was 0.7, the target height SDS was 0.42. When they reached NFH the height SDS was 0.01. In the whole group, the mean NFH of the children in whom treatment was not initiated (n: 38) and in whom treatment was initiated with the prediction of early menarche (n: 6) were 158.4 cm and 160.8 cm, respectively, and there was no significant difference between them (p: 0.726). When the EAH-SDS - NFH-SDS difference (delta SDS) was compared according to 7 different EAH values, it was found that EAHs calculated according to BoneXpert-TW-RWT and BoneXpert-AHP were the closest (p < 0.001) to the NFH (Table 1).

Conclusion: BoneXpert automated bone age determination may be a more objective option for EAH calculation in cases of precocious puberty; however, larger case series are needed.

	Clinician -BP (EAH-1)	Clinician -RWT (EAH-2)	BoneXpert-GP-BP (EAH-3)	BoneXpert-GP-RWT (EAH-4)	BoneXpert-TW-BP (EAH-5)	BoneXpert-TW-RWT (EAH-6)	BoneXpert -AHP (EAH-7)	p
EAH	160.8	161.20	161.25	161.4	163.2	162	162.6	<0.001
EAH-SDS	-0.39	-0.30	-0.33	-0.29	0.00	-0.19	-0.07	<0.001
Delta SDS	0.34	0.2	0.11	0.12	-0.24	-0.04	-0.08	<0.001

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P1-542

Comparation between syndromic and non-syndromic central precocious puberty: a 10-year experience

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Introduction: Central Precocious Puberty (CPP) has recently been described in patients with isolated or syndromic neurodevelopmental disorders, with greater attention from the scientific community. We carried out this study to compare the main aspects of non-isolated and isolated forms of CPP.

Methods: We conducted a retrospective monocentric study, collecting all treated cases of CPP from 1st January 2013 to 31 December 2022. We distinguished two groups: syndromic CPP (sCPP), composed of patients affected by genetic syndromes or neurodevelopmental disorders, and isolated CPP (iCPP), composed of patients not affected from underlying chronic diseases. Of each patient we evaluated anamnestic, auxological, hormonal and instrumental data at diagnosis and during follow up.

Results: 289 patients were included in the study: 233 in the iCPP group and 56 in the sCPP group. The proportion of males was significantly higher in sCPP (21.4%) than in iCPP (3.9%) group ($p<0.05$). The cumulative incidence showed an increase in the sCPP proportion from 16.9% in the 2013-2017 period to 22.3% in the 2018-2022 period.

The most frequent disturbances found in the sCPP group were: neurocognitive developmental delay (24/56), Neurofibromatosis type 1 (7/56), autism spectrum disorder (5/56 cases), epilepsy (5/56 cases) and Narcolepsy type 1 (4/56).

No statistically significant differences were found between the two groups regarding auxological, hormonal and ultrasound data at diagnosis and during follow-up. Brain-saddle MRI was performed in 102 patients from the iCPP Group and 35 from the sCPP Group. The neuroradiological outcome was significantly abnormal in the sCPP compared to the iCPP group (22.8% vs 8.8%) ($p=0,0004$). Comparing the MRI outcome, we differentiated hypothalamic and non-hypothalamic lesions. While the proportion of hypothalamic lesions was comparable between the two groups (3.92% in the iCPP and 5.71% in the sCPP), the proportion of non-hypothalamic ones was significantly higher in the sCPP forms (17.1% of the sCPP group vs 4.9% of the nsCPP)(p.0.011).

Conclusions: The results of this study confirm an higher frequency of males in the non-isolated forms of CPP. In this group, however, it is interesting to underline that the proportion of hypothalamic lesions is the same compared to isolated CPP, while non-specific non-hypothalamic lesions are mostly found. Moreover, the characteristics of CPP in these two groups seems comparable. The results of this study and the role of non-hypothalamic lesions in the pathogenesis of CPP will be further investigated with prospective studies on a larger sample of the population.

P1-543

Phenotype and genotype in patients with growth hormone difenciency and pituitary morfology abnormality

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Introduction: Congenital hypopituitarism is a heterogeneous disorder with isolated hormone deficiency(IPHD) or combined(CPHD). Main risk factors for CPHD include H-P abnormalities such agenesis corpus callosum(ACC), anterior pituitary hypoplasia(APH), ectopic posterior pituitary(EPP), pituitary stalk interruption(PSI), septo-optic dysplasia(SOD), and holoprosencephaly(HPE).

Patients and Methods: Prospective and longitudinal review of pediatric patients with GH deficiency and pituitary morphology abnormality in a third level hospital.

Inclusion Criteria: patients under 18 years at diagnosis with short stature (<-2SDS), GH deficiency and pituitary morphology alteration on MRI.

Genetic Studies Include: NGS-panel (*HESX1, IGSF1, LHX3, LHX4, OTX2, PAX6, POU1F1, PROK2, PROKR2, PROP1, ROBO1, FGF8, FGFR1, GLI2, GLI3, SOX3*), array-CGH or clinical exome.

Follow-up data was collected annually by reviewing the medical records including hormonal status (previous, at diagnosis of GHD and during follow-up), pituitary imaging, genetic study and treatment.

Results: Thirty-nine patients, 23 IGHD and 16 CPHD. Twenty-eight patients were males.

Median Age at Diagnosis: 0 years (+/-3DS) at CPHD group. Ten patients were diagnosed during neonatal period, they presented severe hypoglycemia and 5 also microphallus, the rest were diagnosed later because of growth retardation at 3 years (+/-2.65DS). **Cerebral MRI:** 11 APH, 3 EPP, 8 PSI, 8 APH and EPP, 1 empthy sella turca, 2 small sella turca, 3 SOD, 1 HPE and 2 hipotalamic-pituitary dysgeneses, in addition 3 patients presented ACC.

Hormonal Deficiencies CPHD Group: TSH deficiency was the second more prevalent (12 patients, 75%) followed by LH/FSH deficiency (10 patients, 62%). ACTH deficiency (6 patients) and ADH deficiency(5 patients).

Genetic Study: The NGS-panel was performed in 29 patients. Heterozygous pathogenic variants were found in 4 (14%): 3 at IGHD group (*HESX1, LHX4, GLI2* genes) and 1 at CPHD group (*GLI2* gene). Clinical exome was performed in 9 patients of the CPHD group: Two patients (22%) presented heterozygous pathogenic variants (*KIF7, FGFR1* genes).

Conclusions: Pathogenic variants in genes typically described in congenital hypopituitarism and H-P abnormalities were observed in patients with IGHD. The performance of our genetic panel is 14% in this group.

CPHD patients had more severe morphological alterations at the pituitary level and presented clinical manifestations at earlier ages.

		Total	IGHD	CPHD
n		39	23	16
Gender	Males	28	16	12
	Females	11	7	4
	APH		9	2
	APH+EPP		6	2
	PIS		2	6
	EPP		3	0
MRI	Small sella		2	0
	H-P dysgenesis		1	1
	Empthy sella		0	1
	SOD		0	3
	HPE		0	1

P1-544

Clinical and laboratory characteristics of arginine vasopressin resistance and high carrier frequency of a novel homozygous variant p.R113C in the AQP2 gene among Buryats

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Background: Congenital nephrogenic diabetes insipidus (arginine vasopressin resistance) is a rare inherited disorder characterized by insensitivity of the kidney to the antidiuretic effect of vasopressin. About 90% cases nephrogenic diabetes insipidus is an X-linked recessive disorder caused by variants in the AVP V2 receptor gene (*AVPR2*). In the remaining cases (10%) the disease is autosomal recessive or dominant and, for these patients, variants in the aquaporin 2 gene (*AQP2*) have been reported.

Aims: Description of 12 cases of arginine vasopressin resistance caused by a novel homozygous variant p.R113C in *AQP2* among the indigenous population of the Republic of Buryatia. Study of the carrier frequency of the p.R113C variant in *AQP2* among Buryats.

Methods: *AQP2* was analyzed by the Sanger sequencing using the Genetic Analyzer Model 3130 sequencer in 12 patients with the phenotype of arginine vasopressin resistance. Genotyping of the nucleotide variant chr12:49951167C>T (c.337C>T p.R113C) was performed by Real-time PCR. 300 healthy individuals of Buryats origin were included in the study. Allele frequencies, Fisher's confidence intervals were calculated using the WinPepi v.11.65 software.

Results: 12 patients from 11 families with arginine vasopressin resistance (female, n=5, male, n=7) were included in the study. The ethnicity of the subjects was Buryats. The mean age of patients was 3.0 years [2.3; 4.5]. All patients suffered from polyuria and polydipsia from the first year of life. Urine SG was decreased in all patients (Me 1001 g/L [1001; 1002]), serum osmolality was increase in 7 patients (Me 301.5 mOsm/kg [293; 307]), sodium levels were maintained at a relatively high level 144 mmol/L [139; 146]. The diagnosis of CNDI was established based on the results of a water deprivation test (lack of response to desmopressin administration). A homozygous variant c.337C>T p.R113C in *AQP2* was detected in all patients.

Among 300 analyzed samples the variant c.337C>T was detected in 5 cases in heterozygous state. The allele frequency of the studied variant was 0.008 (n=5/600, 95% CI=0.0017-0.016). Accordingly, the frequency of heterozygous carrier was 0.0167 (n=5/300). The frequency of arginine vasopressin resistance caused by variant c.337C>T in AQP2 among Buryats was 1: 14400 or 6.9 per 100,000 (95%CI=1:3906–1:346021 or 0,3-26 per 100,000). The frequency of heterozygous carriers of c.337C>T variant is 1:61 subjects (95%CI=1:32–1:294).

Conclusions: The results demonstrate high frequency of arginine vasopressin resistance due to the homozygous mutation p.R113C in *AQP2* among Buryats, which is most likely attributed to a founder effect.

P1-545

Challenges in Diagnosing and Managing Paediatric Metastatic Paraganglioma: A Case Report

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Background: Paragangliomas are rare tumours that originate from neural crest cells. Diagnosing and managing patients with paragangliomas pose several challenges.

Clinical presentation: A 14-year-old female presented with consecutive development of bony lesions lasting for more than 2 years before definitive diagnosis.

MRI of the initial bony lesion was suggestive of osteomyelitis, biopsy was suggestive of chronic recurrent multifocal osteomyelitis. Bony lesions continued to develop, bone marrow did not reveal abnormal cells, and was negative for synaptophysin and chromogranin. She experienced a few episodes of abdominal pains and headaches but no reported sweating, palpitations, or tremors.

Two years after the initial presentation, she had acute cardiovascular collapse, was admitted to PICU, and needed inotropic support. Repeated imaging showed pulmonary nodules and new bony lesions involving the left parietal bone, a biopsy of which showed granulation tissue with no evidence of malignancy. While on inotropic support, plasma normetanephrine and plasma 3-methoxytyramine were 22500 and 188 pmol/L respectively.

A PET CT showed PET-avid lesions and a biopsy from a rib lesion finally revealed findings consistent with a paraganglioma with strong and diffuse positive staining with NSE, chromogranin, and synaptophysin. A repeat plasma normetanephrine and plasma 3-methoxytyramine were 20600 and 257 pmol/L respectively.

An MIBG scan showed an MIBG-avid para-aortic/aortocaval mass, suspected to be the primary lesion.

Genetic testing revealed a heterozygous variant of the SDHB gene NM_003000.2:c.423+1G>A

Alpha blockade was commenced in incremental doses then beta blockade was added. Her blood pressure was successfully controlled, with a postural drop, in preparation for further treatment.

The family was counselled about the diagnosis, therapeutic options, and the relatively unfavourable prognosis.

Challenges discussed in the NET MDT meeting included that the lesions were not amenable to surgical excision, MIBG therapy was the most suitable for her but was not available so Lutetium dotatate therapy (LuDO) was pursued as a clinical trial, which requires isolation for radioisotope administration at another centre, and the importance of genetic counselling in an extended and complex family.

The girl was reluctant to agree to treatment and struggled in the hospital setting but with support from the MDT, both the patient and her mother agreed to receive targeted radionuclide therapy.

Conclusion: This case highlights the challenges in diagnosing metastatic paragangliomas, which should be considered in the differential diagnosis of multiple bony lesions of uncertain aetiology. It illustrates the practical challenges in treating such a rare case in paediatrics.

P1-546

SEMA3A gene variant may cause situs inversus, incomplete cleft palate, and congenital pituitary hormone deficiency

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Introduction: Congenital multiple pituitary hormone deficiency (CMPHD) is a clinical condition that manifests in the early years of life. In most cases, pituitary stalk interruption syndrome (PSIS) can be detected by MR imaging. The current study presents a case with a novel candidate pathogenic gene Semaphorin 3A (SEMA3A) in CMPHD by whole-exome sequencing (WES).

Materials and Methods: Genomic DNA was extracted from the blood sample following the manufacturer's standard QIAamp DNA Blood Kit procedure. The WES results of 1 pediatric patient were analyzed with the "Integrative Genomics Viewer" and "Franklin by Genoox" data analysis programs.

Case Presentation: A female patient was born with a weight of 3,010 grams and a height of 49 cm in the 36th week of pregnancy from a twenty-eight-year-old mother's first pregnancy by vaginal delivery. Postpartum nasal polyps and an incomplete cleft palate were noticed. In the abdominal ultrasonography, there was a situs inversus in the abdominal organs, and an atrial septal defect (ASD) was detected on echocardiography (no dextrocardia). Nasal polyp excision was performed at 11 months, cleft palate repair at 15 months, and atrial septal defect closure at 2.5 years old. Large anterior fontanelle and low free T4 hormone levels were noted at two years old. She was referred to the endocrine department because of short stature at 3 years-9 months. Central hypothyroidism was detected, and l-thyroxine treatment was started. A low dose (1 mcg) adrenocorticotrophic hormone stimulation test was normal during this period. A 5.5-year-old patient admitted to the emergency department with hypoglycemia was diagnosed with central adrenal insufficiency. Then growth hormone was started due to growth hormone deficiency. PSIS was detected on MRI. The prolactin value was within normal limits. The heterozygote missense variant (c.1450C>T, p.Arg484Trp) was detected in the SEMA3A gene by whole-exome sequencing. This variant (rs137871935) was classified as a variant of uncertain significance (VUS).

Discussion: Semaphorin protein (SEMA3) plays a role in developing the nervous system, including the hypothalamus. A deletion in this gene has been identified in a case with short stature, heart, and skeletal anomalies. In another case with PSIS, a pathogenic variant was found, while in yet another case with cardiac, skeletal, and genitourinary system anomalies, a different variant was identified. We predict that patients with incomplete cleft palate, partial situs inversus, cardiac anomaly, and PSIS could effectively explain the pathogenesis of the disease, and the SEMA3A gene is a novel candidate pathogenic gene in PSIS.

P1-547

Evaluation of Electrocardiographic Changes in Girls Receiving Gonadotropin-Releasing Hormone Analogs for Central Precocious Puberty

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Background and Aim: Gonadotropin-releasing hormone analogs (GnRHa's) are the standard medical treatment for precocious puberty. Studies on their side effects in adults have shown that these drugs can cause changes in electrocardiography (ECG) along with some cardiovascular effects; however, the number of studies on children is limited. This study aims to investigate the effect of these drugs on ECG parameters in children diagnosed with central precocious puberty (CPP).

Materials and Methods: This prospective study included 44 girls who presented to Adana City Hospital Pediatric Endocrinology Clinic between April 2020 and December 2021 and were initiated on GnRHa treatment (Leuprolide acetat) with a diagnosis of CPP. ECG was performed before the treatment for patients whose diagnosis was confirmed after hormonal and biochemical evaluations. ECG was repeated at 6 months of treatment in those who regularly used the drug. While puberty examination and laboratory values were evaluated by a pediatric endocrinologist, ECG parameters were estimated by the same pediatric cardiologist who was unaware of the clinical status of the patients. Estimated parameters included heart rate, PR, QRS, QT and, QTc interval, QT and, QTc dispersion.

Results: The mean age of the children who participated in the study was 9.13±1.55 years. The mean dose of GnRHa was 112.87±33.01 µg/kg. The comparison of the pre-treatment and 6-month ECG parameters of the patients revealed a prolonged QT interval after the treatment, with a statistically significant difference (p<0.001). There was no significant difference in pre- and post-treatment values of PR, QRS and, QTc interval, QT, and QTc dispersion (p>0.05). Multivariate linear regression analysis was performed to determine the correlations between ECG parameters and GnRHa dose (µg/kg). For the adjusted regression model, a significant negative correlation was observed between GnRHa dose and PR, QRS, and QT interval (p=0.039, p=0.004, p=0.026, respectively), while no significant correlation was found between GnRHa dose and QTc interval (p=0.386).

Conclusion: Despite a significant increase in QT interval on ECG with GnRHa compared to pre-treatment ECGs in children, this increase was attributed to variability in heart rate. There was no significant change in other parameters studied, including, QT and, QTc interval, QT and, QTc dispersion after the use of GnRH agonists. Therefore, regular ECG monitoring should be considered after the initiation of GnRHa treatment though GnRHa are believed to be safe in childhood as there is not enough evidence yet.

P1-548

Evaluation Of Long-term Height and Pubertal Outcome Of Boys Presented With Delayed Puberty Due To Constitutional Delay In Growth And Puberty And Isolated Hypogonadotropic Hypogonadism

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Background and Objective: Delayed puberty is defined as a lack of the physical signs of puberty in boys by 14 years or beyond the reference age of population standards. This study aims to evaluate the pubertal development and final height (FH) outcome in patients presented with delayed puberty due to hypogonadotropic hypogonadism (HH) and constitutional delay in growth and puberty (CDGP).

Design and Participants: The hospital files of 1654 male patients older than 14 years of age who were evaluated for delayed puberty between 01.012002 and 01.04.2022 in Hacettepe University İhsan Doğramacı Children's Hospital Pediatric Endocrinology Department outpatient clinics were reviewed retrospectively. 191 patients who met the inclusion criteria were included in the study.

Results: The mean age of admission of the patients included in the study was 14.59±0.92 years (Range:3.51). The final diagnosis considered was CDGP for 149 patients while 42 patients had HH. There was a statistically significant difference between the age of presentation for patients with CDGP (14.43±0.60) and those with HH (15.15±0.99)(p=0.036). At the first presentation, the height-SDS of the patients with HH (-1.1±1.2) was higher than those with CDGP (-1.66±0.92) (p=0.03). The mean FH-SDS of patients with HH (-0.09±1) was higher than those with CDGP (-0.64±0.91) (p=0,003). In total, 118 out of 128 patients (92.2%) with CDGP and 36 out of 39 patients (92.3%) with HH had reached an FH consistent with their target height (TH). There was no statistically significant difference between the FH-SDS of patients with CDGP who received testosterone therapy for induction of puberty and those of patients who did not receive (-0.46±0.97SD, -0.74±0.87SD;p=0.094). Besides, the growth rate at six months, in the first year, and during the entire follow-up period was similar in patients who received and did not receive induction therapy.

Conclusion: Results of the present study showed that individuals presented with delayed puberty due to both CDGP and HH reaching their FH consistent with their TH to a large extent. Although patients with HH had lower growth velocity their FH was longer than those with CDGP. This was attributed to the higher presenting height and the higher TH of this patient group. Induction of puberty with testosterone in a boy with CDGP seems not to have a clinically meaningful impact on the FH and long-term pubertal progression. We, therefore, recommend an individualized approach for this group of patients.

P1-549

Single nucleotide polymorphisms (SNPs) of the LIN28B gene and age at menarche in a sample of Greek girls

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Objectives: Menarche is defined as the first menstrual bleeding in females, and the age of onset varies and depends on a complex interaction between genetic and environmental factors. The LIN28B gene single nucleotide polymorphisms (SNPs) rs314276, rs7759938 and rs314280 appear to be associated with cases of premature and early menarche. International databases report that the presence of a G allele of rs314280SNP shifts menarche 1.2 months earlier, a C allele of rs314276 SNP 1.44 months earlier and a T allele of the rs7759938 SNP 1.14 months earlier. The aim of this study was to investigate the relationship between the age at menarche (AAM) of girls of Greek origin and the LIN28B gene SNPs rs314276, rs7759938 and rs314280.

Methods: Girls of Greek origin with menarche up to 18 years were included. Both girls and parents or legal guardians were informed and consented to participate in the study. Blood sample was collected and DNA isolation was performed in order to proceed with polymerase chain reaction (PCR) and Sanger sequencing for identification of LIN28B gene SNPs rs314276, rs7759938 and rs314280.

Results: Two-hundred girls were included in this primary analysis. Major allele homozygotes of rs7759938 SNP (TT) were 116/200 (58%) and mean AAM was 11.64 ± 1.58 years, minor allele homozygotes (CC) were 18/200 (9%); mean AAM 11.31 ± 1.29 years and heterozygotes (CT) were 66/200 (33%); mean AAM 11.54 ± 1.56 years. Accordingly, in rs314280 SNP major allele homozygotes (GG) were 77/200 (38.5%); mean AAM 11.47 ± 1.56 years, minor allele homozygotes (AA) were 26/200 (13%); mean AAM 11.57 ± 1.41 years and heterozygotes (GA) were 97/200 (48.5%); mean AAM 11.66 ± 1.58 years. Finally, in rs314276 SNP major allele homozygotes (CC) were 108/200 (54%); mean AAM 11.58 ± 1.71 years, minor allele homozygotes (AA) were 16/200 (8%); mean AAM 11.43 ± 1.8 years and heterozygotes (AC) were 76/200 (38%); mean AAM 11.61 ± 1.24 years. At least one major allele of the SNP rs7759938[T] was present in 74.5% of the population, major allele of rs314280[G] in 63% and major allele of rs314276[C] in 72.8% of the population.

Conclusion: The aforementioned SNPs of the LIN28B gene associated with earlier menarche were found at high rates in our sample. Although the mean age at menarche of the girls was within normal limits, the presence of the major alleles could be used as a basis for further investigation in larger samples.

P1-550

The endocrine phenotype of SWI/SNF-associated Coffin-Siris syndrome includes pituitary endocrinopathies, pituitary hypoplasia, and septo-optic dysplasia

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Introduction: Coffin-Siris Syndrome (CSS) is a rare multisystem genetic disorder which arises from genetic abnormalities within genes encoding for the SWI/SNF complex (*ARID1A, ARID1B, DPF2, SMARCA4, SMARCB1, SMARCA2, SMARCE1*). Endocrinopathies have been associated with CSS, including idiopathic short stature, hyperinsulinism, obesity, growth hormone deficiency, and cryptorchidism. Here, we describe the endocrine features of a series of children with SWI/SNF-associated CSS.

Methods: Case note review of eight children with CSS caused by pathogenic variants in the SWI/SNF complex attending a tertiary endocrine centre (*ARID1B* n=6; *ARID1A* n=1; *DPF2* n=1).

Results: Of the six children with *ARID1B* variants, one has confirmed growth hormone deficiency (GHD) with pituitary hypoplasia (*ARID1B*, c.1518dupC, p.Gly507fs) and one has short stature, bilateral undescended testes, and a hypoplastic corpus callosum. Two others do not have endocrinopathies but have abnormal pituitaries and/or septo-optic dysplasia (*ARID1B*, c.4063C>T, p.Gln1355*; *ARID1B* c.5993_5994del, p.Glu1998Glyfs*3). The fifth child has a normal pituitary gland, polycystic ovarian syndrome, insulin insensitivity, and anosmia (*ARID1B*, c.3862+1G>A). The sixth has no endocrine nor pituitary abnormalities (*ARID1B*, c.5345del, p.Ser1782Ilefs*8). The child with the *ARID1A* variant (c.1213C>T, p.Gln405*) has septo-optic dysplasia with no endocrinopathies. The child with the *DPF2* variant (c.894_904+6del; p.Cys298Trpfs*) has delayed puberty, GHD, and anterior pituitary hypoplasia. All of these variants are novel, have not been associated previously with CSS, and are predicted pathogenic in *in silico* prediction models.

Discussion: CSS exhibits a complex, multisystem phenotype. Here we expand the spectrum of SWI/SNF-associated CSS to include pituitary endocrinopathies, anterior pituitary hypoplasia, and midline brain abnormalities on the septo-optic dysplasia spectrum. This is consistent with the phenotype seen in mice heterozygous for *Arid1b* loss-of-function variants. We describe novel variants in CSS-related genes, emphasising the genetic heterogeneity of this condition. The SWI/SNF complex modulates chromatin structure and carries key roles in transcription and cell differentiation, which may explain the aberrant pituitary development seen in a subset of patients with CSS.

P1-551

Alteration of sex steroid levels in boys with pubertal gynecomastia

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Introduction: Pubertal gynecomastia (PG), the benign enlargement of breast in adolescents, is a condition whose etiology has not been fully elucidated. Its peak incidence is at mid puberty and decreases thereafter. In many cases breast undergoes full or almost complete regression with advancement of pubertal development, but in others it persists into adulthood. There are still controversies on the precise hormonal imbalance that leads in some adolescents only to glandular proliferation of breast tissue and its lack of regression in others.

Methods: A total of 95 boys with PG were included in the present study. They were divided into three groups according to pubertal stage. Anthropometric measurements and hormonal investigations were collected and compared with a group of 64 healthy controls without PG matched in pubertal stage and anthropometrics.

Results: The hormonal investigations in the group with early pubertal development (Tanner stage 2) proved statistically significant elevation of estradiol (E 2 =125, 34 pmol/l) and decrease in testosterone/estradiol ratio compared to control group (E 2 =79, 53 pmol/l, p=0,023). The same is not found in groups of boys with Tanner stage 3, 4 and 5. Difference of the level of testosterone (T), free T, bioavailable T and Free androgen index (FAI) were not proved between patients and control group at the beginning of puberty, but the level of free androgens due to elevated sex-hormone binding protein (SHBG) were found significantly lower in mid puberty (3-rd and 4-th pubertal stage).

Conclusion: A significantly higher level of estradiol at the very beginning of puberty may be the reason for the development of PG, while in the heyday of puberty the low index of free androgen with a higher SHBG may explain the presence of PG.

P1-552

What girls know about puberty ?

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Introduction: Puberty is a very sensitive period in the life of every adolescent. Having enough knowledge about this physiological phenomenon would allow them to better understand the morphological and psychological changes and to better accept themselves. And therefore, to know how to distinguish between what is pathological and what is normal. This awareness is crucial to diagnose pubertal pathology in time. Hence the important role of school medicine in ensuring that all schoolgirls are well prepared for these changes.

Objectives: To assess school girls' knowledge of body, psychological and behavioral changes during puberty.

Methods: We conducted a quantitative cross-sectional observational study by anonymous questionnaire over 2 months (February, March 2023). It included children aged between 9 and 14 years. The statistical analysis was done through SPSS 23.0 software, including the description (frequency and percentage).

Results: One hundred and nine schoolgirls were collected. The average age was 11 years. Most of girls came from families with an average socio-economic level. Almost half of the respondents did not know what puberty is but recognized the normal age of puberty. Almost half recognized the first sign of puberty while 37% did not know the last sign of puberty. In 59% of the cases, the adolescents did not know that the palpation of a lump in the breast indicates a visit to the doctor, as well as very painful periods (39%). As for psychological changes during puberty, 51% did not recognize any signs that would prompt medical advice. Indeed, 39% indicated that increased appetite was part of the behavioral changes of puberty, while 50% were unable to recognize any signs. Bulimia or anorexia were reasons for seeking medical attention for nearly 60% of the schoolgirls, while only 15% thought that having sexual behavior problems required medical attention.

Conclusion: There is a lot of information that schoolgirls do not know about possible changes during puberty. It is therefore incumbent upon the education sector to ensure that all students are prepared for these changes and to make them aware of any pubertal pathologies so that early diagnosis can be made.

P1-553

A 12-month, open-label, single-arm, phase 3 trial of the efficacy and safety of triptorelin 3-month formulation in Chinese children with central precocious puberty (CPP)

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Background: CPP is commonly treated with triptorelin, a gonadotropin-releasing hormone (GnRH) analogue. It is available as 1-month and 3-month prolonged-release (PR) formulations, but only the former is approved for CPP in China. Overseas studies have proved the efficacy and safety of triptorelin 3-month PR formulation; this study evaluated efficacy and safety in Chinese children with CPP.

Methods: In this 12-month, open-label, multicentre, single-arm study (NCT04736602), Chinese children with CPP received four doses of triptorelin pamoate 15 mg (Diphereline®, Ipsen; delivering 11.25 mg of triptorelin) on Day 1 and Months 3, 6 and 9. Primary endpoint was the proportion of participants with luteinising hormone (LH) suppression (stimulated peak LH ≤3 IU/L after GnRH stimulation) at Month 3. Secondary endpoints included changes from baseline in hormone levels, pubertal stage, auxological parameters, difference between bone and chronological age, uterine length (girls) or testicular volume (boys), and treatment-emergent adverse events (TEAEs).

Results: Overall, 32 patients were enrolled (90.6% female; mean age 7.6 [SD, 0.8] years), of which 31, 30 and 29 completed Month 3, 6 and 12 assessments, respectively. At Month 3, 100% had LH suppression to ≤3 IU/L after GnRH stimulation; this was maintained in 93.5% at Months 6 and 12. Mean basal and peak LH and follicle-stimulating hormone levels were substantially suppressed throughout follow-up in females and males. Sex hormone suppression to prepubertal values (girls, oestradiol ≤20 pg/mL; boys, testosterone ≤0.3 ng/mL) was demonstrated in 100%, 96.8% and 93.5% at Months 3, 6 and 12, respectively. 92.9% and 89.3% of girls had stable breast development at Months 6 and 12, respectively; all boys had stable genital development until Month 12. Mean growth velocity was 8.07, 5.24 and 6.94 cm/year at Months 3, 6 and 12, respectively, and mean difference between bone and chronological age fell from 2.85 years at baseline to 2.39 years at Month 12. In girls, uterine length was stable or reduced at Months 6 and 12 versus baseline, while testicular volume decreased in boys. Eighteen drug-related TEAEs were reported in 10 patients (34.5%), and 2 (6.3%) had serious TEAEs (both pneumonia; unrelated to study treatment). No TEAEs led to treatment discontinuation, and there were no deaths.

Conclusions: Treatment with triptorelin 3-month PR formulation for 12 months demonstrated similar efficacy and favourable safety in Chinese children with CPP compared with previous studies elsewhere. Findings support triptorelin 3-month PR as a viable option for this population.

P1-554

The Evaluation of Cranial Magnetic Resonance Images of Rapidly Progressive Early Puberty Cases

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Purpose: We aimed to determine the frequency and distribution of intracranial pathologies in patients over 8 years of age by evaluating MRI images of patients diagnosed with early puberty-rapidly progressive.

Materials and Methods: The study comprised 118 female patients diagnosed with precocious puberty (PP) and rapidly progressive early puberty (RPEP). The onset of puberty in girls before the age of 8 years is defined as PP. Early puberty is characterized as the onset of puberty between the ages of eight and nine. RPEP was identified by the following indicators: *(i)* breast development after 8 years of age which reached Tanner stage 3 or 4 within 3-6 months, *(ii)* breast development before the age of 9 at Tanner stage 3 or 4, *(iii)* onset of menstruation before the age of 10, or *(iiii)* a predicted adult height below target height with a decline during follow-up. The patients were divided into 2 groups, normal and abnormal, according to MRI findings. According to recent literature brain insults of Abnormal MRI findings were classified into 3 groups: Pathological findings, Questionable relationship with CPP, and Incidental findings. The patients were divided into 4 groups according to MRI findings (normal or abnormal) and PP or RPEP (PP +Normal MR, RPEP + Normal MRI, PP years +Abnormal MRI, RPEP +Abnormal MRI).

Results: Seventy-four of the 118 girls were included. MRI was normal in 54% (n:40) of the cases, abnormal MRI was detected in 46% (n:34). No malignant lesion was detected in cases with abnormal MRI findings. The MRI findings were abnormal in 46% of cases PP group and MRI findings were abnormal in 45% of cases RPEP group. The most MRI finding was incidental findings in both groups. The rate of the cases with the Pathological, Questionable relationship with CPP was similar in both groups(p:0.06). Basal LH concentration of the patients was found to be higher in the RPEP+ Abnormal MRI group compared to the PP +Normal MRI group(p:0.01)

Conclusion: Our study showed that there was no difference in terms of intracranial findings between cases with precocious puberty the age of 6-8 years and cases with rapidly progressive early puberty above 8 years. Exaggerated LH response may be a warning sign for pathological findings on MRI in rapidly progressive early puberty cases.

P1-555

Genetic bases of familial central precocious puberty

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Background: Nowadays, single nucleotide polymorphisms in genes KISS1, KISS1R, MKRN3, DLK1 have been described as the leading cause of precocious hypothalamic-pituitary axis activation in children. Genetic testing in patients with hereditary forms of precocious puberty (PP) can expand our knowledge in underlying molecular mechanisms of the disease. The diagnosis of genetic bases is necessary for genetic counselling. AIM To access clinical characteristics and define genetic defects in patients with hereditary forms of gonadotropin-dependent precocious puberty.

Materials and Methods: 21 patients with positive family history were enrolled into the study: 8 patients were with paternal disease history, 6 – with maternal. 7 patient had siblings with diagnosed PP. The full-exome sequencing was conducted in all the patients.

Results: The median of patients age at the time of the examination was 7,2 years [6,5; 7,7]. Single nucleotide variants were identified in 62% of patients. MKRN3 gene defects were the most common: 10 out of 13 patients had defect in this gene. The rest of group had defects in genes associated with neuroontogenesis and neuroendocrine regulation mechanisms of hypothalamic-pituitary axis: MAPK8IP3 (OMIM no. 605431), POU1F1 (OMIM no. 173110) and NPFF1R (OMIM no. 607448).

Conclusion: MKRN3 defects are the most common genetic cause of hereditary forms of gonadotropin-dependent PP which is consistent with worldwide data.

P1-556

Oxytocin Improved Neurobehavioural Dysfunction in an Adolescent Post-Craniopharyngioma Surgery: A case report

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Background: Craniopharyngioma is a benign tumour that develops in the sellar and surrounding parasellar regions, including the hypothalamus and the pituitary gland responsible for the production and regulation of neuropeptides. Oxytocin is a hypothalamic neuropeptide that has been identified as a key modulator of appetite drive and social cognition. Here, we present a case of parent-observed improvements in neurobehavioural dysfunction following administration of intranasal of oxytocin in a male, post-craniopharyngioma resection.

Case Presentation: A 16-year-old male with panhypopituitarism following surgical resection and proton beam therapy for adamantinomatous craniopharyngioma developed severe hyperphagia, food-related obsessive-compulsive features, and obesity. Specific neurobehavioural features included an overall preoccupation with food (e.g., writing food lists, watching food-related shows, constant food seeking), emotional lability, and anxious-depressive mood. Intranasal oxytocin was administered on a daily dosage of 4 IU/day (increasing to 8 IU/day) and the patient demonstrated improvements in food-related obsessive-compulsive features (e.g., decreased anxiety about obtaining food), reduced desire to eat (e.g., fewer snacks, no longer waking up during night to eat), and improved overall anxious-depressive mood and behavioural functioning. Naltrexone (100 mg/ day) was added after 6 months. The patient was treated with intranasal oxytocin for more than 3 years with no side-effects. Despite neurobehavioural and emotional improvements, his weight gain continued and he maintained a body mass index (BMI) within the obese range (BMI z score from 2.62 to 3.92). Due to shortages in supply, the patient is no longer on oxytocin and his food-related obsessive-compulsive features and symptoms of anxiety and depression have returned, and continue to severely impact his quality of life.

Conclusion: In this patient with post-operative craniopharyngioma, treatment with low dose intranasal oxytocin resulted in reduced food-related obsessive-compulsive features and improved mood symptomatology. The treatment trial was well tolerated, but had no effect on BMI. Future investigations into the potential therapeutic benefits of intranasal oxytocin are required to develop optimal treatment plans for patients with hypothalamic dysfunction and associated neurobehavioural difficulties.

P1-557

Novel LHX4 rare variant in three patients affected by congenital hypopituitarism, presenting a further co-occurrent desease causing variants in GLI2 and IGF1R

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Background: Congenital hypopituitarism (CH) genetics is highly heterogeneous. The massive use of NGS identified at least 21 desease causing genes. Not fully understood inheritance mechanism, incomplete penetrance and variable expressivity explain the complexity of phenotype-genotype correlations. To further complicate the scenario, the co-occurence of more than one desease-causing genes variants can geopardize the phenotype. Herein, we report the heterogeneous genotype and phenotype retrieved in 3 patients with growth deficiency (GHD) belonging to 2 distinct family. All patients carried a novel identical mutations in LHX4 gene, whose disruption causes CPDH4. Besides, a GLI3 variant in patient-1 and IGF1R variant family B was identified.

Case Presentation: Patient-1(family A) presented at 17months of age in suspicion of short stature(SS) genetically due. His height was -2SD, BMI and head circumference (HC) were normal, facies composita and brilliant neurodevelopment. Hormonal data confirmed diagnosis of GHD and central hypothyroidism. Brain RMI revealed important radiological abnormalities: severe pituitary hypoplasia, neurohypophisis ectopia and stalk interruption. Patient responded adequately to replacement therapies. Siblings of family B, patient-2 and 3, aged 8.3 years and 9 months old respectively, were referred for poor growth since birth and familial SS. They were born SGA. Clinical examination revealed severe SS (-6.18SD and -4.11SD for patient-2 and 3 prespectively). Normal BMI and adequate neurodevelopment. Patient-3, also presented small HC (-1.56SD) and hypotelorism. Hormonal data confirmed GHD and, for patient-2, hypothyroidism. Brain MRI documented in both: pituitary hypoplasia, thin stalk and ectopic neurohypophisis. Patient-3 also had olfactory bulb and tract hypoplasia-agenesia. They responded poorly to rGH treatment.

Genetics: exome sequencing highlighted the unreported LHX4 variant(c. 481C>G) in heterozygous state in all patients. In patient-1, the variant was paternally inherited. The father presented short stature and low IGF1 levels. Family B patients inherited from their healthy mother. Brain scan revealed minor pituitary abnormality in parents with LHX4 mutation. Additionally, another heterozygotic gene variant was present: family A proband carried a maternally-inherited GLI3 mutation (c.250C>A), while family B patients shared a paternally-inherited IGF1R mutation(c.166G>A).

Conclusion: CH has a complex and in some cases polygenic inheritance. In family A, the association of GLI3 and LHX4 variants, genes involved in midline embriology, caused a severier radiological abnormalities in patient-1 compared to his parents, while IGF1R mutation in family B explains their IUGR and poor treatment response.

P1-558

Do perinatal history and mode of delivery affect age at menarche? Preliminary data of girls with Greek origin

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Objectives: Age at menarche depends on genetic, environmental, epigenetic and other factors. Studies have shown that aspects of perinatal history, including birth weight, mode of delivery (caesarian section or vaginal delivery) and gestational week at birth influence the onset of puberty. The purpose of this study was to record the age at menarche in a sample of Greek girls and to correlate it with their perinatal history, the mothers' age at menarche, the position in the number of family members and the place of residence.

Methods: Recruitment involved 100 girls of Greek origin aged up to 18 years with first vaginal bleeding (menarche). Informed consent was obtained for girls and parents or legal guardians. The participants were divided into two groups according age at menarche; the study group with menarche before 11 years and the control group with menarche after 11 years. Data on perinatal, family and personal history were recorded. Statistical analysis was performed and the limit of statistical significance was set at 5% ($p < 0.05$).

Results: The mean age of the girls at recruitment was 12.51 ± 2.59 years. Menarche before the age of 11 years was reported by 43% of girls (early group), while 57% reported menarche after the age of 11 years (control group). Girls living in rural areas consisted the 43% of the study population, while those living in cities were the rest 57%. Regarding mothers' menarche 76% reported menarche after the age of 11 years and 24% menarche before the age of 11 years. In the early group 12% were SGA neonates, while in the control group only 8% were SGA ($p=0.043$). Type of delivery differed significantly between the groups; the cesarean section rate was significantly higher (36%) in the early group compared to controls (12%) ($p<0.001$). Vaginal delivery was recorded in 45% of the control group compared to the early group (7%) ($p<0.001$). No statistically significant difference was found in other parameters.

Conclusions: In the present study, girls born SGA are reported at a higher frequency among those with early menarche. Accordingly, girls with early menarche present more frequent caesarean section than vaginal delivery. These findings are consistent with the current literature, although confirmation of these associations is expected to be further explored in larger population samples.

P1-559

Longitudinal psychological and behavioral assessments in girls with precocious puberty

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Background: Precocious puberty (PP) in girls is defined by the appearance of secondary sex characteristic before the age of 8 years. Numerous studies reported no deficit of final adult height in girls with pubertal onset between 6-8 years compared with their genetic height, however, there were limited studies on the aspect of psychological outcomes of PP girls compare with the same age prepubertal girls.

Objective: To evaluate potential differences of the psychological characteristics in girls with PP compared to the same age prepubertal girls, at the time of diagnosis and six months follow-up

Methods: A prospective cohort was conducted in 6-8 years old girls and their parent, who attend in Pediatric OPD of Phramongkutklao hospital in 2020-2022. Girls were allocated into two groups according to pubertal status: the puberty (PP) group and the prepuberty (control) group. Three Thai-standardized questionnaires were used as psychological assessment tools, including Children's Depression Inventory (CDI); completed by the girls, Parent Screen for Child Anxiety Related Disorders (SCARED) and Parent-Strengths and Difficulties Questionnaire (SDQ); completed by their parents. The psychological scores were compared between the two groups at the time of diagnosis and six-month follow-up.

Results: Eighty-five participants were enrolled, 46 in the PP group and 39 in the control group. After 6 months, 52 participants completed follow-up assessments, comprising 33 in the PP group and 19 in the control group. At time of diagnosis, no significant difference in psychological and behavioral problems assessed by CDI, SCARED and SDQ between groups However, the SDQ subgroup dimension reveals the PP group exhibited a significantly higher proportion of "risk and problem" for emotional problems compares to the control group (15% vs 0%, p 0.01) while the control group exhibits the significantly proportion of "risk" for peer problems (15% vs 0%, p 0.007). The mean score of CDI was significantly higher in the PP group compares to the control group (8.1±7.2 vs 3.7±2.3, p 0.007). There was no significant difference in psychological outcomes between the PP and control groups at the 6-month follow-up assessment.

Conclusions: Girls with precocious puberty had more "risk and problem" related to emotional problems and higher CDI score at the time of diagnosis but no significant psychological and behavioral problems compare to the control group thereafter. Therefore, behavioral and depression problems should be closely monitored in the PP girls.

P1-560

The Difference in Newly diagnosed Precocious Puberty Before and During the COVID-19 Pandemic: A Systematic Review and Meta-Analysis

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Keywords: precocious puberty, COVID-19

Background: Studies have reported an increase in precocious puberty (PP) cases during the COVID-19 pandemic, but there is inconsistency in the findings. Various influencing factors have been proposed to explain this surge. The present study aimed to investigate the PP trend following the pandemic, examine potential influencing factors, and investigate the dose-response relationship between time points and the risk of PP.

Methods: We searched for four databases until Feb 20, 2023, to seek articles reporting various indicators relevant to the incidence of PP before and during the pandemic. We included participants visiting pediatric clinics for suspected PP for the first time. The number of events and total observations were extracted. Meta-analyses were conducted to compare the risk of PP and the differences in other factors between the two periods. Subgroup, meta-regression, and sensitivity analyses were pre-planned.

Main Findings: COVID-19 was associated with an increasing Incidence of PP among children referred for PP (OR 1.96, 95% CI 1.56–2.47, I2 = 54%, $p < 0.01$). Sensitivity analysis showed that our findings were robust. Entering the COVID-19 pandemic, children had earlier PP onset and earlier clinic visits, but similar to Tanner's stage at first presentation. BMI SDS of children pre- and during COVID-19 was no different. The PP incidence since the COVID-19 outbreak has increased more rapidly compared to the pre-pandemic period.

Conclusions: Our results indicated that there was a dose-dependent increase in the PP incidence and an acceleration in the timing of puberty following the COVID-19 pandemic. Many environmental factors could contribute to this phenomenon.

P1-561

Copeptin as a reliable marker in differentiating Nephrogenic Diabetes Insipidus (NDI) and Central Diabetes Insipidus (CDI)-a case study

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Introduction: Arginine vasopressin (AVP) and thirst are the main determinants of water homeostasis maintenance, and dysregulation leads to polyuria-polydipsia syndrome. This comprises of three key conditions: CDI due to insufficiently secreted AVP; NDI, due to renal AVP insensitivity and Primary Polydipsia (PP), caused by excessive fluid intake resulting in physiological suppression of AVP. Differentiating between these three conditions is important, as the treatment strategies differ and incorrect treatment can be dangerous. The standard water deprivation test has been the "gold-standard" for differentiating these entities, but relying on this has its limitations, with difficulty in reliably differentiating between CDI and NDI. In addition the long duration of the test and sampling requirements make this test difficult to perform. Measuring AVP upon osmotic stimulation would theoretically overcome the limitations of the water deprivation test, but it is not used in clinical practice due to technical limitations of the AVP assay. Copeptin on the other hand is secreted in equimolar ratio to AVP in response to osmotic, haemodynamic and stress-related stimuli. It has been shown to be a reliable, stable and easily measured marker which is useful in the differential diagnosis of these states.

Case Presentation: Our patient presented at 14 months of age with failure to thrive, with all growth parameters below 0.4th centile. There was also a history of polyuria, polydipsia and some concerns regarding mild developmental delay. Routine blood tests had shown hypernatremia (160-170mmol/L). His plasma osmolality was high (316 mosm/kg) and paired urine osmolality low (110 mosm/kg). The neurohypophyseal bright signal was absent on MRI scan, suggesting a diagnosis of CDI. However, he failed to respond to treatment with increasing doses of desmopressin (10mcg-240mcg twice daily). His baseline Copeptin results showed very high levels (285.6 pmol/l), confirming the diagnosis of NDI and he was commenced on appropriate treatment with Cholrothiazide. The results of cytogenetic investigations are awaited.

Discussion: The MRI findings in this child were suggestive of a diagnosis of CDI. It is hypothesised that the posterior pituitary bright signal is due to the presence of AVP in the neurosecretory granules. It is possible that in NDI, due to hypersecretion of AVP,

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the neurosecretory granules are depleted of AVP, leading to loss of the bright spot in the posterior pituitary on MRI scan.

This case highlights the ease and reliability of using Copeptin in differentiating NDI and CDI.

P1-562

Concurrent premature gonadotrophic activation and gonadal insufficiency in young girls with a brain tumor

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Background: It is well known that endocrine comorbidities occur frequently in children with cancer, especially in those with a brain tumor. In those children, increased intracranial pressure or hydrocephalus may lead to central precocious puberty. Furthermore, chemotherapy, especially alkylating agents, increases the risk for gonadal insufficiency. In this case series we describe 3 young girls with a brain tumor, who develop premature gonadotrophic activation, but without estrogen production as result of simultaneous premature ovarian insufficiency.

Cases: Girl A was known with a supratentorial embryonal tumor with midline shift at age 1 year. She was treated with neurosurgery followed by chemotherapy. At relapse, second neurosurgery, proton radiotherapy involving 0.05 Gy to pituitary and metronomic chemotherapy were given with a cyclophosphamide equivalent dose (CED) of 45,6 g/m^2. At age 3.7 years during relapse therapy she presented with impaired longitudinal growth, no thelarche and no bone age advancement (-0.1 years). Biochemical evaluation showed LH 3.8 IU/L, FSH 34 IU/L, estradiol <40 pmol/L and AMH <0.03 µg/L.

Girl B was known with increased intracranial pressure at age 2, due to a large supratentorial primitive neuro-ectodermal tumor with mass effect. After surgery she was treated with chemotherapy (CED of 75,8 g/m^2) and focal proton radiotherapy. At age 7.8 years she presented with normal longitudinal growth, no thelarche and delayed bone age (-0.8 years). Biochemical evaluation revealed LH of 1.7 IU/L, FSH 34 IU/L, estradiol <40 pmol/L, AMH <0.03 µg/L.

Girl C had been diagnosed with an atypical teratoid rhabdoid tumor at age 10 months leading to hydrocephalus. After surgery she received alkylating chemotherapy (CED of 53,2 g/m^2). At age 5.8 years, she showed impaired longitudinal growth, no thelarche and delayed bone age (-0.7 years). Biochemically, a LH of 7.6 IU/L, FSH of 64 IU/L, estradiol <40 pmol/L and AMH <0.03 µg/L were found.

None of the girls had been treated with GnRH analogues. In all, during follow-up of at least 7 months, LH and FSH remained increased with no signs of thelarche or measurable estradiol.

Discussion: This case series illustrates that young girls with a history of brain tumor have an increased risk to develop premature gonadotrophic activation with simultaneous gonadal insufficiency. Although these findings do not require clinical intervention, the early diagnosis of gonadal insufficiency enables timely counselling of the children and their parents in terms of pubertal induction and future fertility.

P1-563

Clinical and analytical presentation of central precocious puberty according to age: a 20-year retrospective study

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Introduction: Central Precocious Puberty (CPP) results from the premature activation of the hypothalamic-pituitary-gonadal axis. Is defined by the onset of secondary sexual characters before 8-years-old in girls and 9-years-old in boys. It's associated with accelerated growth and advanced bone maturation and can lead to early epiphyseal fusion and reduced final height at adult age.

Aims: To evaluate and compare the differences in both clinical and analytical presentation in children with CPP, according to age.

Methods: Retrospective, descriptive and comparative study in children with the diagnosis of PPC, followed at a Pediatric Endocrinology unit, in a tertiary center. The first medical appointment occurred between January2002 and April2022. Medical records were consulted and collected data was: gender, nationality, family history of precocious puberty(PP), parental target height, CPP etiology, gestational age, birth somatometry, age of pubertal onset, age at referral to consultation and at first consultation. Regarding the first medical appointment, weight, height, body mass index(BMI) and growth rate were obtained, as well as the respective standard deviation(SD) according to the chronological age, using the World Health Organization(WHO) criteria. Laboratory data (Luteinizing hormone(LH), Follicle-Stimulating Hormones(FSH), estradiol and testosterone) and imaging findings were also collected. Statistical analysis was made using SPSS.

Results: Fifty-two children were included, 84.6%(n=44) female. Girls median age at puberty onset was 6.79years and at first consultation the mean age was 8.13years. Girls age of referral was significantly lower than boys (7.65vs.8.50 years; p=0.045). Idiopathic etiology was the most prevalent in both sexes. Basal and peak values of LH and FSH were higher in females(p>0.05). In girls, thelarche, as an initial clinical manifestation, appeared at higher mean ages (6.79 vs. 6.02years; p=0.09), whereas pubarche and growth acceleration were associated with lower ages of puberty onset (6.07±0.91years; p=0.034). Age of puberty onset was negatively correlated with the BMI SD(p=0.023).

The first consultation´s age was positively correlated with the bone age and was associated with younger ages when performing the Gonadotropin-Releasing Hormone test. There were no statistical differences between age and somatometry at birth, gestational age, number of pubertal signs, auxological parameters at first consultation, growth rate, laboratory parameters and CPP etiology.

Conclusions: Our results are consistent to the ones reported in literature, with higher CCP incidence in girls and idiopathic etiology being the most frequent. Our findings are also in accordance with the knowledge of obesity and CCP association.

P1-564

A case of Klinefelter Syndrome and peripheral precocious puberty

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Background: Klinefelter syndrome (KS) is a genetic disorder consisting in a variable number of additional X chromosomes in a male individual. KS patients can rarely develop peripheral precocious puberty (PPP) caused by extragonadal germ cell cancers (eGCCs) producing hormones with androgenic activity. KS patients are at higher risk for eGCC when compared to the healthy population

Case Report: We report the case of M., a 8 years old boy with a genetic diagnosis of KS made at age 2 for delayed speech. M. was born at 40 weeks of gestational age, with no complications during delivery. At age 8 and 6 months he underwent his regular endocrinological assessment to evaluate growth. The auxological parameters were height 140 cm (+0.85 SDS), weight 28.7 kg (+0.67 SDS) and growth velocity 9.2 cm/year (+3.6 SDS). Physical examination showed Tanner stage G2 with testicular volume 5 ml bilaterally. No axillary or pubic hair was found. Basal levels of gonadotropins were suppressed (FSH < 0.3 mIU/Ml, LH < 0.3 mIU/ml) with high level of total testosterone (14 nmol/L). This finding was confirmed by GnRH test. No alteration of adrenal androgens was detected. Germ cell tumor markers assessment showed a high level of hCG (10.4 mUI/ml, nv < 2 mUI/ml) and slightly increased levels of alpha-fetoprotein (12.1 ng/mL, nv < 12 ng/mL). Hand X-ray evaluated according to Greulich & Pyle showed an advanced bone age (10 years + 7 months) compared to a chronological age (8 years +7 months). CT of thorax and abdomen was performed and revealed a triangular shaped formation (24 mm) with inhomogeneous enhancement after contrast medium administration in the thymic region. We decided to start therapy with bicalutamide 25mg daily in order to hamper puberty progression. At age 9 years + 2 months, he underwent total thymectomy. Histological analysis confirmed the diagnosis of mediastinal germ cell tumour of mixed type (according to WHO 2021). After surgery normal germ cell markers were observed. Two months after surgery we stopped bicalutamide therapy and started triptorelin 3.75 mg i.m every 28 days for central precocious puberty diagnosis (FSH 5.0 mIU/mL, LH 3.6 mIU/mL, TT 5nmol/L).

Conclusion: KS patients have an increased risk of several malignancies, especially male breast cancer and extragonadal germ cell tumors, primarily localized in the mediastinum. We suggest to closely monitor patients with KS and provide therm and their parents with adequate information on the risk of malignancy.

Sex differentiation, gonads and gynaecology or sex endocrinology

P1-166

Treatment with triptorelin and estradiol in transgender girls. should we use SDS for assigned sex or SDS for affirmed gender?

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Introduction: International guidelines recommend puberty blocking using GnRH analogs and subsequent association with estrogen therapy in transgender girls who require for medical treatment. They have been shown to have a bone mineral density calculated as standard deviation score (BMD-SDS) for their assigned sex lower than the mean at baseline, and there is a potential risk of impairing peak bone mass as treatment result.

Objective: To study the effects of double therapy in transgender girls based on anthropometric data and BMD. To compare the evolution of weight and BMD, calculated in SDS for assigned sex and SDS for affirmed gender.

Material and Method: Retrospective study of 20 transgender girls (45% Tanner II-III) who were treated with triptorelin and subsequent estrogen therapy. Variables included age, weight/height (SDS for age and assigned sex) and BMD (LUNAR Densitometer, GE HealthCare; measurement of g/cm2, in L1L4 and total body excluding the head; SDS for age and assigned sex). Variables analyzed pre-treatment, one year after triptorelin therapy and 12 months after the associating of transdermal estradiol. We compared weight-SDS and BMD-SDS for assigned sex with those corresponding to SDS for affirmed gender.

Results: BMD g/cm2 increased during treatment but BMD-SDS/Assigned sex decreased as treatment progressed. The mean one year after estrogen therapy BMD-SDS is lower than pretreatment but this decline wasn't observed using BMD-SDS/Affirmed gender scores. Similarly, weight-SDS/Assigned sex was lower than the mean pretreatment and decreased during therapy, however this wasn't observed if we refer to the weight-SDS/Affirmed gender.

Conclusions: Over the two first year's treatment in transgender girls, weight-SDS and BMD-SDS/Assigned sex have decreased although SDS values for the affirmed gender have maintained.

	Pre-Treatment	**Triptorelin**	**Estradiol**	**p**
Age (years)	12.9±2.4	14.2±1.2	15.1±1.1	-
BMD L1L4 (g/cm^2)	0.92±0.19*	0.94±0.16	1.03±0.14*	0.001
BMD L1L4-SDS/Assigned sex	-0.34±0.9*	-0.79±1.0	- 0.97±1.0*	0.001
BMD Body (g/cm^2)	0.99±0.11*	1.03±0.11	1.07±0.11*	0.01
BMD Body-SDS/Assigned sex	-0.1±1.03*	- 0.38±0.84	-0.83±0.92*	0.001
	Pre-Treatment		**Estradiol**	
Weight-SDS/Assigned sex	-0.19±1.2		-0.56±1.3	0.04
Weight-SDS/Affirmed gender	0.19±1.7		0.58±1.7	ns
Height-SDS/Assigned sex	-0.06±1.7		-0.45±0.85	0.013
BMD L1L4-SDS/Assigned sex	-0.34±0.9		- 0.97±1.0	0.001
BMD L1L4-SDS/Affirmed gender	-1±1.07		-1.05±1.1	ns
BMD Body-SDS/Assigned sex	-0.1±1.03		-0.83±0.92	0.001
BMD Body-SDS/Affirmed gender	-0.2±1.1		-0.43±1.3	ns

Wilcoxon test; *statistically significant comparison of means.

P1-167

Low-dose pioglitazone for polycystic ovary syndrome in adolescent girls:differential fat-mass redistribution by HOTAIR rs1443512 genotype

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Introduction: Adolescent polycystic ovary syndrome (PCOS) is characterized by androgen excess and oligo-amenorrhea, and often results from ectopic lipid storage due to a mismatch between early adipogenesis and later lipogenesis. Endogenous HOTAIR and exogenous pioglitazone are enhancers of subcutaneous adipogenesis, particularly in the gluteofemoral region. The A allele of HOTAIR rs1443512 is an equivalent of a natural knock-down and is thus a candidate to influence the redistribution of fat by pioglitazone in adolescent PCOS.

Subjects & Methods: We performed a post hoc analysis – by HOTAIR rs1443512 genotype – of auxological, endocrine and body-composition results from 24 adolescent girls (mean age 15.6 years) with PCOS-without-obesity, all of whom received pioglitazone (7.5 mg/d for 1 year) as part of a randomised combination treatment (with spironolactone and metformin) in reported studies (ISRCTN29234515; ISRCTN11062950). All data had been obtained in a blinded-to-genotype way.

Results: The HOTAIR rs1443512 genotype in pioglitazone-treated girls did not detectably influence the measures of androgen excess, hyperinsulinaemia or abdominal fat (either subcutaneous, visceral or hepatic fat, by magnetic resonance imaging) but associated with differential – and even opposing – changes in other fat depots, so that girls with A allele of HOTAIR rs1443512 (N=12) gained fat while the other girls (N=12) did not: hip circumference (+2.3 ± 1.9 vs -1.7 ± 3.1 cm; P<0.001), total fat (by dual X-ray absorptiometry; +2.2 ± 1.8 vs -0.9 ± 2.2 kg; P<0.001), truncal fat (+0.8 ± 1.1 vs -1.2 ± 2.0 kg; P<0.01), gluteofemoral fat (+0.6 ± 0.4 vs -0.1 ± 0.5 kg; P<0.001) and leg fat (+1.2 ± 1.0 vs -0.05 ± 0.9 kg; P <0.01).

Conclusion: The redistribution of fat mass during prolonged low-dose pioglitazone treatment in adolescent girls with PCOS-without-obesity differed markedly by HOTAIR rs1443512 genotype. Early PCOS, in particular the variant presenting without obesity and with A allele of HOTAIR rs1443512, merits further testing as a candidate indication for low-dose pioglitazone from adolescence onwards, as to prevent complications such as diabetes in adulthood.

Trial registration ISRCTN29234515; ISRCTN11062950

P1-168

Parental perceptions and concerns in a cohort of infants with unoperated hypospadias

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Background: Hypospadias surgery is usually performed during infancy at which time parents act as proxy decision makers. Parental decisional regret, a common phenomenon after hypospadias surgery, may be affected by the process of informed consent where decision making between parents and healthcare provider is shared based on available evidence and individual concerns.

Objective: To identify short- and long-term parental concerns and related factors in a cohort of infants with hypospadias prior to surgery.

Materials and Methods: Infants attending our tertiary hypospadias clinic for the first time (n=139) were prospectively recruited to participate in this study. Over 21 months, 113 families (81.3%) accepted to participate. After examination parents were informed about hypospadias, the possibility of surgical management, its pros and cons, and the percentages of potential postoperative complications. Subsequently, parents (mothers n=113, fathers n=110) were asked to express their level of concern regarding the hypospadias diagnosis in childhood and in adulthood on a 5-point Likert scale. Parents were further asked to state their primary concern in a free text space.

Results: The Likert scores reflected a significantly higher level of concern for adulthood (mean 3.1, standard deviation (SD) 1.2) than childhood (mean 2.7, SD 1.1) (p <0.001). Mothers were significantly more concerned than fathers about child- (mean 2.8, SD 1.1 and mean 2.6, SD 1.2 respectively, p <0.001) and adulthood (mean 3.2, SD 1.1; mean 3.0, SD 1.2, p <0.001). Levels of concern rose significantly with lower maternal educational levels (c=-0.186, p=0.048). Concern scores were not associated with hypospadias severity, parental age or perinatal events (assisted reproduction (n=14), previous spontaneous abortions (n=32), extranumerary ultrasound scans (n=74), amniotic fluid sampling (n=6), placental biopsy (n=13), pregnancy related health problems (n=39), or prematurity (n=18)). Parents most often stated concern with regards to sexual life (n= 50), bullying (n= 50), self-esteem (n=48), and functionality (n=45).

Discussion: Parental concern about long-term outcomes occurs early in the course of their son's hypospadias diagnosis. Hypospadias severity did not correlate to concern scores which may reflect that parents have difficulties understanding the information given possibly due to information overload as expressed by parents in other studies.

Conclusion: Future topics to include during the decision-making process regarding hypospadias surgery should include consideration of current knowledge on long-term outcomes. Processing information on this topic appears to be difficult and future decision-making tools may assist the process.

P1-169

RXFP2: validating its role in autosomal recessive bilateral cryptorchidism and a novel association with male infertility

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Background/Aims: Cryptorchidism or undescended testis is a prevalent congenital urogenital condition affecting male newborns with an incidence rate ranging from 1.0 to 4.6%. Mouse models have implicated INSL3 and its receptor RXFP2 (formerly known as GREAT or LGR8) in the development of the condition. RXFP2 acts as a G protein-coupled receptor that triggers the generation of cAMP by binding INSL3. But despite the established role in testicular descent, so far only one family with cryptorchidism has been reported with defects in *RXFP2*.

Methods: Whole exome sequencing of the differences of sex development gene panel was carried out in an index case with bilateral cryptorchidism and infertility. Segregation analysis was performed in his brother with the same phenotype. Testicular biopsy in this brother showed a maturation arrest at the spermatocytes – spermatids stage. Single nucleotide variants were classified using the ACMG guidelines, and the exome data was analyzed for copy number variants using the ExomeDepth algorithm. Further characterization was conducted through structural modeling and a cyclic AMP (cAMP) reporter gene assay. To examine the association with infertility, publicly available single-cell RNA (scRNA) sequencing data were used.

Results: An intragenic deletion of exon 1-5 in *RXFP2* (NM_130806.5) was found *in trans* with a hemizygous missense variant c.229G>A, p.(Glu77Lys) in both brothers. The missense variant was classified as pathogenic based on in silico modeling and in vitro functional analysis. No changes in cell surface expression and ability to bind INSL3 were observed, but the absence of a cAMP signal in response to INSL3 indicated a loss-of-function, thereby confirming its causative role in the bilateral cryptorchidism of this family. Additionally, besides its role in testicular descent during fetal development, several animal studies have demonstrated a postnatal function of INSL3 and RXFP2 in germ cell survival. Furthermore, scRNA sequencing data shows expression of *RXFP2* at the early spermatid stage which corresponds to the stage of maturation arrest as seen on the biopsy of one of the patients.

Conclusion: As the second report, this study further establishes *RXFP2* as a cause for bilateral cryptorchidism in an autosomal recessive manner. *RXFP2* should therefore be added to any gene panel testing for differences of sex development. Additionally, this study supports for the first time an association between *RXFP2* and male infertility.

P1-170

Explaining variations of menarcheal age by anthropometrical factors - the GrowUp Gothenburg study

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Background and Aim: Menarche is a milestone of female pubertal development as well as an important sociocultural and psychological event during adolescence. Age of menarche has changed with time, and there is a broad individual variation in timing. Many factors are associated with menarcheal age, where further research is needed. The QEPS-growth model makes it possible to conduct detailed analyses of growth[1,2]. The aim of the study was to investigate anthropometric factors explaining variations in menarcheal timing.

Material and Methods: The timing of menarche was analysed in a longitudinally followed population, the GrowUp1990Gothenburg cohort (community-based setting)[3,4]. The analysed study group included 755 healthy females born at gestational week (GA) 36+2–41+6, with information of menarcheal age. Height at 7 years and specific pubertal growth was calculated by the QEPS-model[2]. The individual timing of menarche was related to birthweight and birth-length (kg, cm), GA, maximal BMI between 3.5–7 years (SDS)4, parental heights, height at pubertal onset (P5%), duration of pubertal growth (P5%–95% of specific pubertal growth spurt) and adult height. Variables with univariate significant relation, was allowed into linear multivariable regression models for explaining the variation of the outcome menarcheal age. Data given as mean (± SDS) or Beta-coefficient (B).

Results: Mean menarcheal age was 12.94 (± 1.33) years. Birthweight correlated with age at menarche (B-coefficient 0.24), whereas birth-length and GA did not. A negative linear correlation was seen between BMI and menarcheal age (B -0.23), and of height at 7 years (B -0.36) – higher BMI and taller childhood height was associated with earlier menarche. In analysis of parental heights, taller maternal height correlated with later menarche (B 0.029), whereas no association was seen with paternal height. In multivariable linear regression models, explanatory significant factors were height at 7 years, height at pubertal onset (P5%) and duration of pubertal growth (time P5%-95%); together explaining 44% of the variation of age at menarche (R-square 0.44). As a control the non-parametric robust regression was performed, with R-square 0.41.

Conclusion: In a cohort of healthy Swedish girls with longitudinal growth data born in the 1990s, timing of menarche was correlated with birth-weight, childhood-BMI, height at 7yrs and at pubertal onset, duration of pubertal growth and maternal height.

References

1. Nierop et al. Journal of Theoretical Biology 2016.Oct7;406:143-65.
2. Holmgren et al. BMC Pediatrics 2017.Apr9;17(1):107.
3. Sjöberg et al. Acta Paediatrica 2012 Sep;101(9):964-72.
4. Holmgren et al. Pediatric Research 2017:81,448–454.

P1-171

National trends in central precocious puberty, isolated precocious adrenarche and isolated precocious telarche before and during COVID19 pandemic

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Background: Decreasing age at the onset of puberty is observed worldwide, several countries report also increasing incidence trends of central precocious puberty (CPP), and some observed an importantly higher number of CPP cases during the COVID19 pandemic. Scarce data report also rising trends in isolated precocious adrenarche (IPA) and isolated precocious telarche (IPT).

Objectives: To determine the national incidence and incidence trends of CPP, IPA and persistent/progressive IPT in Slovenia.

Population and Methods: In a retrospective study, data were collected from the electronic system of the only national pediatric endocrinology referral center at University Children's Hospital in Ljubljana, using the corresponding MKB10 codes and verified by examining each individual medical documentation. The incidence was assessed annualy between 2011 and 2021 for CPP, and between 2014 and 2021 for IPA and persistent/progressive IPT. The risk population was defined as girls aged 7 years or younger and boys aged 8 years or younger living in Slovenia in a given year. The incidence was calculated as (new cases (in a given year)/at-risk population (in the same year)) X 100,000.

Results: The overall incidence of CPP was 23.11/100,000 in girls and 4.42/100,000 in boys. While 83% of girls had idiopathic CPP, 77% of boys had an organic cause of the disease. A balanced sex distribution of non-idiopathic CPP cases was noted (34 girls and 30 boys). In girls (but not in boys), the annual incidence was rising from 12.57/100,000 in 2011 to 34.31/100,000 in 2021. During the COVID19 pandemic the incidence trend was not further accelerated, incidence in 2019 being 29.62/100,000. The incidence of IPA was 37.82/100,000 in girls and 5.21/100,000 in boys, showing an increasing trend only in boys. The incidence of persistent/progressive IPT in girls was stable, being 6.38/100,000.

Conclusion: An almost 3-fold rise in the CPP incidence in girls was observed in only 11 years of observation. No such trends in girls were noted in IPA and persistent/progressive IPT, indicating that etiological factors associated with these conditions differ. During the COVID19 pandemic the CPP incidence in girls continued to rise; however, the trend did not seem to be further accelerated as compared to the previous years.

P1-172

Mutation in FAN1 gene causes impaired DNA damage response and Ovarian Dysgenesis

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Background: Severe Ovarian Dysgenesis (OD), a rare heterogeneous XX disorder of Sex Development (XX-DSD) presents clinically with primary amenorrhea, hypergonadotrophic hypogonadism and infertility. The genetic basis of OD remains unknown in about 70% of cases. To identify novel causes of OD, we study patients in which known genes have been excluded.

Methods: Whole-exome-sequencing was performed on DNA extracted from peripheral lymphocytes of a 16y old female from consanguineous Israeli-Arab family who presented with lack of spontaneous pubertal development primary amenorrhea and hypergonadotrophic hypogonadism. Imaging studies detected a small uterus while no ovaries could be identified. DNA damage response (DDR) and chromosomal stability were tested using Mitomycin C (MMC) in chromosomal breakage assay.

Results: A homozygous missense mutation; c.C1972T, p.R658W was identified in the FAN1 gene, a DDR pathway gene. Segregation was consistent with recessive inheritance. Structural analysis revealed that R658 acts as an anchoring point of DNA upon FAN1 homo-dimerization and stabilize DNA bifurcation into single strand. As such, R658W destabilizes FAN1 interaction with the DNA and prevents its binding to FAN1 dimers. Chromosomal breakage assays revealed significantly higher number of DNA breaks in patient-derived leukocytes compared to control. DNA breaks increase occurred following DNA damage induction with MMC in a dose dependent manner. Induction of breaks with 150nM MMC resulted in: 1.63±0.28 breaks per cell (bpc) in the patient vs. only 0.70±0.31 in controls ($P=0.003$). Induction of breaks with 300nM resulted in 4.00±0.55 bpc in patient vs. 1.87±0.29 in controls ($P=0.0005$).

Conclusions: The novel homozygous missense mutation in FAN1 is accompanied by impaired DDR and suggests FAN1 as a novel genetic etiology for ovarian dysgenesis in humans. This further expands the crucial role of DDR pathway in normal ovariogenesis, and indicates the importance of the chromosomal breakage assay in the differential diagnosis for OD. The implication on routine clinical cancer surveillance in the patient and family members is under further studies.

P1-173

Magnetic Resonance Imaging (MRI) Findings and Predictive Factors of Gonadal Neoplasia in Complete Androgen Insensitivity Syndrome

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Introduction: Complete Androgen Insensitivity Syndrome (CAIS) is characterized by a complete external genitalia appearance and testicular development in 46,XY individuals harboring pathogenic allelic variants in the AR gene. Due to growing evidence regarding the low risk of germ cell tumors (GCT) in AIS. Prophylactic gonadectomy has been debatable in the CAIS management, mainly due to the absence of an accurate biomarker for GCT.

Objective: to evaluate the presurgical pelvic MRI data with the histopathological exams of gonads from CAIS patients who underwent prophylactic gonadectomy in order to identify predictive factors of GCT development.

Methods: We evaluated 30 gonads from 15 CAIS patients with proven AR mutation. All performed pelvic MRI before gonadectomy through the same MRI machine and were included in the MRI data analysis. Three blinded radiologists specialize in urology performed the image analysis. The immunohistochemical markers PLAP, c-KIT, OCT3/4, SALL4, ER, alpha-inhibin, CD99, and calretinin were performed.

Results: Nine (60%) performed gonadectomy after puberty (>16 years old). We identified one case of classical seminoma and one case of Sertoli cell neoplasia (at 18 and 19 years of age, respectively). Overall, the prevalence of neoplasia was 13.3%. No case of premalignant intratubular germ cell neoplasia was detected.

Histological data revealed a high prevalence of benign lesions (xx%), all of them bilateral. Leydig Cell Hyperplasia (67%), stromal fibrosis (53%), and Sertoli Cell nodules (47%), hamartomatous nodules (40%) and paratesticular cysts (67%) which are more frequent after puberty (p<.01). MRI detected heterogeneity in all cases harboring hamartomatous nodules, Sertoli cell nodules, and testicular neoplasia. Regarding the MRI data, the presence of testicular cystic mass (by tumoral necrosis) on MRI and tumor size (higher among malignancies) correlated with malignancy (p=.008 and p=.03, respectively), whereas gonadal location (inguinal/abdominal), presence of solid nodules, T2WI and postcontrast features, nodule diffusion restriction, and presence of perigonadal cysts did not. Chronological age >16 years was associated with malignancy with a 4.3 OR (1.6 – 11.69).

Conclusion: Pelvic MRI is able to detect gonadal nodules in CAIS patients, regardless of the gonad position, but most nodules are benign. Testicular malignancy should be suspicious in the presence of testicular cystic mass and large testis size in CAIS patients after puberty.

P1-174

Ovarian Reserve in Children with Juvenile İdiopathic Arthritis Using Biologic Disease-Modifying Anti-Rheumatic Drugs

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The aim of the study is to assess the effect of juvenile idiopathic arthritis (JIA) and biologic disease-modifying anti-rheumatic drugs (bDMARD) on ovarian reserve in children. A cross-sectional study was performed from March 2021 to March 2022 and included 81 patients with JIA and 49 healthy children. Serum anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol levels were analyzed using electrochemiluminescence methods. The mean of current age (13.5±3.2 vs. 14.4±2.4 years), height SDS (-0.35±1.18 vs. -0.44±0.94), BMI SDS (0.12±1.33 vs. 0.25±1.28) and the median weight SDS [-0.13 (-2.27- 3.23) vs. -0.52 (-3.4- 3.3)] were similar in JIA patients and controls (p > 0.05). Patients with JIA were divided into two groups according to their treatment regimens: treated with methotrexate (MTX) (biologic naive) (n=32) and treated with MTX plus bDMARDs (n=49). No significant differences were detected between the 3 groups regarding menarche age, menstrual cycle length, and flow duration (for all p > 0.05). The median serum concentration of AMH was 2.94 (1.12-7.88) ng/ml in the control group, 3.02 (0.36-8.54) ng/ml in the biologic naïve group and 3.01 (0.99-8.26) ng/ml in MTX plus bDMARDs group. There were no significant differences between 3 groups according to serum AMH, FSH, LH, and estradiol levels (p>0.05). Biologic DMARDs are reassuring in terms of ovarian reserve in girls with JIA and demonstrate that AMH is unaffected by treatment. Prospective studies with larger sample sizes are needed to confirm our findings and to evaluate the impact on the future fertility of patients.

P1-175

The IGF system shows changes in the follicular fluid of women with PCOS

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Background: Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder among women of reproductive age and is characterised by chronic low-grade inflammation, ovulatory dysfunction and hyperandrogenism, and often by insulin resistance. The IGF system is involved in glucose metabolism regulation and is altered in chronic inflammation where both IGF-I and –II can be reduced. We previously described increased HMGB1 content in follicular fluid (FF) in PCOS. HMGB1 is related with both inflammation and insulin resistance, and the IGF system regulates ovarian function; specifically, IGF-II promotes follicular maturation. The aim of this study was to investigate changes in the IGF system in FF from PCOS with respect to controls and to evaluate possible relationships with HMGB1.

Methods: 72 women with PCOS [CA:34.1±4.7yr; BMI:25.6±5.5kg/m^2] diagnosed following the Rotterdam criteria, and 72 healthy controls [CA:36.9±3.6yr; BMI 23.1±4.2kg/m^2] were included. Induction of multiple follicular development for IVF was conducted according to a specific long luteal GnRH agonist protocol. FF were collected from dominant follicles during oocyte retrieval and centrifuged to remove red blood cells and debris. IGF-I, IGF-II, IGFBP-1, IGFBP-2 and HMGB1 were measured in FF using specific ELISA kits. Student's T-test was used for comparison between PCOS and controls. Data are mean±SD.

Results: IGF-II levels in FF were lower in PCOS women with respect to controls (386.2±208.4 *vs* 518.6±152.0ng/ml, respectively; p<0.0001) whereas IGF-I (104.4±36.3*vs* 107.1±36.0ng/ml, IGFBP-1 (9.1±4.0*vs* 9.3±4.5ng/ml) and IGFBP-2 levels (673.9±199.9*vs* 647.7±211.0ng/ml) were similar in both groups. Interestingly, the stratification of the PCOS population based on BMI showed that obese women (BMI>30Kg/m^2;N=19)had a lower content of both IGF-I (80.7±18.8*vs*107.1±36.0ng/ml; p=0.01) and IGF-II (368.9±173.9*vs*518.6±152.0ng/ml;p=0.003), while IGFBP-1 and -2 were unchanged with respect to controls. IGF-1 levels were negatively correlated with BMI both in PCOS and controls. HMGB1 FF levels were confirmed to be higher in PCOS patients compared to controls (40.6±22.0*vs*28.9±19.7ng/ml;p=0.001), and were not associated with any IGF system peptide.

Conclusions: FF IGF-II content was reduced in PCOS and could contribute to explain reduced follicle development. As both IGF-I and -II content was reduced in the obese PCOS women this could reflect both increased insulin resistance, and effects of body weight/adipose tissue on changes in the ovary. Being HMGB1 an indirect measurement of both inflammation and glucose metabolism this could explain the lack of any correlation with the IGF system in the ovary.

P1-176

Mechanism of mutagenesis and phenotype implications of small indels in the Androgen Receptor gene in Androgen Insensitivity Syndrome

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Indels are highly abundant in human genomes and have contributed massively to genome evolution. However, the role of indels and their underlined mechanisms of mutagenesis in Mendelian disorders still needs to be appreciated. To explore the contribution of indels in a monogenic disorder, we analyzed all indels already described in the *AR* gene, including three novel indels found in our cohort. We analyzed the indel distribution through the AR coding region, compared with genomic and exonic populational data, and analyzed their impact on the AIS phenotype and their likely mechanism of mutagenesis. We present 82 different indels in the AR gene reported in individuals with AIS. In most cases (n=78; 95.1%), the phenotype is complete AIS (CAIS). There are four AR indels reported in mild AIS. Most short indels in the AR gene among AIS are frameshift indels (n=64; 79%). Indels are distributed along the entire AR gene, with NTD domain predominance (n=45; 54.9%), followed by LTD domain (n=28; 34.1%). Most are small deletions (n=49; 59.7%), followed by small insertions (n=29; 35.3%) and complex frameshift indels (n=4; 4.8%). Most indels are short (<10 bp; n=81 = 98.8%), with an average of 2.4 nucleotides by indel. Most indels are at non-repetitive sequences with no changes in copy counting (n = 68; 82.9%). Thirteen indels were identified within tandem repeats (15.8%), whereas seven indels were at homopolymers run (8.5%). Trinucleotide regions (Poly-Q, Poly-G) are prone to indels, but indels also happen in other trinucleotide stretches (Poli-L, Poly-P). Regarding the change in copy counting, thirty-nine (47.5%) indels are CCC indels. All small indels reported in MAIS are located at tandem repeats, while all at non-repetitive sequences caused CAIS. 3.65% of AR indels are at a 6bp consensus sequence (TG A/G A/G G/T A/C). In summary, indels represent a significant portion of the variants identified in the AR gene in patients with AIS. Unlike the non-synonymous variants related to this gene, there is a genotype-phenotype correlation (indel - CAIS congruency). However, small NFS indels at small triplet runs can slightly compromise AR function leading to the mild phenotype. Homopolymer runs, and trinucleotide repeats are exonic regions at risk for indels. Slippage explains half of the cases of AR indels. These results increase the molecular understanding of the androgen receptor disruption and the underlined mechanisms of indel mutagenesis in exonic regions and their implication on phenotype.

P1-177

The consistency between Assigned Gender and Individual Gender Identity in Disorder of Sex Development Cases: Long-Term Results from a Single Center

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Introduction: In cases of disorder of sex development (DSD), the change between the gender assigned at birth and the individual's chosen gender identity can occur especially after puberty.

Aim: was to determine the relationship between genetic sex, gender assigned at birth and gender identity, and the importance of molecular diagnosis.

Method: 154patients older than 14years of age, who were followed up with the diagnosis of DSD from 1983 to 2023 were included.

Table 1. The variation between genetic sex, assigned gender, and individual gender identity.

	n	Gender Assigned at Birth	Individual Gender Identity
46,XXDSD			
Anatomical defect	12	12F	12F
Congenital adrenal hyperplasia	44	38F 6M	40F 4M
Gonadal dysgenesis	6	6F	6F
Syndromic	1	1F	1F
Total:46,XXDSD	*63*	*57(%90.5)F* *6(%9.5)M*	*59(%93.6)F* *4(%6.4)M*
46,XYDSD			
Defects in Androgen Action			
Androgen insensitivity syndrome	6	5F 1M	5F 1M
Undetermined causes	11	3F 8M	2F 8M 1 NSO
Defects in Testosterone Metabolism			
5-alpha-reductase 2deficiency	14	5F 9M	1F 13M
Defects in Androgen Production			
17-beta-hydroxysteroid dehydrogenase type3 deficiency	8	8F	5F 3M
3-beta-hydroxysteroid dehydrogenase deficiency	1	1M	1M
Impaired Leydig cell differentiation	2	2F	2F
Undetermined causes	6	2F 4M	2F 4M
Abnormalities of Gonadal Development			
SF1	2	2F	2F
WT1	2	1F 1M	1F 1M
Testicular regression syndrome	5	5M	5M
Undetermined causes	9	8F 1M	8F 1M
Other			
Vanishing testis	3	3M	3M
PMDS	3	3M	3M
Syndromic	3	3M	3M
Total:46,XYDSD (n=75)		*36(%48) F* *39 (%52) M*	*28 (%37.3) F* *46 (%61.3) M* *1 (%1.4) NSO*
Sex chromosomeDSD	16	9F 7M	10F 6M

F:female, M:male; NSO: no sexual orientation

Results: The mean age at admission was 7.7years ± 6.4. Sixty three (41%) patients had 46,XXDSD and 75 (48.7%) patients had 46,XYDSD. Sex chromosomeDSD was identified in 16 (10.3%) patients. Of the 46,XX cases, 2 (9.5%) of 6 cases reared as male chose female gender identity during follow-up. With 46,XY cases, female gender identity was maintained in 28 of 36 (48%) cases who were raised as female, female-to-male gender transition occurred in7 (19.5%) cases and 1 case was uncertain. One of the 7 (43.7%) patients with sex chromosome DSD and assigned male gender identity preferred female gender identity (table1).

Conclusion: Gender determination is always a complex, challenging experience for clinicians. Gender reassignment management should be individualized in collaboration with a multidisciplinary team to preserve gonadal function, avoid irreversible surgeries, and align gender identity with the assigned gender.

P1-178

Inhibin B- a functional marker to screen gonadal function in CAIS patients?

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Introduction and Objective: Gonadectomy was carried out for a long time after the diagnosis of complete androgen insensitivity syndrome (CAIS). It is now recommended to leave the gonads in situ in order to guarantee endogenous hormone production. It is unclear how best to clinically monitor testicular function. The aim of the study was to investigate whether inhibin B can be used as a future follow-up parameter to screen for gonadal function in CAIS patients.

Material and Methods: A total of 57 adolescent and adult CAIS patients who presented to two DSD centers (Lübeck and Pisa) were included. Hormonal parameters were retrospectively evaluated. Ideally, we included different time points: during puberty (12-16 years), in early adulthood (17-21 years) and later adulthood (22-50 years). We evaluated the testosterone/LH ratio as a measure of Leydig cell function and the inhibin B/FSH quotient which is normally used as a marker for Sertoli cell function.

Results: Testosterone levels were elevated and within the typical male reference range (6.20 ng/ml +/- 3.08). FSH values increased with age. Inhibin B levels were high and even above the typical male reference range (383.8 pg/ml+/- 206.5 SD). Throughout adulthood, inhibin B levels decreased by 52.53% (p=0.0030) and the inhibin B/FSH ratio by 75.56% (p=0.0103).

Conclusion: Our data show that inhibin B and the inhibin B/FSH ratio are suitable functional markers for gonadal function in CAIS patients. From adolescence onward, these parameters and testosterone levels may be useful to examine gonadal function and to possibly detect a loss of function that may necessitate hormone replacement in CAIS patients.

P1-179

Clinical characteristics and genetic expansion of 46, XY disorders of sex development children in a Chinese prospective study

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Disorders of sex development (DSD) refer to a group of congenital diseases with inconsistencies between chromosomal karyotypes, external genitalia, and gonadal development. Diagnosis and management strategy of DSD is difficult and various due to heterogeneous phenotype and genotype. Under widespread use of genomic sequencing technologies, multiple genes and mechanism has been identified and proposed as genetic causes of 46, XY DSD. In this study, 178 46, XY DSD patients were enrolled and underwent gene sequencing (either whole-exome sequencing or targeted panel gene sequencing). Detailed clinical phenotype and genotype information were summarized which showed that the most common clinical manifestations were micropenis (56.74%, 101/178), cryptorchidism (34.27%, 61/178), and hypospadias (17.42%, 31/178). Androgen synthesis/action disorders and idiopathic hypogonadotropic hypogonadism were the most frequent clinical diagnoses, accounting respectively for 40.9% and 21.59%. From all next-generation sequencing results, 103 candidate variants distributed across 32 genes were identified in 88 patients. The overall molecular detection rate was 49.44% (88/178), including 76.70% (79/103) pathogenic/likely pathogenic variants and 23.30% (24/103) VUS (variants of uncertain significance). Of all, 19.42% (20/103) variants were first reported in 46, XY DSD patients. Mutation c.680G>A (p.R227Q) on SRD5A2 (Steroid 5 Alpha-reductase 2) (36.67%, 11/30) was a hotspot mutation in Chinese population. New candidate genes [GHR (Growth Hormone Receptor) and RIT1 (Ras like without CAAX 1)] related to DSD were identified. Overall, this was a large cohort of 46, XY DSD patients with a common clinical classification and phenotype spectra of Chinese patients. Targeted gene panel sequencing (TPS) covered most of the genes contributing to DSD, whereas whole exome sequencing (WES) detected more candidate genes.

P1-180

Clinical, radiological and laboratory characteristics of thelarche variant: a retrospective analysis

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Background: 'Thelarche variant' (TV), also known as 'unsustained/slowly progressive puberty' or 'exaggerated thelarche', is a term used to describe girls with premature thelarche and intermediate features between isolated premature thelarche (PT) and central precocious puberty (CPP). Despite being characterized by a FSH predominant response and by a peak LH response <5 IU/L to GnRH test, a univocal definition is lacking.

Methods: Retrospective monocentric analysis on 104 girls with premature thelarche (< 8 years) who underwent GnRH test from January 2019 to December 2022. Considering the heterogeneous literature definitions of TV, we relied on the laboratory diagnostic criteria. Patients were divided into the aforementioned groups: CPP (LH peak >5 IU/L; n=32, 31%); TV (FSH peak >20 IU/L, LH peak <5 IU/L; n=18, 17%) and PT (FSH peak <20 IU/L, LH peak <5 IU/L; n=54, 52%). Several auxological (height, target height, height velocity), laboratory (basal/peak LH / FSH, oestradiol) and radiological (bone age, uterine body-to-cervix ratio, ovarian volume) features were studied.

Results: TV (median age 5.51 years) were younger than both PT (7.49 years, p <0.01) and CCP (7.52 years, p <0.01), and presented no higher height or significant discrepancy between height and target height. At GnRH test, TV showed higher levels of both basal and peak FSH than PT (respectively 2.5 versus 1.9 IU/L, p<0.01 and 26.6 versus 12.8 IU/L, p <0.01) and higher levels of peak FSH than CCP (26.6 versus 16.2 IU/L, p <0.01). There were no significant differences between oestradiol levels between the three groups (median value 24 pg/mL in TV). Surprisingly, TV had lower difference between bone and chronological age (0.80 years) than PT (1.40 years, p 0.04) and CCP (1.42 years, p 0.02). The pelvic ultrasound showed a median smaller ovarian volume (0.60 cm^3) in TV than both PT (1.35 cm3, p <0.01) and CCP (1.80 cm^3, p<0.01) and a higher percentage of uterine body-to cervix ratio > 1 in the CPP group (82%), if compared with both PT (51%, p <0.01) and TV (36%, p <0.01).

Conclusions: Using solely the objective laboratory parameter of FSH peak >20 IU/L to define TV, we identified a group of patients that differs from the heterogeneous (and often confounding) literature definitions, showing no advanced bone age and no signs of activation on pelvic ultrasound. Our data are consistent with reported benign evolution and good stature prognosis of this condition.

P1-181

Physicians' Knowledge, Experience, and Attitudes Towards Children and Adolescents with Gender Dysphoria/Incongruence in Turkey

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Keywords: Gender Dysphoria/ İncongruence, child and adolescent, attitudes toward transgendered individuals

Objective: To investigate physicians' knowledge and attitudes evaluating children and adolescents with gender dysphoria/incongruence (GD/GI) concerning care and treatment.

Materials and Methods: A questionnaire targeting the knowledge and experiences of physicians and a scale measuring the attitudes toward transgendered individuals (ATTI) were designed in Google form. We contacted pediatric endocrinologists(PEs) and general pediatricians(GPs) via email and/or phone.

Results: 105 PEs and 100 GPs participated in the study. Of the PEs and GPs, the proportion of female were 62.5% and 63%, the median ages were 38(27-67) and 34(24-65) years, the median duration of employment was 5(1-30), and 7.5(1-42) years, and 37% were fellows, 31% were residents respectively.

32.4% of the pediatric endocrinology physicians, were familiar with hormone treatment protocols, 29.5% knew the treatment follow-up, 36.2% were familiar with alternative methods such as binding, compression, filling, and packaging, 39.1% could plan health screenings, 56.2% could provide information regarding treatment side effects. Although 95% of the PEs considered psychiatric evaluation necessary, only approximately 25% considered psychiatric assessment adequate for diagnosing GD/GI. 62.9% of PEs stated that it was their ethical responsibility to treat individuals with GD/GI, the proportion of those who felt that subjects were ready for treatment and felt comfortable treating them was lower (35.2%,27.6%,respectively). The number of PEs who didn't approve puberty suppression, contrary sex hormone therapy, and surgical interventions before 18 years old were 18%, 33.4%,87.6%, respectively.

PEs and GPs stated the evaluations they would perform for the first presenting GD/GI individuals as 97%, 85% physical examination, 36%, 68% karyotype, 31%, 74% pelvic/scrotal USG, 58%, 69% hormone measurement, 96%, 94% referral to a psychiatrist, respectively. Among PEs, the proportion of fellows who thought that karyotype and pelvic/scrotal USG should be performed was statistically higher (p=0.044,p=0.012, respectively). However, the proportion of physicians who stated that they knew the treatment protocol and could give information about side effects were higher (p=0.005, p=0.002, p=0.001, respectively).

The ATTI score decreased as the duration of occupation of the PEs (r=-0.303,p=0.002) and the age of the GPs increased (r=-0.251,p=0.012).

Conclusions: A significant number of the participants had encountered individuals with GD/GI. However, competency rates in terms of effective treatment and familiar approach were low. Improved training and increased awareness will positively impact the understanding, management, and treatment of GD/GI individuals.

P1-182

DNA Ligase IV Deficieny Identified in a Patient with Hypergonadotropic Hypogonadism: A Case Report

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DNA ligase IV (Lig 4) deficiency (MIM #606593) is a rare autosomal recessive disorder related with impaired DNA damage-response mechanisms. Lig 4 syndrome has a broad clinical presentation; microcephaly, facial abnormality, sensitivity to ionizing radiation, combined immunodeficiency, progressive bone marrow failure and predisposition to malignancy. We describe the patient with Lig4 syndrome presented lissencephaly, growth failure and hypogonadism.

The patient is a 18-years-old girl from Turkish consanguineous parents, admitted to our clinic was 13 years old due to growth retardation and short stature. She was born from 32 weeks, unfollowed pregnancy, weighing 2015 grams with normal delivery. She had dysmorphic facial features; long face, sloping forehead, high arched eyebrows, a low hairline at the back of the neck, malar hypoplasia, mild hypotelorism, narrow palpebral fissures and bulbous nose. She had lissencephaly and mental retardation. Her weight was 30 kg (sds:-2.58), height was 129 cm (sds:-4.17), head circumference was 46.7 cm (sds:-5.98), bone age was 10 years old. She has not had clinical signs and symptoms for immundeficiency but IgM level was below the average (<2SD) and leukopenia was presented. L-dopa and clonidine growth hormone stimulation tests were done and the results were diagnosed as growth hormon (GH) deficieny. GH treatment was not started because of unresponsive leukopenia. Primary amenorrhea and hypergonadotropic hypogonadism (FSH: 80.92 mIU/mL, LH: 14.59 mIU/mL, E2: <12 pg/mL, AMH:<0.001 ng/mL) was detected at the follow up, estrogen treatment was given for two years and then combined oral contraceptive treatment was started. "Nijmegen Breakage Syndrome (NBS)" and "Short stature, microcephaly, and endocrine dysfunction (MIM #616541)" were thought for differential diagnosis. However genetic analysis for *NBN* ve *XRCC4* were normal. Homozygous early stop codon mutation on Lig 4 gene was detected (NM_206937.1), c.2440C>T (p.Arg814Ter) in Whole Exome Sequencing.

Lig 4 syndrome should be considered in the differential diagnosis in cases with growth retardation, microcephaly, and gonadal failure. It is important to avoid ionizing radiation exposure in these patients. Patients with LIG 4 syndrome should be followed up immunodeficiency and malignancy.

P1-183

Lipid profiles and HbA1c in transgender adolescents after one year of cross-hormone treatment

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Background: Transgender adolescents may be treated with gender affirming hormone therapy (GAHT) consisting of gonadotropin-releasing hormone agonists (GnRHa) and cross-sex hormones. Limited data are available regarding the metabolic effects of GAHT in adolescence.

Objective: To evaluate the lipid profiles and HbA1c in transgender adolescents after one year of cross-hormone treatment.

Patients and Methods: 117 adolescents assigned female and 38 assigned male at birth who started GAHT between May 2016 and September 2020 were retrospectively identified in a national cohort treated in a single-center setting. Non-fasting lipid profiles and HbA1c were collected from patient records. Seventy-six trans males and 22 trans females who had lipid profiles controlled 1 year ± 4 months after starting cross-sex hormones, were included in the study. In 33 trans males and 9 trans females HbA1c was also obtained. Age when starting GAHT, lipid profiles and HbA1c were compared between trans males and trans females using the student's t-test. Lipid profiles and HbA1c were compared with normal reference intervals.

Results: The mean (SD) age in trans males and trans females when starting GnRHa was 16.6 (1.2) versus 16.3 (1.5), p=0.38, and when starting cross-hormones 17.0 (0.9) versus 17.0 (1.1), p=0.19. After one year of receiving cross-sex hormones, there were no significant differences between trans males and trans females in mean (SD) cholesterol (mmol/L) (4.1 (0.8) versus 4.1 (0.8), p=0.62), low-density lipoprotein (LDL) (mmol/L) (2.6 (0.8) versus 2.4 (0.6), p=0.82), high-density lipoprotein (HDL) (mmol/L) (1.29 (0.26) versus 1.57 (0.33), p=0.13), or HbA1c (mmol/mol) (33 (4) versus 31 (2), p=0.13). Twelve% of trans males and 14% of trans females had cholesterol above the normal reference intervals (<5 mmol/L), 23% of trans males and 24% of trans females had LDL (mmol/L) above the normal reference intervals (<3.0 mmol/L). Twelve% of trans males and 9% of trans females had HDL (mmol/L) below the normal reference intervals (>1.0 mmol/L). HbA1c was within the normal reference intervals (<48 mmol/mol) in all cases.

Conclusion: In this national cohort there were no significant differences in lipid profiles or HbA1c between trans males and trans females one year after starting cross-sex hormones. HbA1c was normal in all cases but a significant number of both trans males and females showed deviating lipid profiles compared with normal reference intervals. Whether cross-sex hormone treatment interferes with lipid metabolism needs to be further explored.

P1-184

Retrospective Analysis of Individuals with Differences in Sex Development (DSD) in a Brazilian Single-Center Study Across the Lifespan

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Context: Differences in sex development (DSD) represent a broad spectrum of conditions that can present at different ages to various healthcare professionals with different backgrounds.

Design: This is a retrospective, observational cohort that includes all DSD subjects referred to a multi-professional DSD team over a period of 41 years (from 1980 to 2021).

Participants: A total of 696 subjects were included in the study.

Outcome Measures: The data collected included DSD diagnosis, age at diagnosis, sex assignment, clinical presentation, and phenotypic features.

Results: The subjects in this study presented at prepubertal, post-pubertal, and adult ages, often with atypical genitalia, undescended testes, or primary amenorrhea. Of the three major DSD categories, sex chromosome DSD was diagnosed in 264 subjects (135 with 45,X karyotype), with 101 being mosaics (45,X/46,Xi(Xq)) and three having chimerism (all ovotesticular DSD). Among the four ovotesticular DSD subjects, three were raised as females and one was raised as male, with no gender changes occurring in this group.

Thirteen chromosome DSD patients with Y material were assigned as male, and two female-assigned patients changed their gender to male. 258 subjects had 46,XY DSD (69 unknown DSD, 64 gonadal dysgenesis, 36 5-αRD2 deficiency, 18 17β-HSD3 deficiency, 11 17α-hydroxylase deficiency, 9 Leydig cell hypoplasia, 25 CAIS, 18 PAIS, 8 AMH defects). Among the 192 XY subjects with atypical genitalia, the sex of rearing was female in 89 (46%), and gender change from female to male occurred in 13%, most commonly in 5-αRD2 deficiency (45%) followed by 17β-HSD3 deficiency (33%). Among those raised as male, only 2.9% changed their gender.

46,XX DSD was diagnosed in 178 patients. Congenital adrenal hyperplasia-CAH (most commonly 21-hydroxylase deficiency) was diagnosed in 123 patients (115 female-assigned). Among the CAH cases, gender change from female to male occurred in six cases, of which most had simple virilizing (VS) form (5/6; p=.004), a late onset of treatment (>2 years old), and poor compliance. Among the remaining 55 patients with 46,XX DSD, 24 had ovotesticular DSD (all with atypical genitalia), and 16 had 46,XX testicular DSD (seven with atypical genitalia).

In conclusion, gender change from female to male was mainly observed among subjects with 46,XY DSD, particularly in those with 5α-RD2 and 17β-HSD3 deficiency, indicating that male sex assignment may be preferable for patients with these diagnoses. Among 46,XX DSD, the SV form of CAH, late initiation of treatment, and poor compliance were associated with female-to-male gender change.

P1-185

Atypical genitalia as a new presentation of ectodermal dysplasia: case report

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Background: Ectodermal dysplasia is considered as an inherited multi-systemic disorder affecting tissues derived from ectoderm (skin, hair, teeth, nails and sweat glands). There are many genes involved in genetic background of this disorder with variable modes of inheritance. The thrombospondin-type laminin G domain and epilepsy- associated repeats (TSPEAR) gene have been found in some patients with this disorder with interesting variable phenotypic spectrum. Biallelic TSPEAR variants present either with sensorineural hearing loss or with involvement of ectodermal-derived structures such as skin, hair, nails, and teeth. The following case report aims at showing the phenotypic features of this mutation with novel association with atypical genitalia.

Case Presentation: A 3-year-old boy presented to Pediatric Endocrinology clinic at Alexandria University Hospitals. His parents sought surgical consultation due to bilateral arrested testes (inguinal) and small sized penis. On clinical examination, external genitalia showed micropenis and bilateral palpable mid-inguinal testes (average sized for age). Furthermore, extragenital examination showed frontal bossing, fine sparse hair, thin fine eyebrows, brittle nails and conical shaped teeth. He had normal sweating and hearing. As a rare presentation of atypical genitalia, hormonal profile before and after HCG stimulation showed normal testosterone response with high testosterone/ dihydrotestosterone ratio. Inguinoscrotal ultrasonography showed average size and vascularity of both inguinal testes. Whole genome sequencing showed ectodermal dysplasia 14, hair/tooth type with or without hypohidrosis (OMIM: 618180) as homozygous mutation of TSPEAR gene.

Conclusion: Atypical genitalia is a novel association with ectodermal dysplasia which needs multidisciplinary team management including pediatric surgery, endocrinology, endodontics, dermatology and psychology.

P1-365

Etiology, histology and long-term outcome of bilateral testicular regression: a large Belgian series

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Background: Long-term outcome studies on bilateral testicular regression (BTR) are currently lacking, hampering counseling of patients and parents. Although a vascular origin was initially reported, recent studies revealed a genetic origin in a subset of patients (i.e. DHX37 gene variants). How this relates to patient outcomes remains unclear.

Methods: Thirty-five patients with BTR were recruited in eight Belgian centers (mean age: 15.0±5.7 years). Cross-sectional exams included clinical exam in all and a DSD-LIFE questionnaire in 17 end-pubertal participants (6 missing). Exome-based panel testing of genes (n=241) involved in gonadal development and spermatogenesis and retrospective analysis of presentation/management were performed. Histological analysis of gonadal rests was done in 10 participants.

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Results: Participants had presented at a median age of 1.2years [0-14years]. Gestational complications, in particular monozygotic twin pregnancy, were common (36.4% and 9.1% respectively). Heterozygous pathogenic missense variants in DHX37 (p.Arg334Trp and p.Arg308Gln) were identified in three participants. They had presented with a microphallus, opposed to 6/31 (19.4%) without DHX37 variant (1 missing). Childhood testosterone therapy to increase penile growth was more effective in those without versus with DHX37 variant. The three participants with a DHX37 variant developed a male, female and non-binary gender identity, respectively, whereas all other participants identified as males. Incremental testosterone replacement therapy (TRT) resulted in satisfactory pubertal development and statural growth (n=25; median age start 12.4years). Penile size remained suboptimal in 45.5% (≤-2.5 SD below the mean for adults). Five (45.5%) participants reported suboptimal understanding of the goals and effects of TRT at the time of puberty induction. Furthermore, only 6/11 (54.5%) and 5/11 (45.5%) indicated they were well informed in the last year about the risks and potential side effects of TRT, respectively.

Histological analysis of two participants with DHX37 variant revealed early disruption of gonadal development with presence of Müllerian remnants in both and undifferentiated gonadal tissue in one. In the eight other analyzed participants, no gonadal remnants were found.

Conclusion: BTR covers a broad phenotypic spectrum, with a more severe presentation in individuals with heterozygous DHX37 variants. In those without coding DHX37 variants, careful analysis of pregnancy details and clinical data suggest gestational complications as a contributing/etiological factor in 36.4%. Histological analysis supports DHX37 as a gonadal development rather than BTR-related gene. Even with adequate TRT, adult penile size often remains suboptimal. Adults indicate they needed a more thorough and understandable explanation of the treatment details, especially when initiating TRT.

P1-366

Trends in diagnosis and management of children with Differences in Sex Development over three decades– clinical experience of a tertiary care center

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Introduction: Differences in sex development (DSD) comprise a heterogeneous group of congenital conditions that affect human sex determination and differentiation. We aimed to describe the clinical diagnoses of children with DSD who were referred to a pediatric tertiary center, and to examine trends in clinical features and management over three decades.

Methods: This is a retrospective, cross-sectional study of children with DSD who were under our care during 1990-2019. The cohort was sub-classified by DSD class and by the year of diagnosis: before and after the introduction of the current DSD consensus guidelines in 2006.

Results: The cohort included patients with 46, XY DSD (n=87, 78.5%); 46, XX DSD (n=15, 13.5%); and chromosomal DSD (n=9, 8%). For patients with 46, XY DSD compared to patients with 46, XX DSD, the mean age at presentation was younger (0.5±2.5 vs. 6.8±8.1 years, p=0.007), and a higher proportion presented by age 1 year (94% vs. 60%, p=0.001).

Forty-four children were diagnosed during 1990-2006, and 67 during 2007-2019. While the proportions of DSD classes were similar between the two periods, prenatal diagnosis was more common in the recent years: 25.4% vs. 4.5% of the patients, p=0.004. Gonadectomy was performed in 22.9% of 46, XY patients; 6.6% of 46, XX patients; and 67% of chromosomal DSD patients. During 2007-2019 compared to 1990-2006, the proportions were lower of patients who underwent gonadectomy (16% vs. 36%, p=0.02), and of patients who had sex reassignment (1.5% vs. 11%, p<0.04).

Conclusions: An increase in the rate of prenatal diagnosis, and declines in the rates of gonadectomy and sex reassignment were shown over the course of three decades. Earlier diagnosis and the introduction of new advanced diagnostic tools enabled earlier and better management, using a patient-centered approach, by a multidisciplinary team.

P1-367

Changes in body composition in transgender adolescents during puberty suppression and hormone treatment

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Context: Transgender adolescents can be treated with puberty suppression (PS) using GnRH agonists (GnRHa), and subsequent hormone therapy (HT). Up to this date, it has not been described at what rate body composition in transgender adolescents changes during the first years of treatment. Also, it is unknown whether Tanner stage at which treatment is initiated, might affect this treatment outcome.

Methods: Transgender adolescents were included in this retrospective study if they were treated with GnRHa prior to HT and had at least one dual-energy X-ray absorptiometry scan during the first three years of PS or HT. Mixed model were used to analyse changes over time in total lean- and fat mass Z-scores using sex assigned at birth as reference. Individuals were divided into early pubertal (Tanner B2-3 or G2-3 at start PS) and late pubertal (Tanner B4-5 or G4-5 at start PS).

Results: In total, 380 trans boys and 168 trans girls were included. In trans boys, lean mass Z-scores decreased by -0.32 (95%CI -0.41;-0.23) and fat mass Z-scores increased by 0.31 (95%CI 0.21;0.41) in the first year of PS and remained stable thereafter. In trans girls, lean mass Z-scores decreased by -1.13 (95%CI -1.29;-0.98) and fat mass Z-scores increased by 1.06 (95%CI 0.90;1.23) over three years of PS.

During HT, lean mass Z-scores increased by 0.92 (95%CI 0.81;1.04) and fat mass Z-scores decreased by -0.43 (95%CI -0.57;-0.29) in the first year and remained stable thereafter in trans boys. In trans girls, lean mass Z-scores slightly decreased by -0.19 (95%CI -0.36;-0.03) in the first year and fat mass Z-scores were comparable to start HT after three years (-0.02, 95%CI -0.20;0.16). After three years HT, the lean mass Z-score in trans boys was -0.61 (SE 0.07) and fat mass Z-score was 0.20 (SE 0.10) using male references. In trans girls, lean mass Z-score was 0.18 (SE 0.10) and fat mass Z-score was -0.32 (SE 0.09) using female references. No differences in these Z-scores were observed between early and late pubertal starters.

Conclusions: The decrease in lean mass and the increase in fat mass Z-scores continued throughout 3 years of PS in trans girls whereas these changes were smaller and stabilized after one year in trans boys. A large increase in lean mass Z-scores occurred only during the first year of testosterone treatment. In trans girls, body composition changed only slightly during HT, possibly because most changes had already occurred during PS.

P1-368

Results of Empower-DSD: a patient education programme for children, adolescents, and young adults with differences of sex development (DSD) and their parents

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Background: Within the government-funded project Empower-DSD, modular training programmes for children and young adults aged 6-24 years with the diagnoses CAH, Turner-syndrome, Klinefelter-syndrome or XX-/XY-DSD (including MRKH) and their relatives were developed to improve diagnosis-specific knowledge, skills and empowerment. Overall, 105 trainings were offered between August 2020 and September 2022 in 5 centres with DSD expertise in Germany.

Objectives: To investigate the health-related quality of life (HQoL), satisfaction with the training programme, emotional stress, coping, burden of diagnose and shame, the participants answered questionnaires before the training (t0), immediately after the training (t1), and 3 (t2) and 6 months after the training (t3).

Methods: Used questionnaires were Candril ladder, WHO-5, KINDL, CODI, BIS and questionnaire for patient satisfaction based on ZUF-8 as well as self-constructed questionnaires for diagnose-specific knowledge. The data collected were analysed descriptively on the basis of the ITT population for children (6-13 years), adolescents (14-17 years) as well as young adults (18 years and older) and relatives separately. Categorical variables are presented with absolute and relative frequencies, metric normally distributed variables with arithmetic mean, standard deviation, minimum, maximum or median and interquartile range for non-normally distributed variables. The analysis of satisfaction was differentiated according to the diagnosis of the respondent.

Results: Overall, 634 person were trained in the 2-day modular structured patient education programme: 103 children aged 6-13 years, 94 youth aged 14-17 years, 56 young adults aged 18-24 years and 381 relatives. The questionnaires were completed at t0 by 610 (96%), at t1 by 574 (91%), at t2 by 465 (73%) and at t3 by 379 (60%) participants. The patient satisfaction was high, with the most satisfied participants in the group of Turner-syndrome and lowest in Klinefelter-syndrome. The main outcome parameter HQoL and further analysis on emotional stress, coping, burden of the diagnose, shame of the participants is pending due to the last questioning in March 2023 and will be finalized soon.

Conclusion: The modular training programme of Empower-DSD was developed for children, youth, young adults with a variance of sexual development and their relatives. The overall satisfaction was high with most satisfied participants in the Turner-group and lowest satisfaction in the Klinefelter-group.

Trial registration: German Clinical Trials Register, DRKS00023096. Registered 8 October 2020 – Retrospectively registered, https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00023096

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WITHDRAWN

P1-370
Growth and final height in Danish transgender adolescents treated with hormone therapy before cessation of puberty and growth spurt

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Background: Linear growth during spontaneous puberty contributes approximately 20% to adult height in healthy subjects. The impact of gender-affirming hormone therapy (GAHT) on final height in transgender adolescents is sparsely studied.

Aim: We aimed to investigate the growth and final height of Danish transgender adolescents.

Methods: Our national cohort of transgender adolescents (2016-2023) comprised 167 adolescents, 38 trans girls (assigned male sex at birth) and 129 trans boys (assigned female sex at birth). They all received GAHT before the age of 18 years. Treatment consisted of Gonadotropin-Releasing Hormone agonist (GnRHa) (n=167) combined with either estradiol (n=32 trans girls) or testosterone (n=117 trans boys). Doses of estradiol and testosterone were adjusted to reach a serum concentration of estradiol or testosterone, respectively, between median and +2SD for the references of the experienced sex. Height, weight, and blood samples were collected at routine visits and compared to Danish references. Height velocities were compared to international references.

Results: Overall, adult heights were within ±2 SD for references of the sex assigned at birth in all trans girls and trans boys. Most trans girls reached adult heights within adult references of cis girls. Half of the trans boys remained short (<-2 SD) compared to cis boys. Growth velocity declined during GnRHa treatment in both trans girls and trans boys. For trans girls with a bone age below 15 years before starting GAHT, we observed a growth spurt when initiating estradiol treatment. We observed a small but significant difference between target height and adult height for trans girls (mean -3.6 cm, p=0.0022) and between height SDS before treatment and adult height for both trans girls (mean -0.31 SDS, p<0.001) and trans boys (mean -0.17 SDS, p<0.001).

Serum IGF-I and IGFBP-3 concentrations were within the references for the experienced sex, and we observed a decrease in serum IGFBP-3 for the trans boys on testosterone treatment.

Discussion and Conclusion: Most transgender adolescents initiating GAHT during adolescence reached a final height within ±2 SD for sex assigned at birth. We found a subtle but significant decline in final height of trans girls treated with GnRH agonist and estradiol before 18 years of age, which may be considered beneficial by some. Whereas trans boys did not experience any height gain.

P1-371
Effect of maternal diet on pubertal stages and ano-genital distance from birth up to 12 months: data from the European LIFE-MILCH project

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The ongoing European LIFE-MILCH project (www.lifemilch.eu), focuses on detecting Endocrine Disrupting Chemicals in mothers, in breast and formula milk and in urine of mothers and infants up to 12 months of age studying relationships with neurodevelopment, growth, distribution of adiposity, pubertal stages, and ano-genital distance(AGD) to establish a risk assessment model to prepare safety guidelines. In this study we evaluated the effects of maternal diet during and after pregnancy on pubertal stages, genital malformations, and AGD from birth up to 12 months of age.

The analyses were carried out on the 254/654 mother-infant dyads enrolled at one of the sites. The mothers were enrolled at 36-40 weeks GA, and were in good health; pregnancies were uncomplicated. All women filled questionnaires related to nutritional habits (daily and weekly frequency of intake of cereals, meat, eggs, fruit and vegetables, fatty food and dairy products) at enrolment, 1, 3, and 6 months after delivery. The duration and type of feeding was registered. All anthropometric measurements were registered and in addition pubertal stages and AGD. One-hundred and twenty-five males and 129 females were analysed both separately and as a whole group.

After delivery mothers ate significantly less vegetables, fruit and cereals, and took more fat food whereas meat intake was unchanged and dairy products intake was variable. When breastfeeding stopped the intake of cereals decreased (p:0.029). The effect of the mothers diet before and after delivery was analysed separately, and the average of the frequency of intake of each food category was considered. Interestingly, a higher intake of dairy products was associated with a lower frequency of hydrocele in males. The breast bud was present longer in the males whose mothers reported a higher cereal intake after delivery, whereas it disappeared earlier in the females whose mothers had a higher cereal intake during pregnancy as well as in those who reported a greater intake of eggs (p:0.048). In females, maternal diet after delivery showed no relationship with thelarche.

Generally, AGD was not associated with mother's nutritional preferences, however, a weak negative association with meat intake during pregnancy was observed in boys at 3 and 6 months whereas a stronger negative association was found with fatty food intake at 3 months.

In conclusion, maternal nutrition during pregnancy and lactation has effects on the clinical signs of minipuberty, possibly on the development of hydrocele, and on AGD, highlighting the need to improve maternal nutrition.

P1-372

Incidence of differences of sex development in Switzerland 2000-2019

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Background: Differences in sex development (DSD) comprise a large group of rare, mostly genetic disorders along the path of human sexual development. Since the Chicago Consensus, health care providers group them in sex chromosome DSD, 46,XY and 46,XX DSD with subgroups regarding their effect on sex hormone synthesis, action or excess, on gonadal development, and others. Incidence of rare DSD is not well established despite public interest.

Aim: The aim of this study was to estimate the nation-wide incidence of DSD in Switzerland.

Methods: This retrospective observational study included children with a DSD according to the Chicago Consensus classification who were born between January 1, 2000 and December 31, 2019 in Switzerland, except in the canton of Ticino. Endocrine care centers from all ten Children's Hospitals in Switzerland and the eight largest private endocrine practices collected data on DSD diagnosis through the DSD registry or case report forms. An independent institution identified duplicate entries through record linkage. Population-based data on live births came from the Swiss Federal Office of Statistics (SFSO).

Results: Over the 20-year study period, we identified a total of 563 children with DSD born between 2000-2019, annually on average 28 new cases of DSD. Almost half (n=267, 47%) had sex chromosome DSD, 179 (32%) had 46,XY DSD and 118 (21%) had 46,XX DSD. Causes for 46,XY DSD were disturbed androgen synthesis or action (37/179, 21%), followed by atypical gonadal development (29/179, 16%), and other reasons (113/179, 63%). The main cause for 46,XX DSD was androgen excess (99/118, 84%), followed by atypical gonadal development (8/118, 7%), and other reasons (11/118, 9%). We found an incidence of sex chromosome DSD of 1 per 5,700 live births. One per 7,500 newborn girls had 46,XX congenital adrenal hypoplasia (CAH). Incidence for 46,XY DSD was 1 per 4,400 newborn boys, and incidence for 46,XX DSD (excluding CAH) was 1 per 37,000 newborn girls.

Conclusion: We found that incidence of sex chromosome DSD was lower than those reported by other studies because of underreporting. We probably missed milder DSD cases, which manifest late or do not require specialist care. For complex cases of 46,XY DSD and 46,XX DSD, we expect nation-wide coverage. Incidence of 46,XX CAH was comparable to national screening data, suggesting good completeness of cases. This study provides a valuable resource for policy-making and (inter)national research on DSD.

P1-373

Methodological considerations on determining sex steroids in children: Comparison of conventional immunoassays with LC-MS/MS

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Objectives: In laboratory medicine, external quality assessment (EQA) schemes have become versatile tools for the detection of analytical flaws. However, for pediatric sex steroid levels EQA schemes are lacking. We aimed to investigate the suitability of different estradiol and testosterone immunoassays in a pediatric setting, in comparison with clinical liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays.

Methods: The study was conducted by staff and the advisory group of endocrinology at Equalis, the Swedish provider of EQA schemes for laboratory medicine. Test material consisted of five pooled serum samples from children either prepubertal or in early puberty. Clinical laboratories enrolled in Equalis EQA schemes for estradiol and testosterone were invited to participate as well as clinical laboratories using LC-MS/MS-assays. Samples were analyzed by either commercial immunoassays (n=18) or in- house LC-MS/MS assays (n=3).

Results: For estradiol, LC-MS/MS assays showed a high degree of conformity with interlaboratory coefficients of variation (CV:s) below 24.2%. Reported levels were (mean±SD); 4.9±1.2; 8.5±1.3; 9.4 ±1.0; 16.6±0.6 and 33.9±1.6 pmol/L (group mean±standard deviation). The direct immunoassays had lower precision, their interlaboratory CV:s were up to 81.4%. Reported concentrations were 25.3±18.1; 32.6±25.3; 27.6±18.8; 32.8±26.7 and 45.7±19.4 pmol/L, a clear overestimation compared to LC-MS/MS. Testosterone LC-MS/MS also showed a high degree of conformity, CV:s were below 13.4%, and reported concentrations were 0.06±0.00; 0.19±0.02; 0.62±0.08; 0.99±0.11 and 1.00±0.11 nmol/L. The direct immunoassays had larger discrepancy between results; CV:s were up to 95.8%, with corresponding concentrations

0.12±0.11; 0.11±0.05; 0.46±0.12; 0.80±0.28 and 0.85±0.23 nmol/L. Both under- and over-estimation occurred.

Conclusions: This study enabled some general conclusions to be drawn for samples from children.

a) Commercially available estradiol immunoassays are not suitable for diagnosis in children.
b) Commercially available testosterone immunoassays have an uncertainty of reproducibility in the low range that each individual user should consider.
c) For safe diagnosis and determination of sex steroids in children, analysis with MS/MS-based methods is recommended.
d) Every pediatric endocrinologist or laboratory scientist should be familiar with the pitfalls of their sex steroid methods used.

P1-374

Metabolic health status and cortisol metabolism of adolescents with gender incongruence / gender dysphoria during process of diagnosis

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Introduction: Gender incongruence (GI) is a condition where a person's gender identity does not match their assigned sex at birth, and can lead to significant distress and gender dysphoria (GD). In various studies it has been associated with a predisposition to developing pathological eating behaviours, which in turn negatively influence the individual's metabolic health. In our study we examine selected markers of metabolic condition and assess surrogates of cortisol metabolism reflecting stress in a population of adolescents with GI/GD during their diagnosis process.

Methods: This prospective study has examined 181 adolescents admitted due to GI/GD to one clinical center between 2017 and 2022. History of gender identity incongruence and gender dysphoria has been analysed alongside hormonal, metabolic and anthropometric parameters. The population has been divided into assigned female at birth (AFAB) and assigned male at birth (AMAB) groups.

Results: The population consists of 181 participants (153 AFAB, 28 AMAB), with the mean age of 15.8 ± 1.7 years and the mean age of gender identity mismatch onset of 11.4 ± 2.8 years. BMI distribution, components of the metabolic syndrome, midnight serum cortisol and glucocorticoids metabolites in the 24hr-urine collection are presented in table (*** - AFAB vs. AMAB* $p<0.05$)

Conclusions: The increased risk of abnormal BMI, mostly increased in AFAB and decreased in AMAB, and higher risk of metabolic syndrome/complications are valuable insights when dealing with patients during the preparation for medical transition. Increased concentrations of glucocorticoids metabolites may reflect excessive stress, especially in the AMAB patients.

Variables		All (n=181)	AFAB (n=153)	AMAB (n=28)
BMI (*centiles*)				
>97		22%	25%	7%
90-97		15%	16%	14%
10-90		51%	50%	60%
3-10		7%	7%	7%
<3		3%	2%	10%
Fasting blood	glucose >100 mg/dl	7%	7%	4%
	triglycerides >150 mg/dl	8%	10%	0%
	HOMA-IR >2.5	36%	36%	36%
	HDL-cholesterol <40 mg/dl	10%	8%	18%
	midnight cortisol >5.7 ug/dl	8%	8%	7%
24-hr urinary collection (steroid metabolom)	THE/tetrahydrocortisone **	11%	7%	35%
	THF/tetrahydrocortisol**	7%	5%	21%
	α THF/ α tetrahydrocortisol	1%	1%	0%
	α-Cl / α-cortolone **	8%	5%	21%
	β-Cl / β-cortolone **	9%	5%	29%
	β-C / β-cortol	3%	4%	0%
	α-C / α-cortol **	10%	5%	39%
	E/cortison**	5%	3%	18%
	F/cortisol**	5%	3%	18%

P1-375

Value of serum AMH and INHB in the diagnosis and treatment of central precocious puberty and early and fast puberty girls

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Objective: To investigate the role of serum anti-mullerian hormone (AMH) and inhibin-B (INHB) in central precocious puberty precocious puberty (CPP) and early and fast puberty(EFP).

Methods: 90 girls with CPP, EFP and premature thelarche (PT) were enrolled in our hospital from January 2021 to December 2022, and 45 girls without healthy development were enrolled. General data, sex hormones, AMH, INHB levels and gonad ultrasound were collected. The data of each group were compared, and the diagnostic value of AMH and INHB in predicting CPP girls and their early warning value in EFP girls were judged by receiver operating characteristic curve, and the correlation of each index was analyzed by Spearman correlation analysis. Girls diagnosed with CPP or EFP at the same time were selected to receive GnRHa treatment. AMH, INHB, sex hormone detection, uterine volume (UV) and mean ovarian volume (M-OV) were evaluated at the 6th and 12th month of treatment. The changes of each index before and after treatment were compared to explore whether AMH and INHB can be used to evaluate the therapeutic effect of GnRHa. Results AMH in CPP group was higher than that in PT group, while INHB in CPP group was higher than that in non-CPP group (PT group and healthy group). The sensitivity and specificity of INHB in the diagnosis of CPP were 0.815 and 0.611, respectively, while the area under ROC curve of AMH in the diagnosis of CPP was less than 0.5. AMH was negatively correlated with LHb, FSHb, LHp and FSHp levels. The sensitivity and specificity of INHB early warning EFP were 0.887 and 0.606, respectively. The sensitivity and specificity of INHB combined with UV early warning EFP were 0.962 and 0.576, respectively.INHB was positively correlated with UV, LHb, FSHb and LHb/FSHb levels in EFP. After 6 and 12 months of GnRHa treatment, INHB decreased significantly in both CPP and EFP, and the decrease rate of INHB was positively correlated with the decrease rate of LHp and FSHp. The change of AMH level before and after treatment was not statistically significant.

Conclusions: This study verified the diagnostic value of INHB in CPP girls. This study suggests that AMH level can be used as a potential indicator to distinguish central precocious puberty from early breast development. INHB level combined with UV detection is significant for early warning of EFP girls in clinic;INHB has important reference value in evaluating the efficacy of GnRHa in CPP and EFP girls.

P1-376

Obtaining clear birth certificates for children with difference in sex development (DSD) undergoing sex reassignment: A new legal process for Sri Lanka

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Introduction: Majority of births in Sri Lanka occur in hospitals, with birth registration completed prior to discharge. When babies with atypical genitalia are missed at birth, and gender re-assignment decided, following later detection and evaluation, families faced many challenges to obtain a "clear" birth certificate (BC), without incriminating details of prior name or sex.

Objectives: To describe characteristics of children with atypical genitalia undergoing gender reassignment after birth registration, and process to obtain clear BCs for such children in Sri Lanka.

Setting/Methods: After obtaining ethics approval (EC–18-092), and informed written consent, data on children with DSD born between 1999-2020 managed at the Professorial Paediatric endocrine clinic, University of Colombo, Sri Lanka, were entered to a patient-registry. Those with gender of rearing different to initial birth certification were identified, contacted by the clinician-in-charge, and offered support to obtain a clear birth certificate.

Results: Among 110 patients aged between 0-23 years, more than half (n= 63, 57%) were born with atypical genitalia. Ten (16% of those born with atypical genitalia) all born between 2001- 2020 at major hospitals, had gender-re-assignment after birth registration. Four were initially registered as males at birth, and underwent subsequent gender reassignment to female. They all had congenital adrenal hyperplasia(CAH) due to 21-hydroxylase deficiency, and female karyotype (46,XX). Among six children registered as female who underwent gender reassignment to male, all had a male karyotype (46, XY), one child had 5-alpha reductase deficiency, one had 3-beta-hydroxy-steroid-dehydrogenase deficiency CAH, and four had 46XY DSD of uncertain aetiology.

Five families requested for support, while two were undecided, and remaining three families did not respond. Those who requested support were provided with a support letter by the clinician, and legal support to facilitate the process After a long process, supported and mediated by The Asia Foundation, a legal protocol to obtain a clear BC for children born with CAH/DSDs necessitating gender change, was formulated. The first clear BC was issued by Registrar General's Department in mid-2022, and a total of four clear BCs obtained by April 2023.

Discussion: When children require sex-change based on an underlying medical condition, the legal system of the country should support issue of a clear birth BC, to minimize psychosocial distress and stigma. A circular to this effect is now being formulated, and education, sensitisation and training of health and legal workers involved in the process is planned.

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P1-377

Prognostic Factors and Long-Term Safety of GnRHa in the Treatment of Idiopathic Central Precocious Puberty in Girls

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Objective: To investigate the relevant prognostic factors and long-term safety of gonadotropin-releasing hormone analogs (GnRHa) in the treatment of idiopathic central precocious puberty (ICPP).

Methods: This was a retrospective study. Data analysis included 142 girls with ICPP who reached final adult height (FAH). Among them, 101 girls were treated with GnRHa while 41 girls were untreated. The Pearson and Spearman correlation test were used to analyze the prognostic factors. The Chi-squared test and Fisher's exact test were used to evaluate long-term safety.

Results: The comparisons of general information between the treatment and control group are shown in Table 1. Height SDS for bone age (HtSDS_BA, R=0.656, p<0.001), height SDS (R=0.621, p<0.001), and target height (R=0.596, p<0.001) were the major prognostic factors affecting FAH of ICPP girls with GnRHa treatment. The follow-up data showed all of the characteristics, including dysmenorrhea, polycystic ovary syndrome, facial acne, hirsutism, and alopecia were not found statistically different in two groups.

Conclusions: This study corroborated the long-term safety of GnRHa treatment for girls with ICPP. HtSDS_BA, height SDS and target height can be valuable indicators for predicting the prognosis.

Table 1. Clinical characteristics of participants in this study

	Treatment Group (n=101)	Control Group (n=41)	MWU-t (p-values)
Before treatment			
CA0 (years)	8.15±0.73	7.61±1.06	0.011
Height0 (cm)	130.65±4.84	129.16±10.01	0.669
HeightSDS0	0.31±0.73	0.52±1.17	0.112
Weight0 (kg)	27.85±4.04	27.32±6.37	0.427
BMI0 (kg/m^2)	16.27±1.83	16.14±1.83	0.707
Peak LH (IU/L)	18.61±14.19	14.81±8.11	0.331
Peak FSH (IU/L)	14.65±5.73	14.66±5.80	0.937
BA0 (years)	10.29±0.76	9.18±1.83	<0.001
HtSDS_BA0	-1.79±0.61	-1.04±0.88	<0.001
BA0-CA0 (years)	2.14±0.70	1.57±1.11	0.003
PAH0 (cm)	150.93±3.31	154.98±4.74	<0.001
TH (cm)	157.20±3.40	156.90±3.79	0.857
Uterine volume (ml)	2.05±1.41	2.59±3.52	0.761
Larger ovarian volume (ml)	2.44±0.63	2.57±0.79	0.265
After treatment / Follow-up			
CA1 (years)	19.89±1.91	20.38±1.95	0.106
FAH (cm)	160.73±3.95	161.13±4.37	0.655
Weight1 (kg)	53.31±6.52	54.35±7.19	0.394
BMI1 (kg/m^2)	20.66±2.67	20.90±2.32	0.336
Duration of treatment (years)	2.48±0.52	-	-
Age at first menstruation (years)	12.15±0.86	11.43±1.22	0.001
Menstruation after discontinuing GnRHa (years)	1.51±0.74	-	-

MWU-t: Mann-Whitney U test. CA: chronological age. LH: luteinizing hormone. FSH: follicle-stimulating hormone. BA: bone age. PAH: predicted adult height. TH: target height. The numbers 0 and 1 indicate the data before and after treatment.

P1-378

Infant with 45, XO DSD presented with Li Fraumeni syndrome, a case report from Kuwait

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Background: X-chromosome monosomy is the most common sex abnormality in females, with a higher prevalence of cancer than the general population. Virilizing adrenocortical tumors are rarely seen in patients with Turner's Syndrome. There have been 2 reported cases of simultaneous TP53 mutations (Li Fraumeni's syndrome) and Turner's syndrome. Here we report first case with this rare association from Kuwait.

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Clinical Case: A six-month-old girl brought by her grandmother with aggressive behavior, virilization, and pubic hair of unknown duration since grandmother just took care of the child after the recent loss of the mother because of leukemia. The examination was limited because the patient was agitated and aggressive. The examination revealed an increased growth with length >95th percentile, weight was 75th percentile, and pubic hair tanner stage II-III. Genital exam showed clitoromegaly of 4 cm, no labioscrotal fusion, and no palpable gonads. Total testosterone was 9.73 nmol/L ,FSH level was 2.28 IU/L, and LH was 0.86 IU/L. Blood glucose and electrolytes were within normal. The ACTH stimulation test: peak cortisol was 544 nmol/L, and peak 17-hydroxyprogesterone was 25.23 nmol/L. Advanced bone age 2-2.5 years. US abdomen reported a normal sized uterus and vagina with no visualized gonads, and a large abnormal configuration of the left kidney. MRI confirmed the previously reported left suprarenal soft tissue tumor measuring 5.2x5.8x6 cm, which was heterogenous, highly vascular, compressing the upper pole of the left kidney with a clear line of cleavage. Karyotype revealed 45 XO, Turner syndrome with negative SRY gene. PET-scan excluded metastasis. Urine levels of epinephrine, norepinephrine, dopamine, vanillyl mandelic acid (VMA), and homovanillic acid (HVA) were within normal range. Left adrenalectomy was done and histopathology report showed adrenal cortical carcinoma, oncocytic type. Targeted Inherited Cancer panel sequencing on DNA extracted from peripheral blood revealed a heterozygous pathogenic variant in TP53: c.374C>G (p.Thr125Arg) which is associated with Li-Fraumeni syndrome.

Conclusion: This is the third case of Li Fraumeni's Syndrome linked to X-monosomy, raising the question of the correlation between the two syndromes, and highlighting the uncommon occurrence of adrenocortical cancers in Turner's Syndrome.

P1-379

Hyperandrogenism in adolescents assigned female at birth during process of gender incongruence/ gender dysphoria diagnosis

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Introduction: Gender incongruence (GI) is a condition where a person's gender identity does not match their assigned sex at birth and can lead to significant distress and gender dysphoria (GD). Some studies have shown a higher prevalence of hyperandrogenism (HA) in transboys/transmen than among the cisgender female population and considered its meaning in the context the of gender identity development. Therefore, further studies confirming this observation and clarifying the relationship between HA and GI/GD is needed. In our study we conducted clinical and biochemical assessment for HA in a population of adolescents with GI/GD during their diagnosis process and before medical transition.

Methods: This prospective study has examined assigned female at birth (AFAB) adolescents admitted due to GI/GD to one clinical center between 2017 and 2022. History of gender incongruence/ gender dysphoria has been analysed alongside clinical and hormonal parameters.

Results: The population consisted of 153 participants, with the median age of 16.1 ± 1.7 years and the mean age of gender identity mismatch onset of 11.7 ± 2.5 years. The prevalence of hirsutism, acne and oligomenorrhoea (>35 days) in study group was 1%, 42% and 10% respectively. Biochemical HA / hyperandrogenemia defined by concentration of serum testosterone (>58 ng/dl), androstenedione (>2.24 ng/ml), DHEAS (>248 μg/dl) and 17-hydroxyprogesterone (>2.0 ng/ml) was confirmed in 14%, 65%, 38% and 24% participants respectively.

Conclusions: This is the first study to assess the prevalence of hyperandrogenism in AFAB adolescents with gender incongruence in Polish population. Our findings point to a high prevalence of biochemical than clinical markers of HA among the AFAB population.

P1-380

A novel mutation of androgen receptor in a patient with complete androgen insensitivity syndrome

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Androgen insensitivity syndrome (AIS) is a rare genetic disease caused by mutation in the androgen receptor (AR). The AR is an essential steroid hormone receptor that plays a crucial role in male sexual differentiation and development. Mutations in the AR gene on the X chromosome cause malfunction of the AR so that a 46,XY karyotype male shows some physical characteristics of a woman or a full female phenotype. Depending on the phenotype, AIS can be classified as complete, partial or mild. Here, we report a patient of complete AIS who showed complete sex reversal from male to female as a result of novel AR mutation. A 2-month-old girl was referred to our hospital for evaluation of inguinal masses. Pelvis sonography revealed that there was no uterus, and testicle-like masses were found in both lower inguinal areas. The patient's karyotype was 46,XY. Genetic analysis of AR, SRY and SRD5A2 was performed, and a hemizygous novel mutation (c.2242T>C, p.Phe748Leu) was identified in AR. No mutations were found in SRY and SRD5A2, respectively. Family screening for genetic counseling was performed, and the same AR mutation was also found in the mother. For individuals with AIS, the standard of care is an orchidectomy to prevent possible malignant degeneration of the testes. The timing of such surgery has been debated. Later orchidectomy allows pubertal development to occur spontaneously with the production of estrogen from the aromatization of the high levels of testosterone normally produced. In our patient, gonadectomy is planned after puberty. Individuals with complete AIS are usually raised as females and need appropriate care.

P1-381

The impact of Covid -19 pandemic on incidence of precocious puberty. A comparative study in pediatric population of Northwest Greece and Crete

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Recent evidence suggests increase of Precocious Puberty (PP) after the Covid-19 pandemic; however, there are no data from Greece in the literature.

The aim of this study was to investigate whether there was an increase in the incidence of PP, during the pandemic period, in Northwest Greece (Ioannina) and Crete (Heraklion) .

A retrospective analysis of prospectively collected data was performed, in pediatric patients assessed in Pediatric Endocrinology outpatient clinics in Ioannina and Heraklion. Group A consists of patients examined before the onset of Covid (till March 2020) and in group B recorded patient's data from visits between April 2020-October 2022.

In the cohort entered girls <8 years and boys <9 years old. In both groups a detailed medical history, a complete clinical examination including Tanner stage, BMI, LHRH test and bone age were recorded.

Statistical analysis of the data was performed using SPSS statistical package. The independence sample t -test was used due to normal distribution of data.

In Ioannina, 4,157 patients were studied. 2,621 (63.1%) were girls and 1,536 (36.9%) were boys. 3,360 (80.8%) belonged to Group A and the remaining 797 (19.2%) to Group B. Overall, 231 children (5.6%) showed PP. Of these, 154 (4.6%) belonged to Group A and 77 (9.7%) to Group B. The difference in the percentage was statistically significant (p=0.001). Analysis by gender showed that the frequency of early puberty was statistically significant for girls (p=0.001), while for boys there was an increase in frequency that was not statistically significant.

Regarding BMI, in Ioannina there was a significant increase in boys in group B (p=0.026) but not in girls.

In Heraklion, the medical records of 6,350 patients were studied. 3,737 (62%) were girls and 2,413 (38%) were boys. The majority, 4,454 (70.1%), belonged to Group A, and the remaining 1,896 (29.9%) to Group B. Overall, 134 children (2.1%) showed PP. Of these, 64 (1.4%) belonged to Group A and 70 (3.7%) to Group B. The difference in the percentage was statistically significant (p=0.001). The analysis based on gender showed that the frequency of PP was statistically significant for girls (p=0.001), while for boys there was an increase in frequency that was not statistically significant.

Regarding BMI in Heraklion there was no significant difference between the two groups.

In conclusion this study show that the frequency of PP has been significantly increased by the Covid-19 pandemic, especially in girls.

P1-382

A new GATA-4 mutation in a child with disorder of sex development and central precocious puberty

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Background: Disorders of sex development (DSD) are often due to disruption of the genetic programs that regulate gonad development. Some genes have been identified in these developmental pathways such as DAX-1, SOX-9, GATA-4 and others. The GATA-4 gene, located on chromosome 8p23.1, encodes GATA-binding protein 4 (GATA-4), a transcription factor that is essential for cardiac and gonadal development and sexual differentiation. Congenital heart disease (CHD) and DSD can be isolated or combined. We report the case of an 8-year-old child with a DSD, central precocious puberty and GATA4 mutation without CHD.

Case Description: Second-born child of healthy non-consanguineous parents, born at term by CT after a normal pregnancy. Birth weight 3900 g, length 54 cm. In the second month of life testosterone therapy was administered for 3 months because of micropenis (1,5x1 cm). At 2 years old, orchidopexy was performed for bilateral cryptorchidism. After 6 years he came back under our observation for increase of sexual pubic hair (pubarche). Auxological parameters: height 147 cm (+2,95 SDS), weight 42 kg (+2,21 SDS), bone age 11.25 yrs vs 8 yrs of chronological age. Physical examination showed hyperthelorism and singular cafe-au-lait macule in abdominal seat. At the GnRH test, the LH peak was 74.7 mIU/ml and we found elevated IGF1, testosterone, LH and FSH basal levels. Testicular volumes were 1 ml at ultrasonography. Pituitary MRI was normal. No organ pathology was detected in echocardiography and thyroid ultrasonography. Precocious puberty was then detected and GnRHa treatments was started, even if the elevation of gonadotrophins to GnRH test could suggest a future diagnosis of hypergonadotropic hypogonadism. So, we decided to perform genetic tests for DSD. Chromosome analysis revealed a 46, XY karyotype. Array-CGH study identified a de novo 815 Kb micro-deletion in 2q34 region that interests a part of ERBB4 gene, not described as associated with DSD and precocious puberty. NGS genetic investigation showed heterozygous variant c.671CG (p.Ser224Cys) in GATA-4 gene. According to The American College of Medical Genetics and Genomics, the latter variant was probably pathogenetic.

Conclusions: The variant c.671CG in GATA-4 gene has not been previously associated with DSD. In addition, a peculiarity of this case is the finding of a clinical pattern compatible with central precocious puberty despite the lack of increased testicular volume. To the best of our knowledge, this is the first case of a DSD due to GATA-4 mutation that develops precocious puberty.

P1-565

Insights into pubertal development among individuals with *NR5A1*/SF-1 variants: Results from the international SF1next study

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Background: *NR5A1*/SF-1 variants result in a wide range of phenotypes including DSD, male infertility, and primary ovarian insufficiency (POI). Little is known of how *NR5A1*/SF-1 variants affect puberty in individuals with or without DSD. This study aimed to assess the impact of *NR5A1*/SF-1 variants on pubertal development and investigate whether abnormal puberty is linked to the severity of DSD in an international cohort with *NR5A1*/SF-1 variants.

Methods & Patients: Collaborators from 55 centres (I-DSD registry and beyond) provided retrospective data on pubertal development and on DSD phenotype of individuals with NR5A1/SF-1 variants. We classified individuals into four DSD phenotype groups to define the degree of DSD based on the deviation of the external genitalia at birth from the typical phenotype for karyotype. We categorized pubertal development as: normal, abnormal, or unknown. Individuals without spontaneous start of puberty, receiving sex hormones, having Tanner stage outside expected range for the given age, or without having menarche by the age of 15, were classified as having abnormal puberty. For family members, we requested clinicians to indicate pubertal development status directly.

(SF1next study group: https://www.dropbox.com/s/wza2bud5naw2ftd/SF1next%20study%20group.pdf?dl=0)

Results: Data on pubertal development were available for 112 individuals. Among them, 68% had a 46,XY karyotype, 30% had a 46,XX karyotype, and 2% had a 47,XXY or 47,XYY karyotype. Out of the 112 individuals, 57 (51%) had a DSD and five had POI. Sixty-two individuals (38 46,XY and 24 46,XX) had normal puberty, out of which 81% did not have a DSD (26 46,XY and 24 46,XX), 11% (7 46,XY) had a mild DSD phenotype and 8% (5 46,XY) had a severe DSD phenotype. Abnormal puberty was observed in 50 individuals, of which 45 had a DSD, with 60% had an opposite sex DSD phenotype (25 46,XY and 2 47,XYY or 47,XYY), 36% had a severe DSD phenotype (13 46,XY and 3 46,XX), and 4% had a typical phenotype (2 46,XX). 71 individuals of the SF1next study cohort were too young to assess puberty.

Conclusion: Individuals with *NR5A1*/SF-1 variants and a DSD are likely to manifest with an abnormal pubertal development compared to those without a DSD. Individuals with opposite sex DSD phenotype have abnormal puberty, while individuals with a mild DSD phenotype have normal pubertal development. Further studies in individuals with *NR5A1*/SF-1 variants without DSD are required to investigate whether *NR5A1*/SF-1 variants contribute to (minor) anomalies of pubertal development or fertility and reproduction in the general population.

P1-566

Inhibin A (*INHA*) and steroidogenic factor 1 (SF-1/*NR5A1*) collaborate in regulating human sex development

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Background: Inhibin consists of two homologous subunits, the α (*INHA*) and the βA or βB subunits (*INHBA*/*INHBB*). Both inhibins play an important role in the hypothalamic-pituitary-gonadal axis by regulating the follicle stimulating hormone levels. *INHA* knockout mice develop mixed or incompletely differentiated gonadal stromal tumours. In females, some *INHA* variants have been associated with primary ovarian failure (POF), while in males, homozygous *INHA* variants were recently described causing decreased prenatal and postnatal testosterone production and infertility. Similarly, variants in SF-1/*NR5A1* may cause a very broad phenotype of variation of sexual development. This study aimed at understanding the combined effect of heterozygous variants in *INHA* [c.675T>G, Ser225Arg] and SF-1/*NR5A1* [c.58G>C, Val20Leu] found in a 46,XY individual with severe undervirilization.

Methods: Genetic family analysis was performed. Different *in silico* tools predicted the possible impact of SF-1/*NR5A1* and *INHA* variants on protein structure and function to classify them according to the ACMG guidelines for pathogenicity. We searched for human *INHA* variants in literature and in databases (ClinVar, HGMD, UniProt and Ensembl), and for interaction between SF-1/*NR5A1* and *INHA* in different species. Using bioinformatic tools, binding sites for SF-1/*NR5A1* in the 5' flanking region of *INHA* were searched and used as templates to generate several promoter-reporter constructs in pGL3. Expression vectors containing the wild-type and missense SF-1/*NR5A1* and *INHA* variants were also generated. Functional studies assessed the transcriptional activation of the *INHA* promoter by WT or mutant SF-1/*NR5A1*, while (in-)direct protein interactions between WT or variant *INHA* and SF1 were assessed by transient transfection experiments in different cell models.

Results: The healthy father of the index patient carried only the SF-1/NR5A1 variant. But in silico analyses suggested that both the SF-1/*NR5A1* and *INHA* variants were pathogenic. Multiple sequence alignment showed conservative amino acids affected. We found no reported interactions between the two proteins. However, 26 *INHA* variants with suggested pathogenicity were reported in different databases, majority missense variants (18/26, 69%), 12 (66%) with unknown significance (VUS), although associated with adrenocortical or ovarian tumours, POF and male infertility. We found several potential SF-1/*NR5A1* and CREB binding sites in the *INHA* promoter that are currently tested for their functional activity using corresponding promoter deletion constructs. Experiments checking *INHA*-SF-1 protein interaction are also ongoing.

Conclusion:

The exact role of *INHA* in human sex development remains largely unknown. Our study suggests an interplay between INHA and SF-1/NR5A1, and possible digenic pathogenicity with genetic variants.

P1-567

An International Delphi Based Study For Developing A Core Outcome Set For Hypospadias Surgery

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Background: Heterogeneity in reported outcomes limits the ability to compare results of studies evaluating hypospadias surgery.

Objective: To identify a core outcome set (COS), a minimal number of defined outcomes, to be routinely measured and reported in all trials across the age span following hypospadias surgery.

Materials and Methods: A study protocol was drafted and the study registered on the COMET database (www.comet-initiative.org) prior to initiation. Age specific (<6 years, 6-10 years, 11-16 years, >16 years) outcomes identified in a literature review were presented in a three round online Delphi survey. Professionals from 25 countries and parents/patients older than 14 years from four centres were invited to participate. In the first Delphi round (DR), participants were asked to add missing relevant outcomes as well as to choose and rank up to five outcomes that were most important to them, for each age category. Free text responses were thematically analysed and presented in subsequent DRs with outcome lists ranked according to popularity.

COS inclusion required more than 70% of votes in a round. By the end of DR 3, the most popular outcomes for each age-category were added to the COS until it included five outcomes.

Results: Professional respondents (DR 1, 2, 3 n= 75, 47, 40, respectively) mainly included paediatric urologists. Responses from parents/patients (DR 1, 2, 3 n= 16, 8, 3) were excluded due to low response rates. The COS for boys younger than 6 years and boys aged 10-11 years were identical (voiding, fistula, re-operation and urethral stricture) except for meatal stenosis (< 6 years) and curvature (6-10 years). The COS in boys aged 11-16 years were cosmesis, curvature, voiding, stricture and psychosocial status. For boys >16 years the COS included cosmesis, curvature, erection, voiding and psychosexual development. Assessment of the preferred method to measure voiding was uroflowmetry (n=39) and signs indicating infra-vesical obstruction (n=30) in non-toilet trained boys.

Discussion: Clear indicators for variables to include in a COS following hypospadias surgery were identified in younger boys. A larger spread in votes was observed in older boys likely reflecting that these boys are less often followed-up resulting in less clarity on relevant outcomes which emphasise the need to expand the work on long-term outcomes.

Conclusion: Collection and reporting of the COS across the age span will undoubtedly minimize the heterogeneity in reporting after hypospadias surgery and will inform best medical practice reporting.

P1-568

Impact of unilateral ovariectomy on ovarian function and pubertal development in girls with Turner syndrome

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Background: A reduced reproductive lifespan is one of the most significant implications for girls with Turner syndrome (TS) and is due to an accelerated loss of ovarian insufficiency. Lately, there has been a surge in scientific research aimed at whether ovarian tissue cryopreservation (OTC) is a viable option for fertility preservation in girls with TS. This required a unilateral ovariectomy for girls with TS who may already have a poor ovarian reserve.

Study question: What is the impact of unilateral ovariectomy on the ovarian function of the remaining ovary in girls with TS undergoing OTC?

Methods: A prospective descriptive study of 28 girls with TS (aged 5-19 years) who underwent OTC and had follicles in the ovarian tissue. Pubertal development and levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), Oestradiol, Anti-Mullerian hormone (AMH) and inhibin B were monitored up to three years after OTC.

Main results and role of chance: Of the 28 girls, 1 girl had 45,X-karyotype, 21 had mosaic-karyotype with 46,XX-cell line and 6 had other karyotypes (45,X/47,XXX or structural aberration of the X-chromosome). Puberty was induced in 1/28 girls and inhibited in 1/28 girls prior to OTC. Of the 13 prepubertal girls at OTC, 7/13 girls were still prepubertal at the end of the follow-up. Of the other 6 prepubertal girls, 4/6 had experienced spontaneous thelarche and 2/6 spontaneous menarche. In 6/6 girls with spontaneous thelarche before OTC, a spontaneous menarche occurred during the follow-up period. Of the 7 girls with menarche prior to OTC, 5/7 continued having regular menstrual bleeding. Of the 28 girls, 5 needed hormone suppletion (1 because of induction of puberty and 4 because of signs of ovarian insufficiency). Girls who experienced ovarian insufficiency had low or undetectable levels of AMH at OTC. In 9/28 girls, FSH rose >10 E/L within 2 years after OTC. However, in 19/28 girls, FSH levels remained below 10 E/L during the three-year follow-up. In 10 girls a biphasic pattern (decrease-increase) of AMH levels could be recognized.

Conclusion: OTC only had a mild influence on pubertal development. In almost 90% of girls the pubertal development continued after unilateral ovariectomy. Ovarian insufficiency occurred in girls who were at a priori increased risk of developing ovarian insufficiency based on their hormone levels.

P1-569

National service evaluation project analysing the quality of care for children and young people with congenital adrenal hyperplasia in the United Kingdom: Data from patients and clinicians

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Background: The variation in the provision of services in secondary and tertiary care for children and young people living with CAH in the United Kingdom is unknown. We aimed to conduct a nationwide service evaluation to inform from both the patient and clinician perspective.

Methods: We conducted an anonymous multicentre survey using online questionnaires for clinicians and CAH patients/carers. Clinical leads from UK centres managing children and young persons with CAH were contacted directly and asked to circulate questionnaires to their colleagues and patients. Patient/carer questionnaires were also circulated by the "Living with CAH" support group. Main themes investigated were frequency of assessment, investigations employed and provision of education for patients/carers.

Results: We received 56 patient responses (33 females) and 125 from carers (63 caring for a female patient). Of 33 clinicians from 18 centres who responded, 73% were consultant endocrinologists and 79% had over 5 years' experience managing CAH. CAH monitoring is largely consistent with international guidelines, with 64% regular use of dried blood spots, and 9% monitoring urinary steroid metabolites. Patients and carers were overall satisfied with the frequency of discussions regarding general wellbeing, and acute and chronic management of CAH, but 33.6%, 36.2%, 49.2% of carers would have preferred more discussion fertility, heart disease, and psychological effects respectively. Clinicians reported that psychological effects of CAH, levels of physical activity, infertility and reduced adult height, ranked highest among topics that are rarely discussed.

Most patients and carers reported high confidence in dealing with the chronic aspects of CAH (68.9% and 80.5% respectively), but fewer carers reported very high confidence in acute illness (50.5%) and emergency (33.9%). Only 12.3% of carers and 6.4% of patients report receiving formal training to manage CAH, whilst 95% of clinicians report provision of formal training to families. A high appetite for further education and self-management training was reported by both carers (86%) and patients (64%). The overall satisfaction with the medical service provided was ranked very good for 62% carers and 47% patients, although only 12% of clinicians were 'completely satisfied' with the service they provided.

Conclusions: Preliminary data shows patients and carers feel confident managing CAH and have good satisfaction with services. Addressing the psychological impact of CAH is perceived as an unmet need by both patients and clinicians. The discordance between what patients and clinicians consider as formal training to manage the disease is another area for improvement.

P1-570

Elucidating The Genetic Basis of Human Disorders of Sex Development Using Clinic-To-Bench Approach

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Background: Diseases of sex development (DSD) are rare heterogeneous disorders ranging from infertility (an estimated 15% of couples worldwide have difficulty conceiving), to severe cases including ambiguous genitalia, sex reversal, and gonadal dysgenesis. The genetic basis of DSD remains unknown in 50% of the severe cases. To identify novel genetic causes of DSD, we are investigating patients in which known causative genes have been excluded. Identifying new genes will help elucidate pathways involved in gonadal development and may allow new interventions for infertility.

Methods: Using a patient-based approach, WES was performed in families with patients diagnosed with DSD. In each family, candidate variants were identified, tested for segregation and evaluated using various molecular assays customized to the specific candidate gene.

Results: We identified three novel genes previously unknown to affect gonadal development in humans. Compound heterozygous frameshift mutations in FIGNL1 cause genomic instability and aberrant chromosomal structures in somatic cells in addition to lack of DNA damage response and cancer predisposition, eventually results in ovarian dysgenesis (OD). A homozygous MCM10 missense mutation demonstrated decreased replication fork rates, resulting in genomic instability and OD. A homozygous TALDO1 missense mutation in the enzymatic catalytic site resulted in reactive oxygen species accumulation and male gonadal dysgenesis.

Conclusions: Identification of the genetic basis for DSD enables relevant treatment and reproductive options. Our studies demonstrate that the clinic-to-bench approach is a powerful tool for identifying new genes and pathways involved in DSD. Moreover, DNA damage response elements are crucial for ovarian development with cancer predisposition implications. Understanding the full cascade and networks of gonadal development, will eventually lead to the development of new therapies for infertility.

P1-571

Early and long-term gender-affirming treatment does not alter final height in transgender youth

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Keywords: transgender, GnRH agonists, gender affirming hormones, final height, growth, puberty

Background: Trans boys (TB) and trans girls (TG) who start medical gender-affirming treatment at Tanner stage 2-3 undergo early puberty suppression (ePS) with Gonadotropin-Releasing Hormone agonists (GnRHa) for several years and subsequently receive gender-affirming hormones (GAH), around 15-16 years. This treatment clearly interferes with the timing of puberty and the hormonal milieu, alters physiological growth, and potentially impacts on final height (FH). Moreover, as height is a sexually dimorphic trait, FH is a concern for many transgender adolescents. This study aims to evaluate the effect of ePS with GnRHa and GAH on growth and FH in TB and TG.

Methods: Retrospective study, including 10 TB and 22 TG at FH. We determined bone age (BA) at start of ePS and at start of GAH (Greulich & Pyle), calculated predicted adult height (PAH) (Bayley & Pinneau's tables) and target height (TH) as adjusted mean of parental height. TH, PAH and BA were determined according to sex registered at birth (SRAB) and experienced gender (EG).

Results: After a total of 5.85 ± 0.51 years (TB) and 5.40 ± 1.37 (TG) of medical gender-affirming treatment, FH did not differ from $\mathrm{TH}_{\mathrm{SRAB}}$ in both TB and TG (as shown in bold in the table below). Age: years; height: cm

	TB	p-value	TG	p-value
Age at PS	12.37 ± 0.74		13.10 ± 1.12	
Age at GAH	15.97 ± 0.46		15.90 ± 0.33	
Age at FH	18.22 ± 0.57		18.50 ± 0.79	
BA$_{\mathrm{SRAB}}$ at PS	12.15 ± 0.41		12.64 ± 1.29	
BA$_{\mathrm{SRAB}}$ at GAH	13.56 ± 0.63		14.18 ± 0.49	
Duration of PS	3.61 ± 0.52		2.80 ± 1.22	
Duration of GAH	2.24 ± 0.19		2.60 ± 0.77	
Total height gain	14.62 ± 4.08 (70% before GAH)		20.68 ± 7.66 (61% before GAH)	
ΔFH - THSRAB	**1.57 ± 3.1**	**0.168**	**-0.98 ± 4.17**	**0.319**
ΔFH -TH$_{\mathrm{EG}}$	-11.43 ± 3.1	< 0.001	12.02 ± 4.17	< 0.001
FH - PAH$_{\mathrm{SRAB}}$ at PS	2.62 ± 3.79	0.056	-2.35 ± 5.2	0.051
FH - PAH$_{\mathrm{EG}}$ at PS	-4.52 ± 5.56	0.03	2.76 ± 6.92	0.082
Height Z-score$_{\mathrm{SRAB}}$ at PS	-0.32 ± 0.34		-0.46 ± 1.11	
Height Z-score$_{\mathrm{SRAB}}$ at GAH	-0.43 ± 0.56		-0.90 ± 1.02	
Height Z-score$_{\mathrm{SRAB}}$ at FH	0.22 ± 0.82		0.10 ± 1.38	
ΔHeight Z-score$_{\mathrm{SRAB}}$ (FH-PS)	0.54 ± 0.72	0.04	0.56 ± 1.21	0.04

Conclusions: Early start of medical gender-affirming treatment, although substantially altering the physiological process of growth, does not appear to impact FH.

P1-572

Prospective Surveillance Of Gonadectomy In DSD – An I-DSD Care Quality Improvement Project

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Introduction: Gonadectomy may be indicated in people with differences or disorders of sex development (DSD). Based on historical data from the International-DSD (I-DSD) Registry that showed considerable practice variation, this I-DSD care quality improvement project seeks to determine, through prospective surveillance, the frequency of gonadectomy in individuals with DSD internationally.

Methods: All existing I-DSD centres were invited to participate; the study commenced in December 2022. Participating centres are sent a monthly email asking if a gonadectomy has been performed in a suspected or confirmed case of DSD. Where informed consent for inclusion in the I-DSD Registry has been obtained in a reported case, a secondary survey is issued to capture additional information on clinical management and outcomes. The study remains open to new I-DSD centres.

Results: Of 208 centres invited, 76 (37%) centres from 33 countries spanning all continents have been reporting monthly. Of the centres, the median (range) number of cases in the registry was 132 (1, 328). During the first 4 months of surveillance, a total of 34 gonadectomies have been reported from 22 (29%) centres in 15 (45%) countries. Of centres reporting a case, a median of 1 (0, 5) gonadectomy has been reported per centre. So far, 13/34 (38%) reported cases have been registered on the Registry with secondary surveys complete from 6 of these. Reported underlying diagnoses were disorder of gonadal development (n=3, [50%]), disorder of androgen action (n=2, [33%]) and chromosomal DSD n=1 [17%]). Five (83%) children were assigned female; median (range) age was 5.5yrs (3, 16). Gonadal position was intra-abdominal in five (83%) children and labio-scrotal in one (17%) child. Indications for gonadectomy included: mitigation of tumour risk in gonads with documented absence of function / gonadal insufficiency (n=3 [50%], all bilateral), abnormal gonad at laparoscopy (n=1[17%], unilateral), current hormone production incongruent with gender identity (n=1[17%], bilateral) and at parental request (n=1[17%], bilateral). Two children had atypical neoplastic change evident at histopathology: gonadoblastoma (n=1[17%]) and both dysgerminoma and seminoma (n=1[17%]). All individuals had been seen by a multidisciplinary team at a specialist centre for at least 1 year prior to gonadectomy.

Conclusions: Approximately 9 gonadectomies are currently reported in total per month in DSD specialist centres that are associated with I-DSD. The I-DSD platform shows clear utility for performing prospective surveillance of rare procedures; such studies are essential for care quality improvement and to inform future studies.

P1-573

Testosterone therapy in Duchenne Muscular Dystrophy and longitudinal bone growth with metacarpophalangeal index

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Background: Testosterone therapy is recommended for management of puberty from the age of 12 years in boys with Duchenne Muscular Dystrophy (DMD) in accordance with the 2018 international standards of care. The majority of boys loose ambulation in mid to late adolescence. Height measurement is problematic in these adolescents s as lower limb contracture can be common and estimated height from segmental body part measurements generally over-estimate height.

Aims: To evaluate the efficacy of testosterone on bone growth in DMD by a retrospective evaluation using metacarpophalangeal index on hand radiographs.

Methods: The 19 tubular bones of the hand were measured by a single observer using the digital ruler on the radiology platform(PACS). Raw bone length measurements were converted to Z-scores based on published paediatric normative data. To produce a single summary descriptor for each patient, the mean of the z-scores for the 19 bones was calculated called the 'composite bone length z-score'. Descriptive data is expressed as median(interquartile range).

Results: Median age at baseline was 14.3 years(1.3). All boys were pre-pubertal (G1, testicular volume<4 ml) with median bone age delay of 2.9 years(4.9). All boys were on daily glucocorticoid with median Prednisolone equivalent dose of 0.4(0.2) mg/kg and this was 0.3(0.3) mg/kg at 12 months of testosterone. At baseline, 8/14(57%) were non-ambulant, and this was seen in 9/14(64%) at 12 months of testosterone. At 12 months, 13 boys were in early puberty (G2-G3) and one boy was in late puberty (G4). At baseline, median bone length Z-scores(metacarpal 1-5; proximal phalanx 1-5; mid-phalanx 2-5; distal phalanx 1-5) were all significantly lower than zero[p<0.05]. Following 12 months of testosterone, all bone length Z scores other than distal phalanx 5 were significantly lower than baseline. At baseline, median composite bone length Z score for chronological age was -2.6(1.9) and this was -3.5(2.3) at 12 months[p< 0.05]. Median rate of composite bone growth was 0.2 mm/year prior to testosterone and this was increased to 0.6 mm/year which equates to a median increase of 238%(282).

Conclusion: Using the metacarpophalangeal index, rate of bone growth increased by over 200% after a year of testosterone therapy in boys with DMD. However, this improvement in growth rate is not sufficient to lead to complete catch-up growth which could reflect the state of growth hormone resistance with long term glucocorticoid therapy.

P1-574

Gonadal histopathology in 17beta-HSD deficiency and 5alpha-reductase deficiency

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Introduction: In various forms of XY disorders/differences of sex development (DSD) the risk of germ cell cancer is increased. In the 2006 DSD consensus statement this risk was estimated to be intermediate in 17beta-HSDtype3 deficiency (HSD17B3D) and low in 5alpha-reductasetype2 deficiency (SRD5A2D) but based on very few cases. Few studies have been performed since; therefore we aimed to review gonadal pathology in an international cohort with these conditions.

Methods: Individuals with HSD17B3D and SRD5A2D aged >16 years in the I-DSD Registry were eligible. When a gonadectomy or gonadal biopsy had been performed, blocks, slides or images of gonadal tissue were requested for uniform analysis. Hematoxylin, eosin, immunohistochemical stainings for SOX9, OCT4, TSPY and SCF (KITL), and double stainings for OCT4 and TSPY were performed.

Results: 118 individuals were eligible. Ten centres from nine countries supplied data of 18 individuals with HSD17B3D (15 females), of whom 13 had gonadectomy, and 18 with SRD5A2D (eight females), of whom six had gonadectomy. Tissue samples from nine individuals with 17betaHSDD were available from gonadectomies at median age 4 years (range 0-16). One, 13 year-old had no germ cells; all others showed severe germ cell loss. The precursor lesion germ cell neoplasia in situ (GCNIS) or malignant germ cell tumours were not observed. Most individuals were

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prepubertal; in one, 16 year-old, spermatogenesis was arrested at the stage of spermatogonia. Remarkable Leydig cell hyperplasia was seen in the individuals aged 13 and 16 years. Dissociation of the poorly developed rete testis and epididymis was frequently observed.

Gonadal tissue was available from one individual with SRD5A2D and photographs of gonadal histopathology from another, collected at age 0 and 11 years. The youngest had normal numbers of germ cells but many germ cells showed regressive features such as polynuclear cells. GCNIS or malignant germ cell tumours were not observed.

In two of eleven males who had testes in situ, monitoring of the testes took place, in one through self-examination, in the other through ultrasound.

Discussion: Despite international collaboration it proved difficult to obtain gonadal tissue for central review due to practical, ethical and legal issues. The absence of (pre)malignant germ cells in nine individuals with HSD17B3D suggests a low risk of germ cell cancer, at least until adolescence. Insufficient data were available to assess the risk in SRD5A2D. Self-examination is advised for all individuals with a history of undescended testes; implementation of this recommendation deserves attention.

P1-575

Gender-Dysphoric Austrian Youth Seeking Gender Affirming Hormonal Therapy: Baseline Somatic and Psychosocial Health, Gender Affirming Treatment Trajectories and Fertility Preservation Rates

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Objectives: The aim of this study is to describe the clinical characteristics of Austrian children and adolescents with gender dysphoria seeking gender affirming medical care, as well as their treatment trajectories.

Methods: In this retrospective study at a large university hospital, a chart review of all patients presenting with gender dysphoria at the pediatric outpatient clinic for differences in sex development between 01.01.2008 and 31.12.2022 was conducted.

Results: Of 309 patients, 229 (74,1%) were transmasculine/assigned female at birth (AFAB), and [RS1] 80 (25,9%) were transfeminine/assigned male at birth (AMAB). The number of referrals increased steeply from 2008 to 2018 whereafter it stabilised at around 50 per year. At the time of initial presentation, the median age of patients was 15,8 years (range 7,1 to 18). AMAB individuals tended to be younger, at a median age of 15 years than AFAB individuals, at a median age of 15,9 years. 35,25% had a BMI > 1 SDS above World Health Organization (WHO) norms, while 11,2% were underweight with a BMI < -1 SDS below the norm. 49,8% reported suffering from depressive symptoms and 28,2% were prescribed antidepressants. Gonadotropin-releasing hormone analogs (GnRHa) were prescribed to 166 (53,7%) individuals at a median age of 16,3 years (range 9,7 to 18,2). Gender affirming (sex steroid) hormone therapy (GAH) was established in 163 (53%) of individuals at a median age of 16,78 years (range 13,2 to 18,4). Chest masculinization surgery was performed in 22 cases, and breast augmentation in two cases between the ages of 16 and 18. Of the 42 AMAB individuals receiving GAH, 5 (11,9%) completed fertility preservation prior to GAH start. Only 1 of the 121 transmasculine adolescents receiving GAH completed fertility preservation.

Conclusion: Our adolescent patient collective showed an overall AFAB/AMAB ratio of 3:1, with a trend towards a lower percentage of AMAB individuals in the past six years. Our findings regarding prevalence of psychiatric co-conditions are consistent with literature published so far. 53% of individuals with gender dysphoria received gender affirming hormone therapy. Regarding fertility preservation, we found very low utilisation of treatment options.

P1-576

Transition from Paediatric to Adult Care in Differences of Sex Development (DSD) – Results from the German Network “DSDCare”

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Introduction: The aim of the project “DSDCare” is to implement standardized care for people with DSD following national and international guidelines and to evaluate structural, process and outcome quality of care at 10 specialized centres in Germany from May 2020 till June 2023. Transition from paediatric to adult care is a crucial phase in chronic and rare conditions. In DSD, “loss to follow-up” is usually not associated with acute complications. However, monitoring of gonadal function, potential hormone therapy or post-operative treatment and psychosocial, sexuality and fertility counselling are important for physical and mental well-being over the lifespan.

Methods: Within the project, structural quality is evaluated by an annual query of data from the participating centres. Process and outcome quality are evaluated by a national registry (“DSDReg”) and patient surveys. Indicators of structural quality of care include implementation of a structured transition program and/or designated consultation hours at the centres. All participants aged 13-21 are asked to complete a survey evaluating health-related transition competence, comprising the three dimensions “work-related preparedness” (3 items), “condition-related knowledge” (3 items) and “health-care competence” (4 items).

Results: From May 2021 till March 2023 164 adolescents and young adults returned the questionnaire, of which 61 had chromosomal DSD, 51 46,XY-DSD, 50 46,XX-DSD and 2 were not classified. 47 patients were 13-15 years, 42 16-17 years and 75 18-21 years old. 20 incomplete questionnaires were excluded from the analysis.

There were no relevant differences of global scores between DSD classifications. The global score was low in the youngest participants and increased moderately with age. Across all age groups scores were highest in the dimension "condition-related knowledge" and lowest in "health-care competence".

At the beginning of the project, no centre had a structured transition program, one offered regular consultation hours for transition. Within the project, a structured transition concept was developed following national guidelines including material as detailed transition readiness assessment questionnaires for patients and care-takers and a structured discharge summary. By the end of 2022, 4 centres had implemented the concept and 2 more had established designated consultation hours, with further centres working on it.

Conclusion: Transition of adolescents and young adults with DSD from paediatric to adult care is still crucial in order to ensure provision of continuous specialized care. To improve outcomes, a structured program has been developed in the project DSDCare and will be implemented and evaluated along with educational programs and interdisciplinary care.

P1-577

High carrier frequency of a splicing c.589G>A variant in the SRD5A2 gene among Buryats

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Background: 5-α-reductase type 2 enzyme catalyzes the conversion of testosterone into dihydrotestosterone, a potent androgen responsible for male sexual development during the fetal period. From 2017 to 2019, a homozygous hg38_chr2:31529414 C>T variant in *SRD5A2* gene have been identified in 3 unrelated patients with DSD 46,XY of Buryat origin. The variant has been previously reported in one patient from China (Song et al, 2019) and listed as a missense substitution (NM_000348.4:c.589G>A p.E197K) in HGMD database (CM1922241). According to ACMG criteria the variant is rated as a variant of uncertain significance (PM2;PP3;PP4).

Aims: To characterize the variant c.589G>A. To study carrier frequency of the variant c.589G>A among Buryats.

Methods: A potential effect of c.589G>A substitution on splicing was evaluated *in silico* using SpliceAI tool (https://spliceai-lookup.broadinstitute.org). For a minigene assay a genomic region containing exon 4 with the flanking intronic sequences of *SRD5A2* from one of the patients' parent was cloned into pSpl3-Flu2-TK vector. The obtained plasmids with wild-type sequence (SRD5A2_E197) and the variant (SRD5A2_K197) were then transfected into HEK293T cells. 48h after transfection, total RNA was isolated and RT-PCR analysis was performed. Genotyping of the nucleotide variant c.589G>A was performed by Real-time PCR. 300 healthy individuals of Buryats origin were included in the study. Allele frequencies, Fisher's confidence intervals were calculated using the WinPepi v.11.65 software.

Results: In silico SpliceAI analysis revealed that the variant can influence splicing by activating a cryptic donor site in the exon. The minigene assay confirmed that the c.589G>A variant leads to activation of a cryptic donor splicing site, resulting in a shortening of exon 4 by 112 nucleotides. This alteration in mRNA structure disrupts the open reading frame and produces a truncated SRD5A2 protein lacking two transmembrane domains. Among 300 studied samples the nucleotide variant c.589G>A in *SRD5A2* was detected in 6 cases in a heterozygous state. The allele frequency of the studied variant was 0,01 (95%CI=0.0028-0.018). The frequency of heterozygous carriers was 0.02 (95%CI=0.0056-0.036). The frequency of DSD 46,XY due to the variant c.589G>A among Buryats was 1:20000 or 5 per 100,000 (95%CI=1:2482–1:176582 or 0.6-40 per 100,000). The frequency of heterozygous carriers of c.589G>A variant was 1:51 subjects (95%CI=1:28–1:179).

Conclusions: The results reclassify the NM_000348.4:c.589G>A substitution as a pathogenic variant (PM2, PVS1, PP4) affecting splicing. The study demonstrates high carrier frequency of the NM_000348.4:c.589G>A variant among Buryats, which is most likely attributed to a founder effect.

P1-578

Klinefelter Syndrome and Fertility - Current practice in a tertiary Children's Hospital

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Background: Klinefelter Syndrome (KS) is the most common chromosomal anomaly in males associated with infertility. Advances in assisted reproductive medicine have made conception possible for some men with KS, with increasing scientific interest gathered around semen cryopreservation and testicular biopsy for sperm extraction (TESE).

Objectives: This project aims to examine the current practice in a paediatric tertiary hospital around fertility of children and young people with KS, against the recommendations of European Academy of Andrology for KS. We also examined the hormonal profile of adolescents who had semen analysis.

Methods: All the patients with KS under the care of the Andrology team were identified and their hospital electronic records were used to extract data retrospectively.

Results: We identified 32 patients with KS. The mean age for referral to Andrology services was 13.6 years. Testosterone was offered to 15/32 (47%) patients and the most common indication was induction of puberty. The mean age for starting testosterone

Table 1. Hormonal profile of patients with azoospermia on semen analysis

	AMH	Inhibin B	FSH	LH	Testosterone
Low	33.3%	50%	33.3%	0%	16.6%
Normal	33.3%	16.6%	33.3%	50%	83.3%
High	33.3%	16.6%	33.3%	50%	0%
Not done	-	16.6%	-	-	-

was 14.85 years. Discussion about fertility was undertaken in 26/32 (76.5%) cases.

Semen analysis was offered in 9 patients who were progressing with puberty spontaneously and were not on testosterone therapy (28%) but only 7 accepted the procedure. Only 1/7 (14.3%) patient had viable sperm which was cryopreserved. His hormonal profile showed normal AMH, Inhibin B and LH, while FSH and testosterone levels were low. Azoospermia was present in 6/7 (85.7%) cases, out of which 2 (33.3%) patients accepted microTESE (mTESE), 2 (33.3%) are considering mTESE and 2 declined mTESE (33.3%). Their hormonal profiles were variable (Table 1).

Conclusions: KS management varies significantly. The yield from semen analysis is low and further interventions including mTESE could be offered. However, fertility discussions could be quite sensitive, and patients and families may not be ready for fertility discussions and interventions. Hence, support from MDT including endocrinologist, fertility specialist and psychologist is essential. Hormonal profile has the potential to support the fertility discussions in KS.

P1-579

Comparison between clinical, metabolic and hormonal parameters in adolescent girls with hyperandrogenism and healthy controls

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Background: Polycystic ovary syndrome (PCOS) and non-classical congenital adrenal hyperplasia (NCCAH) are the most common hyperandrogenic disorders in adolescent girls. Though their etiology and pathogenesis differ, there is a significant overlap between physiological, clinical and hormonal findings and physiological phenomena. Adult patients with PCOS have increased prevalence of obesity, metabolic disturbances, increased cardiovascular risk, risk of impaired fertility, obstetric and gynecological complications some of which are potentially preventable with timely diagnosis, life-style and pharmacological interventions.

Objectives: To compare clinical, metabolic and hormonal parameters between adolescent girls with hyperandrogenism and healthy controls.

Materials and Methods: After ethical approval, 50 adolescent girls consented to participate in the study. The mean age was 16.1 (±2.4) years. Patients were divided into 3 groups. Group 1 included 20 NCCAH patients diagnosed with standard ACTH test, group 2 - 20 PCOS patients, fulfilling the ICPE 2017 diagnostic criteria for adolescent PCOS, group 3 - 10 age and BMI-matched controls without menstrual irregularities and hyperandrogenism. Same auxological, physical, metabolic and hormonal parameters were obtained in all groups. Pelvic US was performed by one experienced echographist. SPSS was used for the statistical analysis.

Results: Weight, BMI and waist circumference were significantly higher in PCOS, compared to NCCAH group ($p=0.008$, 0.04 and 0.014). Ferriman-Gallwey score was significantly higher in hyperandrogenic groups, compared to controls ($p<0.001$), without a significant difference between PCOS and NCCAH. The incidence of menstrual irregularities was significantly higher in PCOS group, compared to the other two groups ($p<0.001$). Insulin levels and HOMA-IR were significantly higher in PCOS group, compared to NCCAH group ($p=0.04$ and 0.023). LH was significantly higher in PCOS group, compared to NCCAH group ($p=0.047$); testosterone and androstendione were significantly higher in the hyperandrogenic groups, compared to controls ($p=0.007$, 0.007, 0.002 and <0.001), without a significant difference between PCOS and NCCAH. AMH was highest in the PCOS group but without statistical significance; SHBG was significantly lower in PCOS group, compared to the other two groups ($p=0.014$ and <0.001) and in the NCCAH group, compared to controls ($p=0.003$). Free Androgen Index was significantly higher in PCOS group, compared to the other two groups ($p=0.026$ and 0.005). No significant differences in the presence of US polycystic ovarian morphology were found between the groups.

Conclusions: There is a significant prevalence of obesity, metabolic disturbances, menstrual irregularities and hyperandrogenism in the PCOS girls. SHBG seems to be a useful biomarker for the diagnosis and differential diagnosis of hyperandrogenic disorders.

P1-580

Characteristics and Hormonal Use Patterns among Transgender Female Youth in Thailand: Findings from a Community-Based Survey

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Background: Transgender youth in Thailand often encounter limitations when accessing gender services, leading many to use non-prescribed hormones. However, there is limited information available on the specific types of hormones used by this population.

Objectives: This study aimed to investigate the characteristics of transgender female youth in Thailand and the types of hormones they use.

Methods: From September 2021 to October 2022, a self-administered questionnaire was distributed via social media platforms including Facebook, LINE open chat, and Twitter.

Results: In this cross-sectional study, a total of 254 transgender female youth participated, of which 89% (n=226) reported previous hormone use. The mean age at first hormone use was 15.5 years (SD 2.5). Most of the hormone users (94.6%) reported disclosing their gender identity, while 60% of non-users had not disclosed to anyone. Among the hormone users, 35.8% reported using a single hormone, 37.5% reported using two hormones, and 26.7% reported using more than two hormones. The most commonly reported hormone used was oral cyproterone acetate (52.3%), followed by oral estradiol valerate (46.2%) and oral estradiol (38.3%). Additionally, 23.7% reported previous use of oral contraceptive pills, 7.5% used oral phytoestrogen, 3.8% used estrogen gel, and 2.2% used estrogen/estradiol injection or Hydroxyprogesterone caproate injection. The mean happiness score was similar between the ever-using hormone(s) group (7.0±1.9) and the never-using hormone(s) group (7.3±1.9).

Conclusion: This study demonstrated that Thai transgender female youth begin hormone use at an early age of approximately 15 years old and often use multiple types of hormones, with a significant proportion reporting previous use of contraceptive pills. These findings underscore the importance of promoting medical accessibility and providing appropriate hormone use supervision to ensure the safety and well-being of this population. Further research is needed to better understand the long-term effects of hormone use among transgender youth in Thailand.

P1-581

A dual centre evaluation of discontinuation of testosterone therapy in boys with Duchenne Muscular Dystrophy

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Background: The 2018 international standards of care for DMD recommend initiating testosterone for management of delayed puberty commencing at a low dose, gradually increasing to adult replacement. No recommendations exist regarding longer term use of testosterone during transition and adulthood.

Aim(s): To report long-term use of testosterone in DMD with outcomes of gonadal function and pubertal development in those who discontinued testosterone therapy.

Methods: 35 boys with DMD were treated with testosterone between two centres. 24 boys included in this report were treated with testosterone for >1 year, with information following discontinuation of testosterone. Results are reported as median(range).

Results: Centre A initiated testosterone with oral testosterone undecanoate or transdermal testosterone gel and transitioned to long-acting injectable testosterone undecanoate at Tanner stage IV virilization, regardless of testis volume. Testosterone was discontinued after at least 16 years of age. Median age at discontinuation of 18.0 years(16.1, 21.8). Centre B initiated testosterone with short-acting injectable testosterone proprionate or transdermal testosterone. Testosterone was ceased with increasing testicular size(at least 6 ml) or if LH levels were detectable and rising even with testes <6 ml. Median age at discontinuation of 17.2 years(14.3, 18.0) Combining both centres data, median age of initiating testosterone was 14.3 years(12.8, 17.8). Median age at discontinuation was 17.6 years(14.3, 21.8). Median age of first assessment following discontinuation of testosterone was 18.3(15,22.4). Median testosterone(samples before 11 am) was 9.9 nmol/L(<0.5, 25.7). 7/24(29%) had testosterone levels <6.9 nmol/L,with median testosterone of 3.3 nmol/L(<0.5, 6.5). In a sub-set of 11 boys, testicular volume was assessed at discontinuation of testosterone and following discontinuation of testosterone. 8/11 had increase in testicular volume with median testicular volume of 10 ml(6,20). Two boys(18%) had no testicular growth: A 17.9 year old with testicular volume 1 ml, adult virilization(G5P5) and early morning testosterone of 4.5 nmol/L; and a 17.1 year old with bilateral inguinal testes, adult viriization(G5P5),no growth on testicular ultrasound and early morning testosterone of 1.4 nmol/L.

Conclusion: We provide early data regarding withdrawal of testosterone treatment for pubertal delay in boys with DMD. Almost 30% of adolescents and men with DMD had testosterone levels <6.9 nmol/L, indicating a need for long term hormone replacement therapy. Clinical pathways in this area are needed and requires attention during the transition period.

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P1-582

Coexisting Disorder of Sex Development and Gender Dysphoria: A case report about an individual with Turner syndrome receiving first female and subsequent male hormone replacement therapy

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Introduction: Disorders of sex development (DSD) refer to a group of conditions, including Turner syndrome in which an individual's physical sex characteristics do not conform to typical male or female patterns, including a range of differences in chromosomes, hormones and anatomy. Gender-specific problems are usually not prominent, compared to other forms of DSD.

Gender dysphoria (GD) is a discomfort between a person's assigned sex based on physical characteristics and their gender identity.

Case Report: Cases of coexisting DSD and GD are rare. Here, we describe genotype, phenotype and hormonal characteristics of an individual with Turner syndrome mosaicism (45, X0 / 47, XXX karyotype), who received female puberty induction and subsequent male hormone replacement with testosterone due to GD.

As is common in people with Turner mosaicism, spontaneous female puberty started and menarche occurred at the age of 12 8/12 years. Subsequently, hypergonadotropic hypogonadism evolved. Hence, hormone replacement therapy with estradiolvalerat and progesterone was started at the age of 13 7/12 years according to standards of care, resulting in Tanner stage PH5, B4.

At the age of 15 7/12 years, the person described a strong sense of not belonging to the assigned gender and identified as other than female, as non-binary, at the age of 16 5/12 years. Transgender feelings and coming out followed at age 17. GD was diagnosed by an adolescent psychiatrist based on criteria according to current guidelines. Gender change took place at age of 17 7/12 years, starting with testosterone substitution (1000 mg i.m. /3 months), and scheduled mastectomy two years later.

Conclusion: In rare cases, individuals with Turner syndrome may identify as other than female. Although DSD and GD have different causes, both conditions can cause significant distress with gender identity and require specialized care. This includes promoting an open-minded and respectful environment to support these individuals on their journey towards self-discovery and gender identity.

Thyroid

P1-186

Comparison of clinical features, therapy, and disease evolution in a population of children and adolescents with Graves' disease and Type 1 Diabetes compared to Graves' disease alone

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Introduction: About 25% of children and adolescents with Type 1 Diabetes (T1D) have one or more associated autoimmune conditions. Although Graves' disease (GD) rarely occurs, considering the potential severity of manifestations, an early diagnosis and appropriate treatment are essential. The first line treatment is methimazole, whose use is not free from side effects; therefore, it is important to start with the most appropriate dosage.

Patients and Methods: We report preliminary data from a multicenter, retrospective, observational study of patients aged 0-18 years with a diagnosis of T1D and GD (group A, 19 patients) compared to patients with GD alone (group B, 27 patients). The aim is to evaluate differences in methimazole dose, at diagnosis and after 30 days (T1), necessary to restore normal thyroid function and to assess clinical features and developmental course of the disease.

Results: Overall, mean age at presentation of GD was 10,9±3,7 years, with a prevalence of female in group B (81% versus 63%). In 5 cases, GD was diagnosed at the onset of T1D or in the first months. Symptoms of hyperthyroidism occurred 63% in group A and 81% in B. Tachycardia/palpitations were the most common symptoms (26% in group A and 59% in B, $p<0,03$), followed by weight loss (26% in both groups), fatigue, diarrhea/gastrointestinal symptoms and mood disorders. Goiter occurred in 5% of group A and 15% of group B. TSH at diagnosis was 0,03±0,06 mU/L in A and 0,02±0,01 mU/L in B, fT3 was higher in B (16,1±7,3 pg/ml versus 10,5±7,6 pg/ml, p<0,05), fT4 (38,8±20,6 versus 30,1±14,9, NS). Methimazole attack dose was lower in group A (0,31±0,15) versus B (0,43±0,17) (p=0,02). At first control (30 days±16), TSH was still suppressed in B (0,01±0,01), while it was improved in group A (1,98±4,53). Moreover, the methimazole dose at T1 was lower in group A (0,24±0,13) versus B (0,24±0,13) (p<0,05). Notably, recurrence rates were higher in A (37% versus 26%), with increased recourse to thyroidectomy (16% versus 7%).

Conclusions: in subjects with T1D and GD, a lower dose of methimazole at attack and at T1 was needed to normalize TSH value. Cardiological symptoms and fT3 values at diagnosis were higher in group A. A higher recurrence rate, with a greater need for surgery, was found in group B.

P1-187

Thyroid nodules and differentiated thyroid carcinoma in children and adolescents. Experience of a tertiary pediatric endocrinology center in Greece

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Objectives: The aim of this study was to report on the frequency and describe the clinical characteristics of the ones diagnosed as thyroid cancer among all suspicious nodules diagnosed in the pediatric endocrinology department and to compare the findings with recent published literature.

Methods: Retrospective study during the last 5 years. Patients aged <18 years, with suspected thyroid nodule malignancy, according to sonographic features (nodule size ≥1 cm, hypo-echogenicity, calcifications, taller-than-wide shape, irregular margin and increased vascularization or a combination of the above), who underwent fine needle aspiration biopsy (FNA) under ultrasound (U/S) guidance and/or thyroidectomy, were included.

Results: A total of 37 patients (56.7% girls) with mean age 12.9±3.88 years, were studied. Thirty-six of them underwent FNA, while one patient was diagnosed intraoperatively, during thyroglossal duct cyst excision. Hashimoto's thyroiditis coexisted in 37.8% of all patients, 24.3% reported family history of thyroid nodule or malignancy, while 24.3% of patients had previous malignancy. Among patients with a malignant nodule, 19.1% had medical history of previous malignancy. Microcalcifications were detected in 34.4% of the nodules, 16.2% had irregular margin, while suspicious pathological lymph nodes were found in 13.5%. The FNA results according to the Bethesda System were II in 38.9 %, III in 8.3%, IV in 2.8%, V in 8.3% and VI in 41.7% of the patients. Fifty nine point five per cent (59.5%) of all patients underwent total thyroidectomy. Histopathology revealed malignancy in 91.3%, and in 100 % of those with malignancy in FNA. In 87% the histological type was papillary and in 4.3% follicular carcinoma. Regarding the extent of the disease, 23.8% of children had capsular infiltration, 33.3% had lymph node metastases, and 4.8% had lung metastases. One patient had postoperative permanent and 34.8% of patients had transient hypocalcemia. Radioactive iodine was administered in 66.7% of patients with malignancy, while two children required a second administration. Comparing children with and without malignancy, Hashimoto's thyroiditis coexisted in a significantly higher proportion among those with malignancy (p=0.006), while the presence of microcalcifications was significantly more frequent in malignant nodules (p=0.024).

Conclusions: Our findings are consistent with those reported in the literature. Girls predominated among children with suspicious nodules. Possible predisposing factors are medical history of previous malignancy and Hashimoto's thyroiditis. The most common histological type of thyroid malignancy was papillary carcinoma. The reliability of our medical team was high in the diagnosis of pediatric thyroid cancer by ultrasonography and FNA.

P1-188

DICER1 Syndrome and pediatric thyroid carcinoma

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DICER1, a gene located on chromosome 14q32.13, encodes a protein ribonuclease (RNase) IIIb that plays a central regulatory role in miRNA processing. DICER1 syndrome has an autosomal dominant inheritance and predisposes affected individuals to a wide variety of tumors, both benign and malignant.

We describe the case of a 6-year-old girl, carrier of a DICER1 germline mutation, and affected by a differentiated thyroid carcinoma. At the age of 6 a first thyroid ultrasound revealed the presence of a solid isoechoic nodule of 21 x 29 x 38 mm with intranodular vascular signals in the left thyroid lobe. At blood tests: TSH 4.13 (0.27-4.2) mU/L, FT4 1.11 (0.93-1.7) ng/dL; negative thyroid autoimmunity, calcitonin 5.3 (vn <6.9) ng/L. Thyroid cytology by needle aspiration was compatible with follicular neoformation, TIR3b sec. Italian Consensus-IS. Genetic analysis by next generation sequencing (NGS) was negative for KRAS and BRAF. The patient underwent at the age of 6 a left lobe-isthmectomy; the histological examination showed a follicular carcinoma, described as encapsulated with focal infiltration of the capsule and angioinvasive; TNM stage pT2, pNX. In consideration of the age and the histological result, genetic investigation was performed by NGS which highlighted a heterozygous germline variant in the DICER1 gene determining the formation of a putative truncated protein p.(Gln249*), classified as pathogenic. After 8 months the patient underwent completion of the thyroidectomy due to the appearance of a solid nodule in the right thyroid lobe; histological examination showed the presence of a papillary microcarcinoma. The patient's father and younger sister were found to be carriers of the same mutation in the DICER1 gene; a first thyroid ultrasound performed in the younger sister showed the presence of a solid nodule. The patient's older sister at the age of 9 underwent surgery to remove the left ovary for a Sertoli cell tumor; a first thyroid US, perfomed at the age of twenty, showed a multinodular goiter; her genetic analysis for DICER1 is currently pending.

DICER1-related pediatric thyroid involvement consists of benign nodular follicular disease, follicular adenoma, differentiated thyroid carcinoma, as well as poorly differentiated thyroid carcinoma. Recently, many progresses have been made in understanding the features of patient affected by DICER1 syndrome, especially the possibile associated tumors and relative age of onset, although the natural history, the growth rate and the prevalence of DICER1-associated tumors remain to be investigated as well as specific sureveillance protocols are needed.

P1-189

Anemia-based Screening for Resistance to Thyroid Hormone Alpha in Children

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Background: Resistance to thyroid hormone alpha (RTH-α) is characterized by varying degrees of symptoms and findings related to hypothyroidism. However, diagnosis is difficult since thyroid-stimulating hormone (TSH) levels are normal. Free triiodothyronine (fT3) and free thyroxine (fT4) levels can also be normal, but normo- or macrocytic anemia is generally present in the reported cases. L-thyroxine can alleviate some symptoms; however, there is limited data regarding screening methods.

Objective: To assess the efficiency of a screening strategy for RTH-α.

Methods: Among the 6540 children who were assessed in the pediatric neurology outpatient clinics during two years and underwent complete blood count and thyroid function test, 432 had anemia. We detected children (n=41) without a neurologic diagnosis who had normo- or macrocytic anemia along with normal TSH, free triiodothyronine (T3) levels in the upper half of the normal range or high, and free thyroxine (T4) levels low or in the lower half of the normal range. One known patient with RTH-α was excluded. Among remaining subjects, clinical evaluation, biochemical assessment, and THRA sequencing analysis were performed on 32 children.

Results: The median age of the patients was 5.7 (5.1–7.4) years, and 22 of them were males (69%). The main reasons for admission were autism spectrum disorder (n=12,38%), epilepsy (n=11,34%), and delay in developmental stages (n=8,25%). Constipation was present in five of the cases (16%), while closure of the anterior fontanelle and tooth eruption were delayed in two (6%) and one case (3%), respectively. The median length/height and weight SD scores were 0.3 [(-0.8)-(1.1)] and -0.1 [(-0.8)-(0.3)], respectively. The median fT3, fT4, and TSH levels were 4.6 (4.2–5.0) pg/mL, 0.9 (0.8–1.0) ng/dL, and 2.2 (1.8–3.1) uIU/mL, respectively. Thirteen of the patients (41%) had high fT3 levels, while none of them had low fT4 levels. The rate of normo- or macrocytic anemia was 47% (normocytic/macrocytic, n=8/7) at the time of reassessment. Creatine kinase was elevated in five of the patients (16%, one of them had anemia). None of the patients had a pathological variant in THRA.

Conclusions: This strategy found one known patient with RTH-α but did not reveal a new patient. Normo- or macrocytic anemia did not persist in nearly half of the patients, and this indicates that presence of other suggestive clinical or biochemical features would be needed before genetic analysis of THRA among patients with neurological problems.

P1-190

Pubertal timing and characterization in children with congenital hypothyroidism: How important is preschool age anthropometry?

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Introduction: The main purpose of the study was to determine whether anthropometric measurements at preschool (PS)-age, in which physiological adiposity rebound is detected, and LT4 dose have an effect on the age of onset of puberty in children with hypothyroidism.

Methods: This is an observational and retrospective study.

Results: Puberty had begun in 44 girls and 25 boys out of 115 children included in the study. Mean follow-up period of the patients was 112.2± 29 months. Two girls and one boy had central precocious puberty. Puberty began at a mean age of 9.77±1.2 years for girls and 11.31±0.6 years for boys. Girls had menarche at a mean age of 12.06±1.0 years. PS-age was mean 6.22 ± 0.2 years (6-6.8 years). At the PS-age, height, height-SD and LT4 doses was statistically different in patients with thyroid agenesis and thyroid hypoplasia. Height-SD at PS-age was positively correlated with the height-SD at the puberty onset in girls and in boys and height-SD at menarche. BMI-SD at PS-age was positively correlated with BMI-SD at the puberty onset in girls and in boys and BMI-SD at menarche. At PS-age LT4 dose was negatively correlated with height-SD and BMI-SD at PS-age, but negatively correlated with puberty onset BMI-SD in girls, and puberty onset height-SD in boys.

Conclusion: In this study, it was found that PS-aged patients with thyroid agenesis were shorter than those with thyroid hypoplasia. It was determined that those who received high-dose LT4 at PS age were short and lean. It was showed that PS-aged height and BMI could be a determinant in predicting height and BMI at the onset of puberty. While the age of onset of puberty in our female patients with CH was similar to their healthy peers and patients with hypothyroidism in recent studies, the age of onset of puberty for boys was younger than both their healthy peers and children with hypothyroidism of previous studies.

P1-191

Paediatric Graves' Disease: Presentation, Treatment and Follow up. A Single Centre Experience from United Kingdom

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Objective: To describe a cohort with paediatric Graves disease followed between 2012 and 2022 at King's College Hospital, London.

Materials and Methods: Retrospective study of 36 patients treated with block and replace regimen of anti-thyroid drugs with a median (range) follow up of 4.25 (1.1-10.8) years. Demographic, clinical, biochemical and treatment data were collected from clinical records. Predictive factors for outcome (age, sex, free thyroxine and tri-iodothyronine concentrations at presentation, duration of treatment and TRabs concentrations at end of treatment) were analysed with Mann Whitney test for continuous variables and Fisher's exact test for categorical variables.

Results: Median (range) age at diagnosis was 13.1 (5-17.1) years. Seven patients were <10 years of age. Majority were females (29; 81%). Free thyroxine and free tri-iodothyronine concentrations ranged between 21.5 and >100pmol/L (median-75 pmol/L) and 7.2 and >50 pmol/L (median-30pmol/L) respectively. Thyroid stimulating hormone (TSH) was undetectable (<0.05 mIU/L) in all patients. When measured at diagnosis, TSH receptor antibodies (TRAbs) were elevated in 96% patients. 79% of patients with elevated TRAbs also had elevated anti-TPO antibodies. There was a positive correlation between TRAbs concentration and free thyroxine concentration (r=0.76; P <0.0001) as well as between TRAbs concentration and free tri-iodothyronine concentrations (r=0.53; P = 0.0079). Median (range) carbimazole starting dose was 0.66mg/kg (0.19 – 1.38). Three patients moved out of area and one patient opted for thyroidectomy during primary course of anti-thyroid treatment. Weight z-scores at 6 months and 12 months were significantly higher than at diagnosis (1.4±1.1 vs 0.99±1.1; P=0.0005, 1.3±1.1 vs 0.99±1.1; P=0.0354). In the twenty-three patients who have completed primary course of treatment with anti-thyroid drugs, the median duration of treatment was 30.5 [19-52] months. Of these, seven patients remain in remission and sixteen patients relapsed after a median (range) period of 6.5 months (0-46 months). Patients who relapsed were significantly younger than those who did not (Median ± Interquartile range 12.1±5.3 vs 15.2±4 years P = 0.0143). Sex, free thyroxine and tri-iodothyronine concentrations at presentation, duration of treatment and TRabs concentrations at end of treatment were not predictors for remission in our cohort (P > 0.05).

Conclusions: Remission rate was 30% in our cohort after a median 2.5 years of anti-thyroid treatment, with age at presentation as the only predictive factor for remission. Excessive weight gain within 12 months of treatment is commonly seen in children treated for Graves' disease.

P1-192

Remission in pediatric hyperthyroidism treated with methimazole

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Introduction: Hyperthyroidism (HT) is a condition characterized by inappropriately high thyroid hormone (TH) activity at receptor level, due to high synthesis and secretion of TH by thyroid gland. Antithyroid drugs as methimazole (MMI) are used as the first-line therapy in children. However, the optimal treatment duration and the predictive remission factors are still controversial.

Objective: To investigate outcome of MMI treatment and remission rate, and to identify associated remission factors in a group of HT children.

Material and Methods: Sixty two patients (F:52 M:10), receiving MMI treatment and followed-up at least for 2 years, were included. Only children with adequate compliance were evaluated up to 5 years. Age, TSH, FT4 and T3 levels, MMI dose and thyroid gland ultrasound were analyzed at start of treatment in order to identify associated remission factors. Remission rate was evaluated at 2, 3 and 5 years in patients with adequate compliance. Remission was defined as a euthyroid state for at least 12 months after discontinuation of MMI treatment. Statistical analysis: R version 4.2.2. Mann-Whitney/T test and Fisher's exact test to evaluate differences between groups.

Results: Median age at start treatment was 11.2 (7.7;12.9) years. Median MMI dose was 0.67 (0.53;0.86) mg/kg/day. Thyroid ultrasound (n=52) was normal in 4 (7.7%) patients. Twenty nine (55.8%) had heterogeneous gland, twelve children had goiter (23%) and seven had thyroid cystic or nodule (13.5%). At diagnosis, median TSH was 0.03 (0.01;0.06) uU/ml, mean FT4 was 4.20 ±

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1.55 ng/dl and mean T3 was 506.97 ± 160.13 ng/dl. Remission was successfully achieved at a median time of 1.53 (0.60;2.45) years. Remission rate increased with treatment duration. It was 27.4% (n=17) in the total group at 2 years, 38% (n=19) in the 50 children followed-up to 3 years, and 65.8% (n=25) in the 38 patients with adequate compliance during 5 years. No significant differences were found between remission and non-remission patients at 2 years in the analyzed parameters at start of treatment.

Conclusion: Long-term MMI treatment is a useful option in children with hyperthyroidism. A longer MMI course was associated with a greater chance of remission in this population. Associated remission factors at start of treatment could not be identified.

P1-193

Thyroid hormone resistance syndrome due to a new mutation in the TRHA gene

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Introduction: Resistance to thyroid hormones is defined as lack of response of peripheral tissues to triiodothyronine (T3) which is the active form of thyroid hormones. In general (85%) a mutation is detected in the thyroid hormone receptor β (THRB) gene and more rarely, the thyroid hormone receptor α (TRHA) gene.

Case: A 4.7-year-old boy, was admitted to the pediatric endocrinology outpatient clinic of Akdeniz University Hospital with an abnormality in thyroid function tests and mental-motor developmental delay. He was delivered by caesarean section (39 wks, weight: 3.1kg, 25th centile). He had no jaundice in the newborn period and was breastfed initially and supplementary food was begun after 6 months. Additional concerns (at age 2 years), including delayed milestones (sitting at 9 months, standing at 14 months, speech and language at 12 months) and gait disturbance, closure of anterior fontanelle at 2 years of age were noted. He failed to gain height and by the age of 4.7 height was 105.8 cm (Z=-0.3, 37.7 centiles), weight was 18.9 kg (Z=0.4), and head circumference was 56 cm (Z=2.9, 100 centiles). Abnormal thyroid function tests (free T4 0.97 ng/dL [normal range: 0.96-1.77 ng/dL]; TSH 2 mIU/L [NR 0.7-5.9 mIU/L]) and IGF1 (9.92 [normal range: 2.87-27.1]) were detected. Also, Hb was 9.1 g/dL (12-16). There was no iron deficiency. The patient suffered from constipation. With ongoing anaemia and abnormal thyroid function tests, a probable diagnosis of resistance to thyroid hormone (RTH) was thought and genetic analysis was performed and heterozygous c.641C>A (p.Ala214As) mutation in the THRA gene was found. Following the genetic diagnosis of RTHα (age 4.7 years), additional features of the disorder ascertained included, dysmorphic facies (broad face, retrognathia, clynodactilia, flattened nasal bridge, hypertelorism, epicanthus) and there was motor dyspraxia. Skeletal abnormalities included abnormal hip x-ray and femoral epiphyseal dysgenesis.

Conclusion: THRA mutations may be more common than expected. In patients with clinical symptoms of anemia, motor-mental development, and skeletal problems a molecular study of THRA defects is recommended.

P1-194

Predicting variables associated with transient congenital hypothyroidism

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Background: Increase in incidence of congenital hypothyroidism (CH) is explained by detection of transient CH (TCH), previously commonly underdiagnosed, due to neonatal screening programs. Current guidelines recommend that treatment be started immediately after diagnosis and that hypothalamic-pituitary-thyroid (HPT) axis be reevaluated after 3 years of age. We aimed to identify the factors associated with TCH, such as the perinatal history or L-thyroxine (LT4) dose per weight.

Methods: Clinical, anthropometric, laboratory and radiological data of 145 children with CH visiting the pediatric endocrinologic clinic between January, 2018 and March, 2023 were retrospectively analyzed. We compared the gestational age (GA), birth weight, maternal history, NST level at screening, initial serum TSH, fT4 level and LT4 dose per weight at every 6 months between TCH and permanent CH (PCH) group. Continuous data were analyzed using the student t-test and categorical variables were analyzed using the χ2 test. To identify the association between covariates and TCH, univariate and multivariate Cox proportional hazards models were performed.

Results: 77 (53.1%) children were classified in the TCH and 68 (46.9%) in the PCH. GA and birth weight between TCH and PCH showed statistical difference, 36.2 weeks versus 38.5 ($P<0.001$) and 2.64 kg versus 3.02 kg ($P=0.008$), respectively. TCH group (n=21/77, 27.3%) had more maternal thyroid disease than PCH group (n=6/68, 8.8%). Preterm birth, low birth weight, maternal thyroid disease, positive for routine test, low TSH level at screening and low L-Thyroxine (LT4) dose at subsequent age were associated with TCH in the univariate analysis. In the Cox multivariate analysis, preterm birth (adjusted HR=2.554, $\text{CI}_{95\%}$ [1.593-4.095], $P<0.001$) and low LT4 dose at 30 months of age (adjusted HR=-0.799, $\text{CI}_{95\%}$ [0.362-0.559], $P<0.001$) remained statistically associated with TCH. LT4 dose at 30 months age of 3.24 μg/kg/day could suggest TCH (sensitivity, 66.2%; specificity, 66.2%).

Conclusion: Our study showed that preterm birth and low LT4 dose at 30 months of age was highly suggestive of TCH.

P1-195

A rare case of thyroid dyshormonogenesis with high urine iodine excretion

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Background: Variety of defective thyroid hormone biosynthesis accounts for 15% of congenital hypothyroidism. Children with IYD gene (formerly DEHALI) mutation, which encodes thyroidal enzyme iodotyrosine deiodinase, cannot recycle iodine in thyroid gland. This results in urinary loss of iodine and hypothyroidism. The condition may be missed by neonatal screening programs.

Case Description: A male baby was born of non-consanguineous Asian parents at 33 weeks of gestation. He has had normal neonatal screening test. Hypothyroidism was diagnosed at 2 months of life with TSH of 340 pmol/l and free T4 of 4.0 pmol/l. Thyroid Isotope scan demonstrated normally situated bulky thyroid gland with intensely avid uptake of radioisotope. Thyroglobulin level was 1061 ug/l, and Thyroglobulin antibody was negative. His urine iodine:creatinine ratio was very high (2361.19 nmol/mmol, reference range 50-360 nmol/mmol) without antenatal or postnatal iodine exposure. Attempted breast milk iodine quantification was unsuccessful. His plasma iodine and mother's thyroid function were within normal limits. Exome sequencing did not identify de novo or autosomal/X-linked recessive pathogenic variant(s). The boy is currently 7 years old and needs only a small dose of thyroxine to be euthyroid. In addition, he has unexplained tachypnoea since birth and developmental delay.

Discussion: In the evaluation of dyshormonogenesis, urine iodine excretion is a valuable test to narrow down the diagnosis of IYD gene mutation. The diagnosis of mild thyroidal dyshormonogenesis is unlikely to explain the association with persistent unexplained tachypnoea and developmental delay but this is the first reported case of such associations.

P1-196

Clinical Pattern and management attitudes of Paediatric Graves' Disease in Saudi Arabia, A 10-Year Experience

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Introduction: Graves' disease (GD) is a leading cause of hyperthyroidism in all age groups. Clinical presentation, methods and overall goals of therapy can be variable in different age groups. We aimed to study the prevalence of GD, the attitude of treating physicians towards management preferences as well as patient response pattern amongst children and adolescents with GD in Saudi Arabia.

Methods: A cross sectional, multicentre study at King Abdulaziz Medical City (KAMC) in Jeddah and Riyadh, Saudi Arabia (2009-2018). Data gathered via electronic medical records system for all patients diagnosed with thyrotoxicosis under 18 years of age. We excluded those with incomplete data.

Results: A total of 93 patients were enrolled. The mean age was 11.5 years at diagnosis with a female predominance (N=68, 73.1%) and unremarkable family history (N=53, 57%). The main causes were GD (N=60, 64.5%) and hashitoxicosis (N=10, 10.8%). Majority of thyrotoxicosis presented with goitre (57%) and tachycardia (55%). GD was mainly associated with exophthalmos, lid lag, sweating, tremor and weight loss (OR 3.71, 3.8, 2.77, 2.34, 2.28) respectively. Thyroid uptake scan showed increased uptake in N=29 (48.3%, P-value =0.029) in those who underwent scanning opposite to non-sensitive thyroid US results P-value= 0.228. Serum FT4 (N=32.6/ P-value= 0.000), FT3 (N=20.3 / 0.000), TSI (N=9.1 / 0.000), Anti TG (N=537.5 / 0.018) and Anti TPO (N=366.5/0.017) had biochemical significance in diagnosing GD as the cause of hyperthyroidism. Majority with GD were treated with only MMT (N=44, 73%), had good compliance (N=44, 73%) and no adverse effects (N=56, 93.3%). A definitive treatment was only used with RAI in (N=14, 23.3%) or thyroidectomy in (N=5, 8.3%) patients.

Conclusion: GD is a leading cause of hyperthyroidism in children and adolescent with updates on different approaches of management. Endocrinologists in Saudi Arabia favour the option of extended use of ATD

P1-197

Effects of methimazole therapy on effector T and B regulatory cells in pediatric patients with Graves' disease

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Introduction: The incidence of autoimmune thyroid diseases (ATD) is constantly rising. Graves' disease (GD) remains the most common cause of thyrotoxicosis in pediatric population, but the exact pathogenesis of GD is still not fully understood. The immunological basis of ATD assumes an imbalance between effector and regulatory T lymphocytes. B regulatory cells (Breg) are able to suppress the pro-inflammatory properties of effector T cells. Methimazole (MMI) is preffered drug to treat GD in children.

Aim: The aim of this investigation was to analyze distribution of chosen effector T cells and to evaluate a potential correlation between effector T cells and Breg in GD pediatric patients. We also tried to explore effects of MMI therapy on the level of those groups of cells.

Material and Methods: A total of 22 pediatric patients with GD diagnosis were involved in the study. The control group consisted of 31 euthyroid healthy children. Peripheral blood was collected from GD patients at the admission and after initiation of MMI therapy. The expressions of the immune cell populations were analysed by four-color flow cytometry using a FASC Canto II cytometer (BD Biosciences).

Results: We reported higher levels of effector T cells (precisely Th1, Th17 and Th22 subpopulations) in GD patients at the diagnosis. Interestingly, there was no significant difference in cells populations in the course of MMI therapy. We also observed loss of dependency between T effector and B regulatory cells in GD patients compared to healthy controls.

Conclusions: Our study confirms that the correct immune responses are ensured by a constant interplay between effector and regulatory cells and any disturbance of this balance may result in autoimmunity. These results may be used as a field to find new treatment methods.

P1-198

Graves' disease in children with Down syndrome

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Introduction: Thyroid abnormalities such as subclinical or overt hypothyroidism are common in children with Down syndrome (DS) with ranges from 4% to 19.5%, whereas Graves' disease (GD) is extremely rare (ranges 0.6%-0.9 %).

Aims: To evaluate clinical features, course, and treatment of GD in children with DS.

Patients and Methods: Among 161 children with GD, diagnosed between 1.01.2004 and 31.12.2021 in three tertiary care centres, we identified 13 patients (8 f, 5 m) with DS (8%). Data were collected retrospectively from patients' medical records.

Results (mean ± SD): GD was diagnosed at a mean age of 10.6 ± 4.5 yrs. (range, 4.1–16.4). The female-to-male ratio was 1.6:1. Eight patients were prepubertal, and five had entered puberty. The most common presenting symptoms were weight loss (n=6, 46%), increased irritability (n=3, 23%), and increased sweating (n=3, 23%). Accompanying diseases were congenital heart disease in two patients, Hirschsprung's disease in one patient, type 1 DM and celiac disease in another patient. Seven of 11 (63.3%) patients with a thyroid ultrasound at diagnosis had a goitre, no patient had orbitopathy. On admission, all patients had TSH levels <0.01 mU/L (normal range (NR): 0.51-4.30), fT3, fT4 and TRABs were 22.2±10.2 pmol/L (NR: 3.5-8.1), 50.2±18.7 pmol/L (NR 12.6-20.94), and 31.1±42.3 U/L (NR:<1), respectively. Patients were treated either with thiamazole (n=10, 77%) or with carbimazole (n=3, 23%); dose 0.54±0.36 mg/kg/day; two patients received additional beta-blocker therapy. The method of treatment was "block and replace" in 10 patients (77%) and "dose titration" in three (23%) patients, with a mean treatment duration of 43.4±11.0 months. Of 13 patients, four are still receiving primary treatment, three are in remission, one patient had two recurrences both treated medically, three underwent surgery without complications, and two patients were lost to follow-up.

Conclusions: There was no pronounced female preponderance. Our results show that the clinical course of GD in patients with DS was similar to GD in children without DS (data not shown). The majority of our patients responded to prolonged medical therapy; definitive treatment with surgery was performed in three patients.

P1-199

Investigating the Incidence of Mild Neonatal Hyperthyrotropinaemia, a Multicentre Study

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Background: Mild isolated neonatal hyperthyrotropinaemia (HTT), defined as elevated thyroid stimulating hormone (TSH) with normal free thyroxine (FT4) concentrations, may be identified by newborn screening programmes for congenital hypothyroidism (CHT) or when neonatal thyroid function tests (TFTs) are performed for a clinical indication. Reported HTT incidence rates vary (from 0.001-0.1%)[1]. Case definition also varies, with some authors using a TSH threshold of up to 30 mU/L[1]. HTT is usually transient and self-resolving, but permanent CHT requiring treatment has been reported[2]. We aimed to ascertain the incidence of HTT in a large Irish cohort.

Methods: A 5 year retrospective, observational review was performed across three sites (National Newborn Screening Centre and two tertiary maternity hospitals). All infants less than one month of age with a serum TSH level above the normal reference range (5.5mU/L) but less than 10mU/L and a normal FT4 value (10-22pmol/L) were identified. Demographic, clinical, and serial biochemical data were reviewed.

Results: Of 64,272 infants born during the study period, 426 neonates were identified as having HTT giving an incidence rate of 0.7%. The incidence in preterm infants was 1.6%. Of the 426 infants with mild HTT, 238 (55%) were male, 188 (45%) were female. Trisomy 21 was diagnosed in 15 infants (3.5% of the cohort). The main indications for thyroid function testing were maternal history of thyroid disease (52%, n=221), prolonged jaundice workup (25%, n=106) and follow up of an elevated newborn screen bloodspot TSH level (16%, n=67).

Conclusion: We report an overall HTT incidence rate of 0.7%. HTT was more common in preterm infants and those with Trisomy 21. The incidence of HTT was higher than previously reported in the literature, suggesting that this condition may be underrecognised and underreported.

P1-383

Clinical and molecular characteristics of 147 patients with primary congenital hypothyroidism: A single-center experience

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Background: Next-generation sequencing (NGS) technologies have improved our knowledge about the genetic basis of congenital hypothyroidism (CH). The objective of our study was to evaluate the molecular genetic etiology in our primary CH cohort by using the NGS-based panel.

Subjects and Methods: The clinical and genetic characteristics of 147 patients (61 female) from 129 unrelated families were evaluated. The patients were categorized as thyroid dysgenesis (TD) and gland in situ (GIS) according to the thyroid ultrasonography and/or thyroid scintigraphy. Clinical Exome Sequencing (CES) was performed using SOPHIA Clinical Exome Solution V2 (Boston, USA) via the Illumina Nextseq 550 platform (San Diego, CA, USA). The Human Gene Mutation Database (HGMD) and ClinVar databases were used to determine whether the detected variants were novel or previously reported. Segregation analysis was performed in selected cases and families.

Results: The median age at admission was 24 days (IQR 14-41 days). The mean for gestational age was 38.4±2.2 weeks. Birth weight was SDS 0.1±1.1, and the SGA ratio was 3.6%. The rate of consanguinity was 30.8%. The hospitalization rate in the neonatal care unit was 27.6%, and neonatal jaundice was reported at 58.1%. The median values of TSH and free T4 at admission were 79.0 mU/L (IQR 21-321) and 8.1 pmol/L (IQR 3.8-12.5), respectively. TD ratio was 27.7% (55.2% ectopy, 24.1% hypoplasia, 13.8% agenesis, 6.9% hemiagenesis) and 72.3% GIS. Clinically relevant pathogenic variants were identified in 32.7% (9.1% in TD, 44.2% in GIS, $p<0.001$) of the cohort. Pathogenic/likely pathogenic variants were detected in TSHR (n=13), TPO (13 cases from 6 families), and DUOX2 (8 biallelic, 3 monoallelic) followed by PAX8 (4 cases from two families), TG (n=2), NKX2-1 (n=1), SLC5A5 (n=1), SLC26A4 (n=1), DUOXA2 (n=1), ELN (n=1).

Conclusion: Clinically relevant pathogenic variants were detected in approximately 1/3 of the cases in our congenital hypothyroidism cohort. The molecular etiology was identified more frequently in cases with GIS compared to dysgenesis.

P1-384

A novel X-linked variant [c.1772delG (p.G591fs*20)] in *IRS4* in a patient with central hypothyroidism

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Central hypothyroidism (CeH) is characterized by thyroid hormone deficiency due to impairment of pituitary TSH or hypothalamic TRH biosynthesis. CeH is often seen as a part of multiple pituitary hormone deficiencies, but it can also be seen as isolated. Diagnosis may be challenging. To date, some variants that can cause isolated CeH have been identified; although in a number of patients the cause has not been clarified. Recently, variants of the insulin receptor substrate 4 (*IRS4*) gene have been reported to be the cause of isolated CeH. Herein, we reported a patient with CeH due to a hemyzygous novel variant in *IRS4*.

Case: A 15-year-and-2-month male was referred to our clinic due to a low serum free thyroxin level, incidentally detected. Last four months, patient's serum fT4 level was low without any symptoms. He was born as the second child of healthy nonconsanguineous parents. In his family history, his sister and a male-cousin were being treated for hypothyroidism. On physical examination, body weight was 70 kg (0.6 SDS), height was 178.1 cm (0.99 SDS). The thyroid gland was non-palpable. His bilateral testicular size was 20 mL, and pubic hair was Tanner stage 4. All systemic physical examination features were unremarkable. Initial laboratory investigations revealed normal blood count, electrolytes and liver-kidney functions. Hormonal evaluation revealed; TSH was 1.97 mIU/ml (N, 0.7-5.97), fT4 was 0.65 ng/dl (N, 0.96-1.77), fT3: 3.5 ng/dl (N, 1.58-3.9), Prolactin was 7.7 ng/ml (N, 4.79- 23.3), ACTH was 54 pg/mL and Cortisol was 9.7 µg/dL. Pituitary magnetic resonance imaging (MRI) was unremarkable. With the findings, isolated CeH was considered and then L-thyroxin treatment was started. Whole exome analysis revealed a hemizygous c.1772delG (p.G591fs*20) variant in *IRS4*, which was predicted to have 'Likely Pathogenic' according to American College of Medical Genetics (ACMG) criterias. Sanger sequencing in other family members revealed heterozygous variant in the mother. fT4 concentrations of the female carrier (mother) was 0.91 ng/dl (N, 0.7-1.4) and TSH was 1.1 mIU/ml (N, 0.35-4.94). The family members', suspected for the disease, genetic analysis not completed yet.

In conclusion we reported a novel *IRS4* mutation in a patient with isolated CeH. Isolated CeH should kept in mind in insistent low fT4 levels without an increase in TSH levels. This study shows that the technique of WES could be an efficient diagnostic tool for congenital abnormalities.

P1-385

Patients with genetic susceptibility syndromes to thyroid cancer in a tertiary hospital

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The new techniques of molecular genetics are revolutionizing our clinical practice. This causes benefits in the diagnosis and prediction of diseases in patients, but also raises new ethical concerns that must be addressed.

One of them is the susceptibility to cancer due to genetic risk. Children can be especially vulnerable in this area, as they do not freely decide the way forward.

Regarding thyroid cancer, it is important to know which genetic syndromes are susceptible to cancer, how likely they are to develop it, and how to monitor these patients.

Objetives: To study patients < 15 years old with syndromes of genetic susceptibility to thyroid cancer (GSSTC) and their clinical-epidemiological characteristics.

Material and Méthods: Review of patients coded in clinical history as GSSTC.

Statistical analysis of data using SPSS program.

Results: 18 cases of GSSTC have been diagnosed: 10 MEN2A, 1 MEN2, 2 DICER1, 2 familial adenomatous polyposis, 1 PTEN, 1 Cowden and 1 ataxia-telangiectasia. The patients have an age between 1-15 years old (median 12 years); 50%M/50%F.

11 of 18 patients had thyroid cancer of genetic origin. 8 had MEN2A, 1 MEN2B and 2 DICER1. In 8 patients, a family history of predisposition to cancer was known (7 MEN2A and 1 DICER1). They consulted: 7 by family history (all of them MEN2A), 3 by goiter (1 MEN2A, 1 MEN2B and 1 DICER1) and 1 by thyroid nodule (DICER1).

5 presented ultrasound abnormalities suspected of malignancy. Ultrasound-guided FNA was performed in 3 of the patients, with a Bethesda result of 1 in one patient and 2 in two patients despite being affected by cancer.

Thyroidectomy was performed on these 11 patients. In 7 MEN2A, prophylactic thyroidectomy was performed due to high risk (requiring one radioactive iodine later). In 4 patients, therapeutic thyroidectomy was performed: 1 MEN2B with suspected ultrasound that also required radioactive iodine and tyrosine kinase inhibitors; 1 MEN2A and 2 DICER1 with suspicious ultrasound.

7 of 18 patients have not developed cancer so far; 3 have been evaluated (2 MEN2A with prophylactic thyroidectomy due to high risk and 1 Cowden who has presented thyroid nodules with FNA with Bethesda 2) and 4 are pending first evaluation in endocrine (1 ataxia-telangiectasia, 2 familial adenomatous polyposis and 1 PTEN).

Conclusions: The follow-up of patients with medium-high genetic susceptibility should be close,

Further studies are needed in this population to better understand their clinical evolution

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P1-386

Very early diagnosis of Monocarboxylate Transporter 8 (MCT8) Deficiency by measuring Free Triiodothyronine (fT3) in Infancy

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Background: Monocarboxylate-transporter 8 (MCT8) deficiency, also known as Allan-Herndon-Dudley syndrome (AHDS), is associated with severe motoric and intellectual developmental delay. The pathophysiology is characterized by central hypothyroidism (due to transporter defect) and peripheral hyperthyroidism with thyrotoxicosis. There is often an increase in the peripheral T3 values and a decrease in the T4 values. In addition, numerous comorbidities can be held responsible for a reduced life expectancy. However, the peripheral T3 hormone in particular is rarely measured in routine diagnostics. The sole determination of TSH can be insufficient here, as TSH is often normal. Since 2019 there have been studies that have shown that triiodothyroacetic acid (Triac) can alleviate peripheral thyrotoxicosis and perhaps also improve the neurological phenotype.

Case Report: We would like to put forward a case of an infant who presented with muscular hypotonia and developmental delay at the age of 5 months. In a first laboratory investigation for the etiological classification of the neurological symptoms, a normal TSH with 5.04 µU/ml (reference 0.73-8.35), a reduced free T4 with 0.6 ng/dl (reference 0.9-2.0) and a significantly increased free T3 of 9.7 pg/ml (reference 2.2-5.8) were found. A targeted genetic test was carried out with the detection of a pathological mutation in the SLC16A2-gen on the chromosome Xq13.2, responsible for AHDS. Except for a somewhat delayed myelination, no morphological abnormalities were found in the MRI. The EEG examination showed a generalized slowing. The clinical examination revealed a lack of head control. After diagnosis, therapy with Triac was started immediately with increasing doses. Drug levels and hormone values were monitored in close cooperation with Erasmus Medical Centre Rotterdam, The Netherlands.

Conclusion: The patient makes slow developmental progress. He still shows a clear dystonic movement disorder and the motor development is clearly behind. Overall, he eats foods himself properly and rarely gags. The further neurological development remains to be observed. With this case report we would like to describe our experience of a very early diagnosis of a patient with an MCT8 deficiency with the greatest potential benefit of early treatment. The typical morphological phenotypic appearances of patients with the AHDS develop over years and are not expedient, especially in the infant phase. The combination of developmental delay and lack of head control (or even just one symptom) should always lead to a measurement of free T3 hormone. In addition, the SLC16A2-gene should always be included in genetic panel-screenings.

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P1-387

Effect of Daily Zinc Supplementation for 12 Weeks on Serum Thyroid Auto-Antibody Levels in Children and Adolescents with Autoimmune Thyroiditis – A Randomized Controlled Trial

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Background: The imbalance between oxidant-antioxidant status plays an essential role in the pathogenesis of many autoimmune diseases, including autoimmune thyroid disease (AITD). Studies have described that children with AITD have reduced superoxide dismutase (SOD), glutathione peroxidase (GPx), and significantly low zinc levels. This study assessed the effect of daily zinc supplementation for 12 weeks on thyroid auto-antibodies - thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb), and oxidative stress compared to standard therapy.

Methods: This open-labeled, parallel, randomized controlled trial was done in a tertiary care teaching institute in south India. Children aged 3 to 18 years with TPOAb or TgAb positivity were included, and those who received zinc for other illnesses in the preceding three months were excluded. Participants were randomized to receive 25mg of elemental zinc daily for 12 weeks or standard therapy alone. The change in thyroid function tests (thyroid stimulating hormone, free T3, free T4), thyroid auto-antibody titers, and oxidative stress markers (GPx, malondialdehyde, SOD, and total antioxidant capacity) were compared.

Results: 40 children, 20 in each arm, were recruited in the study. We observed a female-to-male ratio of 7:1. Low weight and height for age (Z score < -2) were observed in 5 (12.5%) and 7(17.5%) children, respectively. The median duration of the disease was 2 (0.25,4.25) years. 37(92.5%) children were hypothyroid, two hyperthyroid, and one euthyroid at enrolment. The requirement of levothyroxine dose was 75(50,100) mcg per day. 23(72%) had ultrasonographic evidence of thyroiditis. 13 children (32.5%) had associated co-morbidities, most commonly type 1 diabetes mellitus and systemic lupus erythematosus, three (7.5%) each. We did not find any significant change in thyroid function tests, thyroid auto-antibody titers, and oxidative stress markers between the two groups. However, the levothyroxine dose requirement was significantly increased in the control arm compared to the zinc group (p=0.03). Two patients in the zinc group and one in the standard group had normalized thyroid antibodies. The compliance rate of zinc was more than 90% in 13 (65%) patients, between 80-89% in three (15%), 70-79% in three (15%), and one had a compliance rate of 60%. The adverse effects, as described by the participants, were generalized body aches in three (15%), metallic taste in one (5%), nausea in one (5%), and one participant (5%) developed diarrhea with no dehydration.

Conclusion: Zinc supplementation did not affect thyroid auto-antibodies and oxidative stress. Zinc-supplemented children did not require escalation in levothyroxine dose.

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Neutropenia in paediatric Graves disease patients occurs more often under Carbimazole than Methimazole

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Introduction: Neutropenia is known as a rare adverse event of anti-thyroid drug treatment (ATD) but has also been reported as pre-treatment neutropenia in Graves' disease (GD). Studies on paediatric patients are rare. To the best of our knowledge, there are no data comparing the effects of methimazole (MMI) and carbimazole (CBZ) treatment in children on the absolute neutrophil count (ANC).

Methods: We analyzed retrospectively the clinical and biochemical data of 161 children (age 11.8 years ± 3.57) diagnosed with GD. 83% were Caucasian, 17% belonged to other ethnic groups such as Turkish or Syrian. Inclusion criteria were elevated free thyroxine (fT4) [normal range (NR): 10 – 25pmol/L], completely suppressed thyroid stimulation hormone (TSH) (NR: 0.5-4.5mIU/L) and elevated thyroid receptor antibodies (TSHRAb > 2.5 IU/l). Neutropenia was defined as ANC <1800/μL, and agranulocytosis as ANC < 500/μL. All patients received ATD with MMI or CBZ.

Results (mean ± SD): Nine patients had neutropenia at diagnosis (ANC: 1348/μL ± 250.12), with spontaneous normalization under ATD. One patient developed agranulocytosis (40/μl) three weeks after start of ATD due to either very high maximal dose of CBZ (1.8mg/kg/d) or thyreotoxicosis (fT3 > 30pg/ml (46pmol/l); fT4 > 8ng/dl (12.9pmol/l), both higher than measurable upper limit, TSHRAb 101.20 IU/l). Further 37 patients became neutropenic (ANC: 1479/μL ± 261.84) while receiving ATD. Neutropenia occurred on average after 551.8 days (range, 10-1376) after diagnosis. All patients achieved ANC normalization without a change in the treatment regime. Low ANC occurred significantly more often in patients receiving CBZ (50%; n=20/40) than in those receiving MMI (16.5%; n=18/109; p=0.0008). The groups do not differ in sex, age, antibody or hormone level. The maximal dose before neutropenia was not significantly different between the CBZ and the MMI group and between the neutropen and the non-neutropen group. The cumulative ATD dosages, analysed at four times when 25%, 50%, and 75% of the children developed neutropenia, were not significantly different between the treatment groups.

Discussion/Conclusion: Agranulocytosis is a rare ATD side effect in children suffering from GD. Neutropenia at diagnosis is not a contraindication for ATD use and mild to medium neutropenia under ATD is no indication for changing the treatment regime, because in both groups normalization of ANC can arise spontaneously. As neutropenia occurred significantly more often under CBZ than MMI in our cohort we suggest that children with GD should be treated with MMI. Further investigation is necessary to detect risk factors for neutropenia in children with GD.

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Long-term follow-up of congenital hypothyroidism and predictors of permanent congenital hypothyroidism

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Purpose: Congenital hypothyroidism (CH) is a state in which thyroid hormones are insufficient at birth. This condition may last for a lifetime or may be transient. Due to the universal newborn screening test, almost all newborns are being screened for thyroid function in Korea. The study was aimed to see the predictors of transient congenital hypothyroidism with long-term follow-up of more than 3 years of CH in a single tertiary center.

Subjects and Methods: Children who has been diagnosed as CH with more than 3 year of follow-up were included in the study. Retrospective review of clinical, laboratory, and imaging data were performed based on medical records and analyzed using R 4.2.

Results: A total of 98 patients were included in the study. They had taken thyroid hormone under the diagnosis of congenital hypothyroidism and been followed more than 3 years in a single tertiary center. Mean T3, freeT4, and TSH levels prior to hormone treatment were 138.8, 1.01, and 84.5, respectively. Mean age at recent follow-up was 8.05 years. They were classified as transient CH (n=62, 63.3%) and permanent CH (n=36, 36.7%) during follow-up. T3 levels prior to medication (preT3) was lower in permanent CH compared to transient CH (113.2 vs. 154.3, P=0.05), and maximum dose of thyroid hormone (DT4max) was higher in permanent CH (71.1 ug vs. 36.6 ug, P< 0.001). Mean TSH levels prior to medication were not significantly different between two groups. 128.5 ng/dL of preT3 (sensitivity 63% specificity 66%) and 47.5 ug of DT4max (sensitivity 81%, specificity 79%) can be used as the cutoff values to predict permanent CH in the study.

Conclusions: The study showed that 63% of CH can discontinue the thyroid hormone replacement during follow-up. Maximum dose of thyroid hormone (DT4max) during follow-up and T3 levels prior to medication can be used as the cutoff values to predict permanent CH.

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WITHDRAWN

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Molecular Genetic Causes In Elevated TSH: Frequency And Genotype-Phenotype Characteristics

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Introduction: The most common cause of elevated TSH is iodine deficiency, and other common causes are drug use, systemic diseases, and underlying genetic conditions.

Objective: We aimed to investigate molecular genetic etiology, genotype-phenotype relationships and the follow-up data in cases with elevated TSH initiated on L-thyroxine treatment

Methods: We retrospectively evaluated clinical features, laboratory values (TSH, free T4), demographics, age of drug onset and withdrawal, ultrasonography (USG), and genetic analysis results of the patients with elevated TSH. The study did not include those with a syndromic disease, concomitant disease, and drug use that may cause TSH elevation. The pathogenicity of the variants detected in the cases that underwent clinical exome sequencing with the targeted next-generation sequencing panel (Illumina TruSight One) was determined by the ACMG criteria.

Results: Twenty-eight of the 43 cases (65%) were male, 15 (35%) were female. The mean age at admission was 1.23±2.88 years. Age at presentation of 16 (37%) cases who were diagnosed with screening was 0.10±0.13 years, TSH 84.3±124 mU/L, fT4: 0.88±0.57 ng/dl at admission and 9 (56%) of these had dysgenesis. In total, 12 (28%) of 43 cases were diagnosed with dysgenesis, and 31 (72%) were diagnosed with dyshormonogenesis. The age of presentation who admitted with incidental TSH elevation outside the neonatal period was 1.64±3.33 years, and their TSH and T4 values were 80.2±137.3 mU/L and 0.96±0.40 ng/dl.

L-Thyroxine treatment was terminated at 2.2±0.48 in 2 patients (12.5%) admitted from screening and at 2.79±1.60 in 4 (15%) in non-screening cases. Seven cases (43%) from screening were evaluated as transient hypothyroidism.

In 5 (12%) of all cases, TG, 4 (10%) DUOX2, 3 (7%) TSHR gene heterozygous variants were detected.

No disease-causing variant was found in 53 genes previously known to be associated with hypothyroidism, in 14 (87%) of 16 patients referred from the screening program and in 17 (63%) of 27 patients with coincidental TSH elevation, in a total of 31 (72%) cases.

Conclusion: There is limited knowledge regarding the genetic etiology of TSH elevation, which frequently occurs in pediatric endocrinology practice. Panel studies in such genetically diverse diseases are critical for increasing the mutation detection rate. More research is needed to determine the etiological causes in this population.

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A case series of multinodular goitres associated with tumour predisposition syndromes

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Thyroid nodular disease, either multinodular goitre (MNG) or solitary nodule, carries a higher malignancy risk in paediatric patients compared to adults requiring closer monitoring and investigation. We present a case series of patients with multinodular goitre who were confirmed to have tumour predisposition syndromes.

Eight patients (six female) with MNG were identified using electronic medical records, based on presence of MNG and/or previous genetic testing confirming either DICER1 or PTEN mutation. Information was collected on demographics, thyroid imaging, histopathology, genetics if available, other medical diagnoses and any family members with the same genetic mutation.

Age at diagnosis of MNG ranged from 6 to 15 years, median 12 years. Five of the eight had presented for investigation of a goitre or nodule, three were detected on screening, due to known PTEN mutations. One patient had an inconclusive fine needle aspirate, 6 were referred directly for surgical resection due to MNG size or unusual appearance (5 total, one hemi-thyroidectomy, with later completion thyroidectomy). One patient has not had any intervention to date.

Of the 7 thyroidectomies, pathology demonstrated follicular thyroid carcinoma (N=2), papillary thyroid carcinoma (N=1), benign histology (N=4).

DICER1 mutation was found in 5 of 8, PTEN in 3 of 8. Of the 5 with DICER1 mutations, two have had Sertoli-Leydig cell tumours (one also has acute myeloid leukaemia), another has an ovarian mass currently under investigation for malignancy. Of those with PTEN mutations, concomitant abdominal possible hamartomas, intra-abdominal lipomata and multiple skin lesions are being monitored. All three patients with PTEN mutations had affected family members. Identified DICER positive family members include several first degree relatives with MNG and one thyroid malignancy.

Multinodular goitre is a common cause for presentation to a paediatric endocrinologist. Until recently they have largely been considered to be benign lesions, often not followed long-term. We present data to suggest that moderately large or ultrasonographically unusual MNG in children and adolescents are often the first presentation of tumour predisposition syndromes, such as DICER1, PTEN and Carney complex mutations. As such, we propose that paediatric patients with MNG should have genetic testing.

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Primary hydatid cyst of the thyroid gland in a Libyan child

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Background: Cervico-facial hydatid cyst is rare. It has a high incidence rate in regions with a mild climate such as Mediterranean countries, Middle East, South America, New Zealand, Australia and Southeast Asia. Hydatid cyst develops most often in the liver and lungs in human beings. The incidence of hydatid cysts in the thyroid gland is rare and it accounts for 1% of echinococcosis locations. Primary hydatid cyst of thyroid gland is an exceptional localization even in echinococcal disease is endemic.

Methods: A 12-year-old male presented with left neck swelling. His medical history and other physical examination findings were unremarkable. The results of blood tests; complete blood count, blood biochemistry and thyroid function tests were normal. Ultrasonography showed one cystic lesions 2.6x3.5x3.7cm in diameter in the left lobe of the thyroid gland and the right lobe was normal. In addition, computerized tomography of the neck described it is as circumscribed, well-defined cystic lesion in the left thyroid lobe without calcification and contrast enhancement. He was scheduled for surgery as a case of left thyroid lobe cyst. He underwent a left thyroid lobectomy.

Results: The postoperative gross examination showed a thick fibrous wall separated the cysts from the surrounding thyroid parenchyma with presence of multiple daughter cystic lesion seen within Left thyroidectomy specimen. Furthermore, the histopathological examination, reported the presence of daughter hydatid cysts of Echinococcus granulosa infection within thyroid tissue. Furthermore, the radiological investigations failed to identify any other evidence of systemic hydatidosis. In addition, the patient was demonstrated in the first month after operation, laboratory evidence of subclinical hypothyroidism with TSH 8 then 10.6 uIU/mL with normal free T4. He started treatment with Levothyroxin tablet. After nine months of follow-up post-operation, he was documented a normal thyroid function and a repeated examination showed no recurrence of the hydatid disease.

Conclusion: hydatid cyst in the thyroid gland is rare. It should be included in the differential diagnosis of cystic lesions of the thyroid gland, especially in endemic regions. Positive diagnosis can be difficult during preoperative period. Exclusively surgical treatment is indicated, ideally for total cystic resection without rupture and the macroscopic aspects with histopathological examination is needed to confirm the diagnosis. Our case represents the first reported patient with primary hydatid cyst of the thyroid gland in a Libyan child.

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Assessment of five domains of neurodevelopment and growth in congenital hypothyroidism: Serial 6-year follow-up study of 408 patients

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Background: There is a link between congenital hypothyroidism (CH) and neurodevelopmental abnormalities, but no longitudinal studies have yet identified reliable quantifiable measures.

Purpose: To evaluate associations between CH and abnormalities in neurodevelopment and growth, and identify the timing of these abnormalities and the best time for intervention.

Methods: Data from the National Health Insurance System (NHIS) were used to analyze 919,707 children born in Korea from 2008 to 2009. Eligible children were tracked annually until the age of 72 months. Claims-based definitions for CH were developed using a combination of ICD-10 diagnosis codes (E03.0 or E03.1) and use of thyroid hormone medication for 5 or more years. The primary outcome was suspected neurodevelopmental disorder in five domains of the Korean Ages and Stages Questionnaires (K-ASQ): gross motor skills, fine motor skills, communication, problem-solving, personal/social ability. The secondary outcomes were anthropometric measures. A generalized estimating equation (GEE) model was used to investigate the relationship of neurodevelopmental outcomes and anthropometric growth.

Results: The prevalence of CH in our population was 0.05% (n = 408). Relative to the control group, the CH group had a higher risk of suspected neurodevelopmental disorders based on the total K-ASQ score (propensity score [PS] –weighted, odds ratio: 4.52, 95% CI: 2.91, 7.02), and significantly increased risk in each of the five K-ASQ domains. There was no interaction of time with outcome based on analysis of the date of the developmental examination (all P for interaction > 0.05). The association of CH with neurodevelopmental disorders was greater when thyroid medication began after the age of 6 weeks than at or before the age of 6 weeks. Moreover, neurodevelopmental outcome during each screening round was worse when initiation of treatment was delayed (all $P < 0.001$). The CH group also had a higher risk for low height-for-age z-score (PS-weighted aOR: 2.97, 95% CI: 1.83, 4.80), but elevated BMI-for-age z-score had no effect.

Conclusions: The CH group had worse neurodevelopmental outcome overall and in each of the five K-ASQ domains, and also had reduced height-for-age z-score, but there was no interaction of time with the outcome measurement. Outcomes were worse when the onset of treatment was increasingly delayed.

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Thyroid Storm with Diabetes Insipidus: Management of A Rare Endocrine Presentation In A Child

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Introduction: Thyroid storm is an acute, life-threatening, emergency in children with thyrotoxicosis. It is extremely rare and could be an initial presentation in previously undiagnosed children. Thyroid storm with diabetes insipidus (DI) has been reported in adults, but no cases have been reported in children. We herein report a child with thyroid storm with transient central DI.

Case Report: A 7-year-old girl, presented to the emergency department with high grade fever, headache, lethargy and an episode of generalised tonic clonic seizure (GTCS). On examination, she was pyrexic (temperature 39.2'C), tachycardic (heart rate 170/min), hypertensive (systolic blood pressure 140 mmHg) and had mottled skin. Intravenous antibiotics & antivirals were commenced suspecting meningoencephalitis. Initial investigations including full blood count, serum electrolytes, liver function test, cerebrospinal fluid analysis and CT brain were normal. C-Reactive Protein was elevated. Worsening of her clinical status resulted in admission to intensive care unit. Noticed to have goitre on subsequent detailed clinical examination which prompted measurement of thyroid function test [free thyroxine >100 (N:11.0-21.2pmol/L), free tri-iodothyronine 17.8 (N: 3.1-6.8pmol/L) and undetectable TSH <0.01mIU/L]. Subsequent focused history revealed 8-months history of weight loss despite excessive appetite, hyperactive behaviour (reduced attention span) and prominence of eyes. In view of clinical presentation and thyroid function test results, diagnosis of Thyroid Storm was made, and started immediate treatment with Carbimazole (0.75mg/kg/day), Lugol's iodine solution (0.3 ml 8 hourly), Propranolol (250 mcg/kg 8 hourly) and intravenous Hydrocortisone (2mg/kg/dose 6 hourly). Elevated TSH-receptor antibodies 10.2 (N<1.75U/L) and anti-TPO antibodies 96 (N<34U/ml) confirmed the diagnosis of Graves' disease. Ultrasound Thyroid showed enlarged and heterogenous thyroid gland with increased vascularity. Other investigations results (Blood and CSF cultures, Renal Doppler, Chest radiograph, Echocardiogram) were normal, not suggestive of another cause for her presentation. She subsequently developed polyuria (11ml/kg/hour), associated with normal blood glucose and high serum sodium (158mmol/L). Paired osmolality for plasma (320mOsm/kg) and urine (310mOsm/kg) indicated partial DI. She responded well to sublingual Desmopressin. Pituitary MRI was normal, including presence of posterior pituitary bright spot. DI resolved spontaneously within 3 days. With anti-thyroid treatment, she showed gradual improvement in clinical and biochemical parameters.

Conclusion: In critically ill children, apart from the usual suspects (Sepsis, Hypovolemia) potential for other offenders should not be overlooked. Detailed history and clinical examination is of paramount importance. A high index of suspicion, rapid diagnosis and prompt treatment is crucial as thyroid storm can be fatal if left untreated.

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Hyperfunctioning follicular adenoma in a 9-year-old boy with Prader-Willi Syndrome

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Background: Thyroid nodules in children are less common than in adult but are about two-to three-fold at risk of being malignant compared to adults. Plummer's adenoma is a very rare occurrence in pediatrics; there is no literature evidence of this diagnosis in Prader-Willi Syndrome (PWS).

Case Presentation: A 9-year-old boy, followed at our Pediatric Endocrinology Outpatients Clinic for PWS (maternal uniparental disomy), diagnosed in neonatal period, presented with the appearance of a rapidly growing palpable mass at the left anterior cervical site in the thyroid lodge. Familiar history was negative for thyroid diseases. The patients, in therapy with recombinant human growth hormone (rhGH) since the age of 1-year-old, had regular growth in height and weight: height 130 cm (+0,05 DS), weight 36.7 kg (+1,48 DS), BMI 21.75 (+1,67 DS); regular growth rate (7.6 cm/year). The child was prepubescent in accordance with the Tanner Stage. Thyroid biochemical assessment, initially within normal limits, over about 2 months shifted toward a subclinical hyperthyroidism: TSH (0.005 uIU/mL; normal value 0.27-4.2), free triiodothyronine (fT3 5.79 pg/mL; n.v. 2.0-4.4), free thyroxine (fT4 20.4 pmol/L; n.v. 12.0-22.0); anti-thyroglobulin (AbTg), anti-perossidase (AbTPO) and TSH receptor (TRAB) antibodies were negative. Thyroid ultrasound documented the presence of a nodule of the left lobe (longitudinal diameters, LD 18 mm) with disomogeneous structure and microcalcifications, with evidence of vascular signs. Fine needle aspiration biopsy (FNAB) was suggesting for non-malignant lesion/adenomatousus struma (TIR 2). A scintigraphic examination was carried out that documented a defined focal uptake of iodine-123 in the nodule with suppressed uptake in the rest of the gland. Due the clinical presentation associated with the laboratory and instrumental findings, patient underwent left hemi-thyroidectomy surgery. The anatomo-pathological examination reported an hyperfunctioning follicular adenoma, confirming the diagnosis of Plummer's adenoma.

Conclusions: Plummer's Adenoma is a rare cause of hyperthyroidism in pediatric population. Surgery is the only therapeutic option in children with less than 10-year-old. Our case describes the first evidence of isolated follicular adenoma in children with PWS. Further evidence are necessary to asses a possible correlation between these two conditions and the existence of potential risk factors.

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Increased frequency of Grave's Disease during COVID-19 pandemic

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Introduction: Increased frequency of Grave's disease (GD) has been reported both in adults and youth during the COVID-19 pandemic. Aim: To compare the frequency of GD prior and during the COVID-19 pandemic.

Methods: Retrospective analysis of children diagnosed with GD over the last 13 years in our Department.

Results: A total of 22 children (31.8% boys) with a mean age of 10.55±3.37 years were diagnosed with GD; 9 were diagnosed from January 2010 until December 2019 (0.69 children/year), whereas 13 (4 children/year) were diagnosed during the pandemic. However, only 4 of them had a confirmed COVID-19 infection prior to diagnosis. One child, diagnosed during the pandemic without prior COVID-19 infection, had a relapse 6 months after the initial remission and 2 years after a COVID-19 infection that occurred 3 months after the diagnosis of GD. Among 9 children with GD diagnosis prior to 2020, two had a relapse during the pandemic. Of those, one had been infected with COVID-19 4 months earlier. An adolescent had a flair-up of TSI antibodies after COVID-19, while under treatment. Within the same group and after a follow-up period of 4.58±2.65 years, only one other child had a relapse 4 years after diagnosis and 1 year after treatment discontinuation. The number of children is too small to yield results of statistical significance, however, among children diagnosed during the pandemic, 38.5% were boys (vs 22.2%), mean age of diagnosis was 11.2±3.19 years (vs 9.76±3.66), 53.9% had a family history of thyroid disease (vs 66.8%),TSH level was significantly lower (0.005±0.001 vs 0.011±0.007 IU/ml), fT4 4.08±2.77 (vs 3.01±2.23) ng/dl and TSI level 13.3±13.69 (vs 8.52±8.07) U/l. Seven children (53.9% vs 33.3%) were symptomatic at diagnosis and 2 children (15.4% vs 11.1%) required additional treatment with b-blockers.

Discussion: Current findings indicate increased frequency of new diagnoses and the aggravation of pre-existent GD during the pandemic. Both direct damage of thyroid cells by circulating cytokines, as well triggering of autoimmunity have been suggested as possible mechanisms. However, not all children in our cohort had a documented prior infection, although asymptomatic disease cannot be excluded, especially since data were collected

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retrospectively. Stress during confinement could also be considered as a trigger.

Conclusion: Although a causal relationship between COVID-19 infection and GD could not be established, an undisputable increase of GD was observed during the pandemic.

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Positive predictive value of dried blood sampling of TSH in diagnosing congenital hypothyroidism in neonates born at a tertiary care hospital

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Background: In children, untreated Congenital Hypothyroidism (CH), can result in permanent neurological defects and growth abnormalities. This can be prevented by early detection and treatment of CH. Newborn screening for CH is considered one of the best tools for the prevention of these long-term complications. In our setting, we use heel-stick dried blood sample TSH (DBS-TSH) as a screening tool to detect CH. The DBS-TSH cut-off level is critical to ensuring that true cases of CH are not missed. The purpose of this study is to evaluate the positive predictive value of DBS-TSH levels in diagnosing CH.

Objective: To evaluate the positive predictive value of DBS-TSH in diagnosing congenital hypothyroidism in neonates born at a tertiary care hospital.

Design: Descriptive Cross Sectional Study

Setting: Aga Khan University Hospital, Neonatal screening program

Sample Size: The study included all neonates (33 weeks or above gestation age) who were delivered during the period from April 2019 to December 2022 and screened for DBS-TSH as a part of routine newborn screening.

Method: All neonates with a value of DBS-TSH more than 10mlU/L were considered as screen positives. All screen positives were contacted by Newborn screening team (NBS Team) and advised to get Confirmatory Serum TSH done. Short-term follow-up was done for all screen positive cases within one week of issuance of initial DBS-TSH results, and continue to follow them for two weeks, and Information about Confirmatory testing, date and results was recorded. Neonates with plasma TSH >20Miu/L were considered as true positives and paediatric endocrinology team followed these patients to start treatment. A follow-up was considered 'Lost to Follow' if due to any reason not able to contact patient or confirmatory test not done after two weeks of initial screen positive.

Results: Newborn screening for CH (DBS-TSH) was performed in 30402 neonates out of which 542 (1.78%) were screen positives. 172 (31.73%) patients were lost to follow and in 379 (69.92%) patients confirmatory Serum TSH was done in which 27 were true positives and diagnosed as CH. The Positive predictive value of DBS-TSH was 0.0712 or 7.12%.

Conclusion: Among those neonates who had a positive screening test, the probability of the disease is 7.12%. We plan to further sub divide screen positives into groups based on initial results (10-20, 20-30 and >30) and calculate the PPVs in order to adjust the cut off values to increase the yield of DBS-TSH.

P1-583

Was newborn screening for congenital hypothyroidism affected by COVID19 lockdown?

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Mandatory lockdown during COVID 19 pandemic obstaculized access to medical attention. Newborn screening (NBS) for congenital hypothyroidism (CH) in Buenos Aires province has been obligatory since 1995 and performed sustainedly. CH causes mental delay if not diagnosed and treated early.

Objectives: The aim of this study was to determine if mandatory lockdown changed time of established NBS diagnosis steps.

Material and Method: Retrospective data were collected from clinical records of patients referred to NBS confirmation to our hospital. We analyzed variables during periods: prepandemic (P1) March 1, 2018- March 18, 2020, and pandemic (P2) March 19, 2020 - December 31, 2021. We compared sex ratio, confirmed cases(CC), time of sample collection (TSC), transit time (TT), time of analysis (TA),NB age at time of screening results (AR), NB age at time of arrival (AHA) ,time between results and hospital arrival (TRC),and NB age at start of treatment (ATS).

Statistical analyses were performed using software R 4.2.2 version. For qualitative and quantitative data Fisher exact and Mann-Whitney tests were used to evaluate differences between periods.

Conclusions: Percentage of confirmed cases was similar for both periods. Age at start of treatment did not show differences between periods, and was similar to historical NBS records. Even though time of sample processing (TA) showed differences between periods, it did not affect time of results, hospital arrival or diagnosis. Despite lockdown, diagnosis was carried out normally, allowing early start of treatment.

Results: Table 1.

	P1:(N=213)	P2:(N=159)	p value
Sex distribution	F:126(59.2%),M:87(40.8%)	F:106(67.9%),M:50(32.1%)	
Sex ratio	1.44	2.12	0.102
CC	167 (79.1%)	122(80.8%)	0.446
TSC	2.0 (2.0, 3.0)	2.0 (2.0,5.0)	0.272
TT	5.0 (2.0, 7.0)	5.0 (3.0, 7.0)	0.486
TA	2.0 (2.0, 2.0)	2.0(2.0, 4.0)	<0.001
AR	10.0 (7.0, 14.0)	10.5 (8.0, 14.0)	0.264
AHA	15.0(11.0, 23.0)	15.0(12.0, 22.0)	0.815
TRC	4.0(2.0, 9.0)	4.0(2.0, 7.0)	0.914
ATS	16.0 (11.0, 25.0)	16.0 (13.0, 25.2)	0.210

P1-584

National multi-center study of reevaluation of thyroid function in premature infants of less than 32 weeks of gestation and/or less than 1500g admitted to neonatal units

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Preterm and low birth weight(LBW) newborns are at risk of thyroid dysfunction during a critical period for neurodevelpment and this dysfunction can be missed in congenital hypothyroidism screening program(CHSP). Consequently, reassessment of thyroid function has been promoted in neonatal units, added to CHSP.

Objectives: To evaluate prevalence and risk factors of thyroid dysfunction in≤32weeksGA and/or 1500g newborn, and compare different neonatal units protocols.

Methods: Multicenter, retrospective, observational study. Maternal and neonatal data, thyroid function(TSH, free T4(fT4), total T4[tT4]) and CHSP results were retrospectively collected during 2021.

Hypothyroxinemia of prematurity(HOP) was defined by fT4<0.8ng/dl and TSH<5mU/L; congenital hypothyroidism(CH) by TSH≥10mU/L and fT4<0.8ng/dl or TSH≥20mU/L regardless of fT4 level and hyperthyrotropinemia was defined as moderate (TSH10-20mU/L) or mild (TSH≥5mU/L), both with normal fT4.

All centers performed CHSP with TSH test at 48-72h (2 regions added tT4). Three regions repeated CHSP at 6,15 days and at discharge.

Three centers performed venous determination(TSH and fT4) at 2nd week and at discharge, and another two at 4th week and at discharge. Levothyroxine was started according to international recommendations.

Results: 657 neonates from 7 spanish hospitals were evaluated. Median(IQR-interquartile range) of GA and weight and height at birth: 30(4)weeks,1217.5(528)g and 38(5.5)cm. 130(20%) were SGA(Small for Gestational Age).

Thyroid dysfunction were found in 161 patients(24%): 8 patients with CH; 22 with moderate hyperthyrotropinemia; 94 with mild hyperthyrotropinemia and 37 with HOP. Twenty-three(3.5%) received oral levothyroxine(8 for CH, 6 for moderate hyperthyrotropinemia and 9 for HOP). Four patients were diagnosed by CHSP, but 4 were false negatives.

The majority(92%) of thyroid disorders were transient, with normal thyroid function at discharge. Fifteen(2.7%) infants still were receiving levothyroxine at discharge. Median(IQR) duration of treatment 9.2(14)months.

Hyperthyrotropinemia showed statistically association with being SGA(p=0.02), receiving intrapartum antibiotics(p=0.03) and being dead(p=0.04). Hypothyroxinemia showed statistically association(p<0.0001) with intrapartum actions and being diagnosed with ductus, hyaline membrane disease, sepsis, grade IV intraventricular hemorrhage, and maternal thyroid pathology.

Conclusion: The prevalence of thyroid dysfunction in this population is high, although the majority are resolved spontaneously. However, some cases may be undiagnosed by CHSP and they would benefit from treatment. For this reason, it is essential to reassess thyroid function and consensuate the most eficient protocol to improve the care of this newborns.

P1-585

Papillary thyroid carcinoma incidentally discovered in young patients - a case series

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Introduction: Thyroid carcinoma in pediatric and young adult population presents contradictory features: it has higher rates of multifocal disease, local and distant metastasis and reccurence compared to the adult population, yet the 5-year survival rate is 98%. The rising incidence seen recently cannot be entirely explained by overdiagnosis, as increasing rates of advanced-stage disease are also observed. The rise consists primarily of papillary thyroid carcinomas (PTC), the most prevalent type also encountered in adulthood, but with distinct histomolecular features (frequent high-risk subtypes and gene fusions). We present the cases of 3 girls without known risk factors, whom were incidentally diagnosed with multifocal, aggressive variants of PTC and had completely different outcomes.

Case Presentations: First patient, aged 18, presented for obesity. Ultrasound examination identified a suspicious nodule that was biopsied (Bethesda IV). She underwent total thyroidectomy (TT) with central and right laterocervical lymph nodes dissection and radioactive iodine therapy (RAI). Histopatological exam revealed diffuse, multifocal, tall-cell PTC with lymphovascular, perineural, perivascular invasion and multiple metastatic lympadenopathies with extranodal extension. Bilateral reccurent laterocervical disease ensued. The patient underwent right laterocervical lymphadenectomy, left dissection being impaired by local fibrosis. Latest cervical ultrasound revealed progression of left laterocervical lymphadenopathies and hormonal dosages indicated increased serum thyroglobulin (90.77ng/ml). Subsequently, a second cure of RAI is scheduled.

Second patient, aged 14, presented for secondary amenorrhea. Being known with nontoxic goitre, ultrasound examination was performed. A nodule with two-fold increase in a month's time was observed. Moreover, an ipsilateral, suspicious lymphadenopathy was identified. FNA cytology identified a Bethesda V lesion. TT with central and unilateral laterocervical dissection was undergone. Pathology examination determined a multifocal, unencapsulated, diffuse sclerosing lesion, with lymphovascular, perivascular and perineural invasion and metastatic lympadenopathies, some with extranodal extension. Immunohistochemistry and RAI are envisioned.

Third patient, aged 20, presented for subclinical hyperthyroidism. Ultrasound showed a suspicious nodule that was biopsied (Bethesda V). TT with central lymphodissection and RAI were carried out. Pathology examination determined a multifocal, unencapsulated, diffuse sclerosing lesion, with both follicular and papillary patterns and lymphovascular invasion. One year later, there was a slight increase in unstimulated thyroglobulin and whole-body scintigraphy identified remnant thyroid tissue on the thyroglossal path, indicating the need for repeated RAI.

Conclusions: Our case series aims to shed light on the unpredictability of PTC in pediatric and young adult population and the need of specific guidelines for these age groups, not based only upon the experience treating adults.

P1-586

Hyperthyroidism caused by severe bacterial infection

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We report on a nearly 4-year-old girl who presented to the emergency room of our paediatric clinic with high fever and poor general condition, swelling of the neck and swallowing difficulties. Laboratory chemistry showed a marked hyperthyroid metabolic state, so that initially a thyrotoxic crisis in Graves' disease was considered (TSH 0.03 mU/L (-), fT4 28.10 pmol/l (+)). Therefore, a short-term therapy with thiamazole was given. The thyroid autoantibodies were negative. The inflammation values were high (CRP 134.6 md/L, leucocytes 22.53 GPt/l). Clinically, there was a slight reddening of the pharyngeal ring, the tonsils were inconspicuous.

Sonography revealed a marked, abscessed, purulent inflammation of the thyroid gland, especially of the left lobe. MRI of the neck revealed an extensive retropharyngeal abscess on the left with extension into the thyroid lobe (left > right) with significant inflammatory surrounding reaction cervically into the upper mediastinum and periclavicular. Strepotoccus anginosus was detected in the blood culture. Intravenous antibiotic therapy with ampicillin and sulbactam was administered for 3 weeks and oral therapy with amoxiclavulanic acid for another 4 weeks. There was a restitutio ad integrum. An immunodeficiency could not be found.

Conclusion: An untreated retropharyngeal abscess in our patient led to severe purulent thyroiditis with hyperthyroidism and sepsis. Antibiotic and supportive therapy led to complete recovery after 7 weeks.

P1-587

Analysis of disease types and prognosis of children with nonthyroid illness syndrome

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Objective: The purpose of this article is to retrospectively summarize the disease types and prognosis analysis of children's nonthyroid illness syndrome (NTIS), improve the diagnostic awareness of children's NTIS, and explore whether thyroxine replacement therapy is required or whether the body has a self-healing trend.

Methods: The clinical data of 47 cases (32 males and 15 females) of NTIS diagnosed in various wards of ordinary children in our hospital from January 2019 to December 2021 were collected, and the diseases causing NTIS in children were counted. 61 normal children were taken as the control group. The thyroid gland function was followed up to one year after discharge. T test was used to compare the count data, and $P < 0.05$ was statistically significant.

Results: The order of diseases leading to children's NTIS was severe infection (sepsis, sepsis, severe pneumonia, etc.), Chronic kidney disease, childhood leukemia and premature birth, which were different from those of adults. The data show that, except for premature infants, the thyroid function of children of all ages recovered with the recovery and recovery of basic diseases after discharge from NTIS, and thyroxine replacement therapy was not started during the course of the disease. In the preterm infants group, thyroid hormone replacement therapy was initiated during hospitalization.

Conclusion: The decrease of thyroid hormone level in children with critical illness is an adaptive protection.

P1-588

The effect of gestational Graves' disease on the mother-infant dyad: a retrospective observational cohort study

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Context: Pregnancy and parturition involve a complex interplay between maternal health and that of her offspring. Graves' disease and its management have been associated with adverse pregnancy, labor and delivery, as well as neonatal outcomes. Adaptation of the hypothalamic-pituitary-thyroid axis can be reflected by measuring thyroid function levels in newborn screening (NBS).

Objective: To investigate the characteristics of the mother-infant dyad of term infants born to mothers with Graves' disease.

Methods: The Israeli National NBS Program thyroid dataset was linked with the electronic medical records to generate a unified database of mothers and their term infants born between 2011 and 2021 at Lis Maternity and Women's Hospital, Tel-Aviv Sourasky Medical Center. The MDClone big data platform was utilized to extract maternal, pregnancy, disease course, labor and delivery, and neonatal characteristics from the medical records of mother-infant dyads. Dyads with maternal Graves' disease were compared to those of the general population.

Results: Out of 103,899 mother-infant dyads, 292 (0.3%) mothers had gestational Graves' disease. A forward multivariate linear regression demonstrated that Graves' disease (history and active) did not significantly affect NBS total thyroxine (TT4) levels (p=0.252). A subgroup analysis of infants born to mothers with active gestational Graves' disease exhibited higher NBS TT4 levels compared to the general population (p<0.001). Mothers with Graves' disease had higher rates of assisted reproductive technology utilization (12.7% vs 9.0%, p=0.012; OR 1.46 [95%CI 1.03–2.07], p=0.031), gestational hypertension (3.9% vs 1.1%, p<0.001; OR 3.53 [95%CI 1.92-6.47], p<0.001) and proteinuria (2.5% vs 0.9%, p<0.001; OR 3.03 [95%CI 1.43-6.45], p=0.004). They had higher rates of cesarean sections (26.4% vs 19.7%, p=0.029; OR 1.46 [95%CI 1.13-1.90], p=0.004), prelabor rupture of membranes (15.4% vs 4.1%, p<0.001; OR 4.3 [95%CI 3.13-5.91], p<0.001), and placental abnormalities (5.1% vs 2.0%, p<0.001; OR 2.64 [95%CI 1.57-4.44], p<0.001). Their infants had lower adjusted birthweight z-scores (-0.18±0.94 vs -0.03±0.90, p=0.007) and were more likely to be small for gestational age (12.0% vs 8.1%, p=0.005; OR 1.54 [95%CI 1.08-2.19], p=0.018). No differences in the infants' hospitalization venue or length of stay were observed.

Conclusions: Our findings demonstrate that neonatal thyroid function levels were affected by maternal Graves' disease only when the disease was active. Moreover, gestational Graves' disease was associated with an increased risk of adverse outcomes for the mother-infant dyad. Further research is needed to elucidate the role of neonatal thyroid secretion in modulating infants' metabolic outcomes.

P1-589

Thyrotropin receptor stimulating antibodies in pediatric patients with Graves' diseases using ultra-rapid turbo bioassay

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Background: Thyrotropin receptor (TSH-R) stimulating autoantibodies (TSAb) are present in 90-100% of patients with Graves' disease (GD). TSAb are functional, impact thyroid function, and are clinically relevant. This study we performed in a pediatric patients with dynamic of Graves' disease before and during methimazole therapy and in patient with Hashimoto's thyroiditis using a novel and ultra-rapid TSAb andTBAb bioassay.

Methods: All samples from AITD patients and healthy controls were tested with a new "TurboTM" TSAb & TBAb bioassay (Thyretain®, Quidel) with a readout that is based on a cyclic AMP-activated luciferase. The negative values for anti-thyroid receptor antibodies were: (< 0,024 IU/L) for Turbo TSAb and (< 40% Inhibition) for Turbo TBAb.

Results: Of 117, selected pediatric AITD patients (Graves' disease and Hashimoto thyroiditis), positive for TSAb and TBAb were 41 and 34 patients, respectively. Median age was 12 years (patients n=82 /controls n=35; 12/10.5 years) and female: male ratio was 1,65. Of 82 samples, 43 (52.5%), 30 (36,5%) and 7 (11%) were hyperthyroid, hypothyroid and euthyroid respectively.The TSH-R-Ab assays were negative in 35 healthy controls devoid of autoimmune thyroid and endocrine disorders. In the TurboTM cAMP TSAb assays was detected TSAb in 36 untreated GD patients (100%) and 3 treated by methimazole (27%) samples. The TurboTM TSAb bioassay highly correlated with thyroid function (p=0.028). Three of 82 (4%) samples showed dual TSH-R-Ab positivity in the Turbo TBAb and TSAb bioassays.

Conclusions: This is the largest reported collective of TSAb-positive samples in Graves' pediatric patients, measured by a rapid and reliable "TurboTM" TSAb bioassay. TSAb markedly affects thyroid function. Furthermore, the novel TurboTM stimulating bioassay is very useful for clinical utility in the monitoring of therapy of pediatric Graves' patients.

P1-590

Predictors of permanent and transient congenital hypothyroidism with eutopic thyroid gland

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Introduction: An increase in the incidence of congenital hypothyroidism (CH) with eutopic gland has been reported worldwide due to neonatal screening programs. Several studies have recently reported factors useful for predicting permanent CH (P-CH).

Objectives: To determine predictive factors that could distinguish between permanent and transient CH (T-CH) in patients with eutopic thyroid gland and normal neonatal screening.

Material and Methods: We conducted a retrospective study of patients diagnosed before 3 years of age with non-autoimmune CH and eutopic thyroid gland, born between 2002 and 2017. All patients were reevaluated from the age of 3, with TSH (µU/ml), T4L (ng/dl) (chemiluminescence), thyroid autoimmunity (anti-TPO and anti-TG), thyroid ultrasound and thyroid scintigraphy (I123). TSH>10 µU/ml was considered for initiation of treatment.

Exclusion criteria: gestational age <37 weeks, birth weight <1500g, congenital heart disease, Down syndrome, surgery, or admission to the NICU.

Variables analyzed were initial and reevaluation TSH and T4L levels, maximum dose of levothyroxine required, family history of thyroid disease, twin gestation, in vitro fertilization, intrauterine growth restriction, age at the first consultation, and age at initiation of replacement therapy. Statistical analysis was performed using SPSS.21. Considered statistically significant p<0.05.

Results: We included 47 patients of which 55.3% were male and diagnosed at a mean age of 12.10 months (SD: 10.16). After reevaluation, 27 patients (57.4%) required restarting levothyroxine treatment and were diagnosed of P-CH. The mean age at diagnosis was earlier in this group (mean: 10.40 months; SD: 8.91) (p=0.009).

We found higher initial TSH levels in P-CH (mean: 12.72 µU/ml; SD: 4.24) compared to T-CH (mean: 10.64 µU/ml; SD: 1.87) (p=0.02). We observed a trend toward a higher levothyroxine dose requirement in patients with P-CH (median: 3.00 µg/kg/day; IC range: 1.00) compared to those with T-CH (median: 2.50 µg/kg/day; IC range: 0.50) (p=0.06). We did not identify any differences in T4L levels at the beginning or throughout the follow-up process.

Moreover, 60.0% of patients with a personal history of twin gestation were diagnosed with P-CH. Similarly, 65.5% of P-CH had a family history of hypothyroidism, mainly maternal. However, sex, history of intrauterine growth restriction, or in vitro fertilization did not present any differences.

Conclusions: An earlier age of onset, higher TSH levels at diagnosis, higher levothyroxine requirements, family history of thyroid disease, and twin gestations may help predict P-CH in patients with eutopic thyroid glands.

P1-591

Health-Related Quality of Life in Patients Diagnosed with Childhood Primary Hyperthyroidism

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Background: Hyperthyroidism is a common condition in general pediatric practice. Several adult studies show hyperthyroidism affects health-related quality of life (HRQoL). However, information regarding HRQoL in the pediatric population is limited.

Objectives: To evaluate HRQoL and psychosocial functioning of patients diagnosed with childhood primary hyperthyroidism compared with healthy controls and to identify the possible risk factors of low HRQoL scores in these patients.

Methods: We performed a cross-sectional analysis, and participants with childhood primary hyperthyroidism were enrolled. The Pediatric Quality of Life Inventory 4.0 Scales (PedsQL4.0) was administered to participants and their caregivers for evaluating HRQoL. The psychosocial functioning was assessed by the Strength and Difficulties Questionnaires (SDQ). For comparison, the survey was also conducted on healthy children.

Results: Fifty-two patients with childhood hyperthyroidism and fifty-one healthy controls were included in this study. The mean score of the self-report total scale and all subdomains, except social functioning, of the patients were significantly lower than those of the controls. In contrast, only the score for emotional difficulties was substantially higher in the patient group, while the scores in all other domains of self-report SDQ were similar between the two groups. Multivariable linear regression analysis showed that only irregular menstruation and clinical diarrhea were significant risk factors influencing the HRQoL score of patients. The levels of anti-TSH receptor antibody (TRAb) were negatively correlated with the self-report total HRQoL scores of the patients.

Conclusions: We found that hyperthyroidism had a negative impact on the quality of life of children with primary hyperthyroidism. This impact persists many years after diagnosis and during treatment. Therefore, in addition to physical health, physicians should also monitor the quality of life in this group of patients.

P1-592

Effect of iodinated contrast on the thyroid function in young children

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Background: Hypothyroidism is a well-known treatable cause of global developmental delay in developing children. In recent years contrast imaging studies are much more commonly employed as diagnostic means in the treatment of various pediatric conditions.

In 2022, the FDA issued a warning recommending thyroid function monitoring in babies and young children who receive injections of iodine-containing contrast media(ICM) for medical imaging. They recommend the thyroid function to be checked within 3 weeks of exposure to ICM. This is based on several studies observing hypothyroidism in children after iodinated contrast use. The pathophysiology is believed to be due to a prolonged Wolff-Chaikoff effect, an autoregulatory phenomenon in which the thyroid gland inhibits thyroid hormone synthesis within the follicular cells after the body is exposed to a large amount of iodine. The immaturity of the young children's thyroid tissue is believed to lack the ability to "escape" the Wolff-Chaikoff effect and hence the patient develops prolonged hypothyroidism.

Methods: This is a retrospective single-center study. A clinical workflow was adopted in the territory-wide pediatric hospital of Hong Kong in patients from birth – 3 years of age, where their blood thyroid function test (TSH and free T4) were checked 3 weeks after they have been administered ICM in contrast CT or contrast angiography exam in the radiology department. This includes patients from all subspecialties. The blood results are retrospectively collected and analysed to identify the prevalence of abnormal thyroid function test.

Results: A total of 117 imaging episodes were performed within a 5 month period. 49% are boys and 51% are girls. Mean age of the patient cohort is 17.7 months (SD +/- 12.5months). 81 patients were scanned. 6 (7.4%) patients with abnormal thyroid function test were identified. 1 (1.2%)of them developed persistent hypothyroidism requiring thyroxine treatment. 2(2.5%) of them had their thyroid function test repeated 2 weeks later which subsequently normalized. 3(3.7%) cases with abnormal thyroid function test were lost to follow-up.

Discussion: The results of this retrospective study shows that young children are indeed prone to develop hypothyroidism after exposure to ICM. Clinicians are recommended be wary of this risk and monitor susceptible patient groups accordingly. It is also worthwhile for clinicians and radiologists to consider this extra layer of risk against the benefit of perform contrast-enhanced imaging studies for young patients.

P1-593

Congenital malformations in permanent and transient congenital hypothyroidism – prevalence and etiology

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Background: An increased prevalence of extra-thyroidal congenital malformations in infants with congenital hypothyroidism

(CH) is well established. However, accurate estimation of prevalence figures requires careful distinction between permanent and transient CH. Moreover, the mechanisms resulting in congenital malformations are not well understood.

Study aim: To estimate the prevalence of cardiac, extra-cardiac and/or syndromic malformation in permanent and transient CH; and to compare patterns and prevalence of malformations in proven thyroid dysgenesis (thyroid ectopia, athyreosis, and thyroid hypoplasia in situ) with thyroid dyshormonogenesis.

Methods: Thyroid status of all newborn screening referrals in Scotland from August 1979 to December 2015 were reviewed. Information on patients in whom status remained uncertain was updated via clinical electronic medical records, and by contacting the appropriate paediatricians.

Results: Of 903 infants referred during the study period permanent CH was confirmed in 661 (73.2%) and transient CH in 218, while status remains uncertain in 22, of whom 14 died before a definitive diagnosis could be made. Malformations were present in 68 (10.3%) permanent, 61 (27.9%) transient and 15 (68.2%) Status Uncertain patients. These prevalence figures fell to 8%, 21.1% and 54.5 % after excluding 15, 15, and 3 patients with Down syndrome.

Malformations and/or syndromes in the 55 transient CH patients comprised cardiac (n=11), extra-cardiac (18) and both (11), with Down syndrome in 15. These patients with transient CH were usually categorised as ‘sick’ at the time of screening.

Of 241 patients with proven dysgenesis on thyroid imaging, 17 (7.05%) had malformation and/or syndromes: cardiac (n=3 [17.6%]), extracardiac (e.g. skeletal) (n=8 [47%]), syndromic (n=6 - Down syndrome n=2, Sotos syndrome n=1, unclassified syndrome n=1). Of 75 patients with dyshormonogenesis 11 (14.6 %) had malformations, comprising cardiac (n=3), extracardiac (n=3) including sisters with metaphyseal dysplasia, and Pendred syndrome (n=2).

Conclusions: Prevalence figures for permanent and transient CH will vary from study to study since they are influenced by syndromic disorders, notably Down syndrome; and the duration of follow-up, since definitive categorisation may take years to establish; while status will remain uncertain in some patients. Mechanisms for transient CH include the effect of factors associated with ‘sickness’ on thyroid function. In thyroid dysgenesis, congenital malformations could result from the teratogenic effect of gene defects and syndromic disorders on both thyroid and extra-thyroidal tissues. By contrast, extra-thyroidal malformations in dyshormonogenesis may reflect the effect of separate recessive genes which have also been inherited from the parents.

P1-594

The relation between psychiatric symptoms and quality of life in children with Graves’ Disease

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Introduction: Graves’ disease (GD) is the most common cause of the hyperthyroidism in children and adolescents. Patients may present with norological, ophtalmological, cardiovascular and psychiatric symptoms. The aim of this study is to present the sociodemographic data (age, gender, etc.), clinical findings, quality of life and psychiatric symptoms of the children diagnosed with Graves’ disease and compare these data with the control group matched as same age and gender.

Material-Methods: This is a case-control study involving 16 patients with GD (81% were female, mean age 15.1 ± SD 2.2 years) and 29 healthy controls (69% were female, mean age 14.6 ± SD 2.2 years). Sociodemographic form, quality of life scale, Anxiety Depression Scale, Strengths and Difficulties Questionnaire, Turgay’ Scale to assess attention deficit and disruptive behavior disorders, Emotional Reactivity Index scale to assess irritability were applied to children and parents.

Results: There was no significant difference between patients with GD and controls in terms of quality of life (child and parent forms), anxiety and depression scores in child and parent evaluations. Patients with GD achieved higher scores in the evaluation of emotional reactivity (parents form), strengths and difficulties questionnaire (parents form), and Turgay scale (p values 0.039; 0.009; 0.023, respectively). Although no significant difference was found in attention deficit and hyperactivity scores in Turgay scale sub-scores, significantly higher scores were found in oppositional defiant and conduct disorder scores (p values were 0.172; 0.294; 0.019; 0.027, respectively). There was no relationship between free T3, free T4, ophthalmopathy, goiter and these results in patients with GD.

Conclusion: Irritability, oppositional defiance symptoms and behavioral disorder symptoms were detected in children with Graves’ disease. It has been observed that these accompanying psychiatric symptoms result in emotional and behavioral difficulties in children’s lives. So, it is important to follow up the children with Graves’ disease in terms of possible accompanying mental disorders and to handle them in a multidisciplinary team.

P1-595

A Case report of papillary thyroid carcinoma diagnosed at an early age

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Introduction: Thyroid cancers are rare malignancies in childhood and their incidence is between 1.5-3% among all childhood cancers. Papillary thyroid cancer (PTC) constitutes more than 90% of childhood thyroid cancers. Risk factors for thyroid cancer include; There are iodine deficiency, radiation exposure, radiotherapy to the head and neck region, and genetic predisposition. We will present an 8-year-old case who presented with a complaint of neck swelling and was found to have papillary thyroid carcinoma as a result of the examinations.

Case: An 8-year-old female patient presented with a swelling in the neck that appeared 1 month ago. No features were found in the resume and family history. On physical examination, height: 135.6 cm (sds: 0.97); weight:30 kg (sds:0.51); body mass index: 16.3; Thyroid grade 3 palpable; S1+ S2+ rhythmic, T1 P1 detected. In the examinations of the patient, fT3: 4.65 ng/dl, fT4: 1.1 ng/dl, TSH: 3.69 mIU/L, thyroglobulin: 421 ng/dl. Thyroid USG results taken in an external center: 6x2.5x4 cm solid formation containing dense vascular multiple punctate calcifications in the right thyroid lobe, 19x14.5x23 mm in size in the inferior of the left thyroid lobe, hypoechoic suspicious spherical lymph node showing peripheral vascularization and reaching 25x12 mm in the right supraclavicular area. A peripheral suspicious pathological lymph node with moderate vascularization, whose central fatty hilum could not be discerned, was detected. Thorax CT: Nodular lesions were observed in both lungs, which may be significant in terms of multiple millimetric metastases. Thyroid FNAB pathology resulted as papillary thyroid carcinoma. Total thyroidectomy and lymph node dissection were planned by the pediatric surgeon. During the operation, thyroid right lobectomy, isthmusectomy, modified radical cervical lymph node dissection were performed due to recurrent laryngeal nerve tumor invasion. Complementary left lobectomy left modified radical cervical lymph node dissection was performed in the patient who had no signs of laryngeal nerve damage in the follow-up. Pathology report: Thyroid papillary thyroid carcinoma, diffuse sclerosing variant was detected.

Radioactive iodine was planned due to distant metastasis. 100 mci RAI treatment was given by the Nuclear Medicine Department. The patient's follow-up continues with the Department of Pediatric Endocrinology, Pediatric Surgery and Nuclear Medicine.

Conclusion: Papillary thyroid carcinoma is rare in childhood. Papillary thyroid carcinoma seen in children has a more aggressive course compared to adults, and lymph node metastases, extension outside the thyroid, and lung metastases at the time of diagnosis are more common than adults.

P1-596

Graves Disease - Longer Term Impact on BMI

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Background: Graves' Disease (GD) is the most common cause of hyperthyroidism in children and develops because of stimulation of the thyroid gland by TSH receptor auto-antibodies (TSHR Ab). An increased risk of obesity has been described in both adults and children following initiation of anti-thyroid drug (ATD) therapy but the longer term impact of GD and it's treatment on physique in children is unclear.

Aims: To assess the BMI of children from 2 tertiary centres in the UK after the first year of treatment and on completion of growth.

Methods: Retrospective case review (2010-2022) of children and young people with GD (positive TSHRAb titres) seen in two paediatric centres in England. Electronic records assessed for thyroid function, height and weight (at diagnosis, 12 months post-diagnosis and most recent). Patients were excluded if pertinent data was not available at diagnosis or 12 months post ATD initiation. Values given are median (range).

Results: 73 patients were assessed (19M: 54F). Age at diagnosis was 13 years (3-17) and age at most recent assessment 16 years (7-22). Patients were White British (n= 48, 65%), Asian (n=17, 23%), Black (n=6, 8%) and mixed race (n=1, 1%). Time to TSH normalisation was 7 months (1.3-43). The duration of follow up was 3 years (1-12). Most children (81%, n=58) received dose titration anti-thyroid drug (ATD) and 18% (n=13) received block and replace. 19 patients remitted off ATD. 3 (4%) received Radio-Iodine and 21 (29%) received thyroidectomy as definitive treatment. 41% (n=30) remain on ATD. The BMI SDS at initial assessment was 0.04 (-4.6-3.5) which was significantly lower ($p < 0.05$) than at 12 months post diagnosis (median 0.6, range -2.74-3.78) and the most recent assessment BMI SDS 0.7 (-3.6-3.9). There was no difference between 12 months post ATD start and most recent BMI SDS ($p > 0.05$). Importantly, median BMI SDS remains within normal range throughout follow-up. 11/73 patients were overweight/obese (BMI > 2.0) at final assessment, 8 (73%) of whom were > 14 years at diagnosis and 2 (18%) who had other conditions predisposing to obesity including Trisomy 21.

Conclusions: We show that although BMI SDS increases from diagnosis through to final height assessment, most excessive weight gain occurs at an early stage and most young people achieve a normal BMI SDS at near adult height (NAH). The risk of sustained excess weight is higher in adolescents who have achieved NAH at diagnosis vs younger children.

Late Breaking

LB1

Familial hCG Syndrome in two Chinese Families with elevated hCG level concurrently in blood and cerebrospinal Fluid

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Background: Familial hCG syndrome is a rare and benign cause of elevated serum beta human chorionic gonadotropin (β- hCG), moreover, elevated β-hCG in cerebrospinal fluid (CSF) has never been reported in familial hCG syndrome .

Object: To report the two Chinese families of familial hCG syndrome with elevated β-hCG concurrently in blood/CSF.

Method: We described the clinical data of 2 cases of familial hCG syndrome in our department in Dec 2020 and Dec 2021, respectively, and reviewed the relative literatures.

Result: Case 1 and case 2 were apparently healthy girls (8y9m, 8y5m) born to non-consanguineous parents from two unrelated families. They were locally diagnosed as central precocious puberty (CPP) and partial CPP at the age of 8y2m and 8y3m, respectively, for early breast development and referred to our hospital both for elevated serum β-hCG level. Serum β-hCG levels(Abbott) were elevated with higher CSF β-hCG levels (Case 1: 45.58 vs 103.22mIU/mL; Case 2: 36.8 vs 139.51 mIU/mL) with normal AFP levels. Whole body positron emission tomography-computed tomography, magnetic resonance imaging of the head, chest, abdomen and pelvis revealed nothing except pineal cyst in Case 1. In case 1, intracranial non-germinomatous germ cell tumor(INGGCT) was diagnosed, and combination chemotherapy was initiated with GnRHa therapy for CPP. Because of unchangeable serum and CSF β-hCG levels after four course, she went to another brain hospital, where radiotherapy and subsequently pinealectomy (without GCT pathological characteristics) were performed without any β-hCG response either. Considering benign condition, we detected her two younger brothers and parents and found elevated β-hCG level in her mense-regular mother and one non-precocious younger brother (64.58 and 43.79 mIU/mL, respectively). Whole exon sequencing was negative. Familial hCG syndrome was finally diagnosed. With the first case experience, in case 2, we soon started to detect β-hCG in the family without initiation of chemotherapy, with the finding of elevated β-HCG in other 3(father, old sister, and grandmother) of 5 of the asymptomatic relatives (parents, sisters, grandparents) (46.13, 55.51, and 89.70 mIU/mL, respectively), with higher CSF level(146.18 mIU/mL) in the father who accepted lumbar puncture. Familial hCG syndrome was also diagnosed. Both of the two family were greatly relievedly.

Conclusion: We firstly report two rare families of familial hCG syndrome with simultaneous elevation of hCG in peripheral blood and cerebrospinal fluid, which broadens the clinical spectrum of familial hCG syndrome.

LB2

Denosumab in the treatment of paediatric hypercalcaemia

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Background: Hypercalcaemia has various etiologies and treatment is often challenging. Therapeutic options include aggressive fluid management, loop diuretics and antiresorptive drugs. Since both hypercalcaemia and bisphosphonates can cause acute kidney injury (AKI), bisphosphonates are not recommended in patients with renal impairment. Denosumab, an antiresorptive human monoclonal antibody, is not associated with AKI and offers a temporary treatment option. However, osteoclastic activity will recover after a few weeks to months with the risk of rebound hypercalcaemia. Treatment of hypercalcaemia with denosumab in the setting of renal impairment may be an alternative to bisphosphonates.

Methods: We reached out to international colleagues, including the ESPE working group on bone and growth plate, experienced with the use of denosumab for hypercalcaemia in paediatrics and collated cases using a custom-made case report form.

Results: Five patients were included in the analysis, with a mean age of 12 years (range 8.2 to 17.7). Indications for denosumab were hypercalcaemia secondary to immobility (n=2), malignancy (n=1), sarcoidosis (n=1) and an undiagnosed genetic condition (n=1). All had renal concerns, including AKI (n=3), solitary kidney (n=1) or bilateral dysplastic kidneys (n=1). The mean serum calcium level before denosumab administration was 3.51 mmol/l (range 3.27 to 3.81) and all patients were vitamin D replete. Denosumab was given at a mean dose of 1.36 mg/kg (range 0.25 to 2.9). Mean time to normalization of serum calcium was three days (range 2 to 4). One patient developed hypocalcaemia (serum calcium 1.7 mmol/l), which resolved by intravenous calcium infusion and oral calcitriol. In one patient hypercalcaemia recurred 47 days after the first denosumab dose (serum calcium 3.84 mmol/l). This patient received a second dose of denosumab 60 days after the first and three months later two sealing doses of zoledronic acid (first dose 0.0125 mg/kg, second dose 0.02 mg/kg) 25 days apart. Two patients stayed normocalcaemic. In two patients, no statement can be made regarding recurrence of hypercalcemia, since they died of their underlying condition.

Discussion: Denosumab effectively lowered serum calcium in all hypercalcaemic patients, but the interindividual dosages used were quite different. Whether recurrence of hypercalcaemia in one of the patients was due to rebound phenomenon or because the underlying cause had not resolved remains unclear. More research is needed to explore safety, dosing and management of hypercalcemia, and of rebound hypercalcaemia, for the paediatric use of denosumab.

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LB3

Congenital Hyperinsulinism due to ABCC8/KCNJ11 mutations and the long-term outcome - a single center experience

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Hyperinsulinism is a common cause of persistent hypoglycemia beyond infancy. Mutations in the ABCC8/KCNJ11 genes are the most common aetiology of congenital hyperinsulinism (CHI), leading to KATP channel mutation. This results in an inappropriate insulin secretion irrespective of hypoglycaemia.

This is a cross-sectional study of the patients attending the paediatric endocrinology unit at the National Centre for Child Health & Development (NCCHD), Tokyo, Japan from March 2022 to March 2023. Only the patients who had a genetic study done were included in this study. The aim of our study is to analyze the patient characteristics of ABCC8/KCNJ11 genetic mutations and the long-term outcome.

There was a total of 31 patients, with 17 (54.8%) patients who were male. The mean age was 10.56 (2.30 – 31.75) years old and the majority of the patients were of Japanese ethnicity, 29 (93.5%). The mean birth weight was 3.53 kg (1.98 – 5.12). There was a total of 16 (51.6%) patients were positive for ABCC8/KCNJ11 mutations. Among the other positive genetic mutation detected in our cohort includes 2 (6.5%) GLUD1 mutation, UPD11 mutation 4 (12.9%), KMT2D 1 (3.2%) while others were negative 8 (25.8%).

Among the patients with ABCC8/KCNJ11 mutations – 9(56.3%) were male, and 14 (87.5%) were Japanese. Among the patients who were born with a birth weight of 4 kg and above, 8 (72.7%) of the patients had ABCC8/KCNJ11 mutation. F-DOPA-PET scan was performed in 13 (81.3%) patients with ABCC8/KCNJ11 mutations. The imaging findings of these patients were diffuse in 4 (25.0%) patients. Others had localized findings including 4 (25.0%) in body and tail, 1 (6.3%) in the focal body, 1 (6.3%) in the focal head, and 1 (6.3%) patient with multifocal distribution in the pancreas. Among the ABCC8/KCNJ11 patients, 9 (56.3%) underwent pancreatectomy and the rest were managed with medications only. Currently, 10 (62.5%) of the ABCC8/KCNJ11 patients still have persistent disease. With regards to long-term complications, among the patients with ABCC8/KCNJ11 mutation, 2 (12.5%) patients had neurological complications, 1 (100%) has pancreatic insufficiency, and for diabetes and dysglycaemia, there were 4 and 2 patients respectively (31.3% altogether).

In conclusion, ABCC8/KCNJ11 mutation is a common mutation among the persistent CHI in our cohort. A low threshold for genetic testing can be considered among the persistent CHI patients who were macrosomic as ABCC8/KCNJ11 mutation need to be suspected. Furthermore, the genetic result is helpful to plan for the management of the patients with ABCC8/KCNJ11 mutation.

LB4

A novel variant in *PRKAR1A* at the exon-intron border leads to aberrant splicing in patients affected by carney complex

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Carney complex 1 (CNC, OMIM# 160980) is an autosomal-dominantly inherited complex tumor predisposition syndrome associated with skin pigment abnormalities and neoplasms of heart, endocrine glands and other organs. CNC is caused by heterozygous constitutional loss-of-function variants in the *PRKAR1A*-gene. *PRKAR1A* codes for the cAMP-dependent protein kinase type I-alpha regulatory subunit, an enzyme that represents an integral part of protein kinase A (PKA) that is involved in inter- and intracellular signaling. We present a case series of four related female individuals (mother and three daughters) carrying the same novel heterozygous intronic *PRKAR1A*-variant NM_002734.4: c.-7+1del, p.(?). The variant was identified by targeted genetic investigation of the youngest daughter (born 2005) after a diagnosis of an ACTH independent Cushing's syndrome at the age of 13 in line with bilateral adrenocortical micronodular hyperplasia that was treated successfully by bilateral adrenalectomy. The girl did not show any dermal or other clinical manifestations of CNC. Thorough investigation of the family history revealed that the mother also has a history of Cushing's syndrome but is otherwise affected rather mildly at the age of 49. The other two daughters (twins born 2002) do not show any manifestations of CNC.

Since the identified variant is located at the first exon-intron border an effect on splicing was suspected. RNA from patient's and control blood samples have been investigated and a set of different transcripts was identified, one of which is exclusively identified in patient's RNA. Sequencing analyses of this transcript predicted three putative start codons upstream of the native start codon due to a partial intron retention. To further investigate whether the use of any of these start codons might result in translation of an aberrant protein, the transcript was inserted into a pEGFP-N3 expression vector. After transfection of HEK293 cells EGFP-fusion proteins were visualized by fluorescent microscopy and western blot analyses confirmed the presence of the fusion protein with the predicted mass weight. The aberrant transcript was degraded in patient's blood cells but degradation could be inhibited by with puromycin which blocks nonsense-mediated decay.

In summary, functional evidence for the identified non-coding variant to be causative for carney complex in the affected individuals is presented. The rather mild manifestation in the mother and (so far) incomplete penetrance in the family reflects the underlying pathogenic mechanism of the variant generating at least one aberrant *PRKAR1A*-transcript resulting in a reduction of the functional gene product.

LB5

Clinical phenotyping of patients with genetic obesity

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Introduction: In rare cases of obesity, genetic defects lead to hyperphagia and severe early-onset obesity. Genetic testing in patients with a suspected genetic obesity phenotype is important, as it can lead to patient-tailored treatment advice. For children, the Endocrine Society (ES) recommends genetic testing in children with early-onset of obesity (<5 years) and hyperphagia. It is unclear whether these recommendations can also be used in adult obesity care. Therefore, we aimed to phenotype adult patients with genetic obesity disorders. In addition, we assessed the suitability of the pediatric ES recommendations in these patients.

Methods: We analyzed clinical data of patients with non-syndromic genetic obesity (NSO) and syndromic genetic obesity (SO), who visited our academic obesity center (Erasmus Medical Center, Rotterdam, the Netherlands). A standardized medical questionnaire, including topics concerning e.g. age of onset of obesity, hunger and satiation, was assessed. Anthropometrics, body composition (bio-impedance analysis), and resting energy expenditure (REE, indirect calorimetry) were measured. Differences between the NSO and SO groups were studied.

Results: Seventy-one patients, of which n=29 with NSO and n=42 with SO, were included: median BMI and age at intake were 40.9 vs 39.6 kg/m2 and 25.5 vs 24.8 yrs, respectively (ns). The median age of onset of obesity was 3.0 [1-5] yrs in NSO and 9.5 [4-143 yrs in SO (p<0.001). Impaired appetite regulation was present in both groups: increased feelings of hunger in 65.5 vs 61.0% and impaired satiation in 54.2 vs 51.4% in NSO vs SO (ns). Binge eating was reported in 63.4% of SO, compared to 41.4% in NSO (p=0.071). The pediatric ES recommendations were fulfilled in 58.6% of NSO and 28.6% of SO (p=0.011). Compared to NSO, SO had a higher prevalence of intellectual deficit (3.4 vs 57.1%, p<0.001), autism (6.9 vs 26.8%, p=0.035) and retinal problems (0 vs 19.0%, p=0.013). There were no differences in body composition or REE.

Conclusion: We report evident differences in phenotypic features such as the age of onset of obesity, appetite regulation, and the presence of intellectual deficit, autism and retinal problems in adults with non-syndromic genetic obesity and syndromic genetic obesity. Additionally, this study demonstrates that the Endocrine Society's recommendations for genetic testing in children with obesity, are too strict for adults with obesity. Recommendations for genetic testing in adults with obesity are needed.

LB6

A concomitant increase in thinness and weight excess in Brazilian schoolchildren: evaluation from 2010 to 2022

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Introduction: The Body Mass Index (BMI) is an essential indicator for the nutritional assessment of children and reflects the exposure to health conditions that are harmful to the development of this population.

Objective: To analyze the temporal trends of the BMI of Brazilian children aged 5-10 between 2010 and 2022.

Patients and Methods: Descriptive ecological study. Data obtained from e-SUS Primary Care. The BMI categories evaluated were: severe thinness (ST), thinness (T), eutrophy (E), overweight (OW), obesity (OB), and severe obesity (SOB). The prevalence rate, the annual percentage changes (APCs), and its trend were calculated by segmented linear regression. Time series analysis performed in Joinpoint version 4.9.

Results: On average, 3.7 million schoolchildren were assessed each year of the historical series. In the evaluation of the country, we observed a growing character of the categories "OW," "OB," and "SOB" (APC:0.78; p=0.007; APC:3.65; p=<0.001 and APC:2.4; p =0.022, respectively), "E" was stationary until 2020 (APC: -0.66; p=0.483) and decreasing since then (APC: -20.3; p=<0.001), while "ST" dropped (APC: -4.82; p=<0.001). In the Midwest region, "T" was stationary until 2017 (APC: -2.06; p=0.088) and increasing since then (APC:3.9; p=0.020). In the South region, "T" showed a decreasing character until 2017 (APC: -2.49; p=0.006) and an increasing character from 2017 (APC:3.7; p=0.003). In the Northern region, "SOB" showed a stationary character until 2018 (APC: -2.85; p=0.110) and an increasing tendency between 2018 and 2022 (APC:10.2; p=0.029).

Discussion: The growing nature of "OW," "OB," and "SOB" in Brazil suggests the inadequacy of the nutritional offered to this population, with hypercaloric diets associated with a sedentary lifestyle. Surprisingly and contradictory, we observed an increase in "T" in the Midwest and South regions in the last five years, highlighting the nutritional disparities in our country. The concomitant increase in "SOB" and "T," and reduction in "E" from 2020 onwards, is interpreted as a possible reflection of the increase in vulnerabilities with the onset of the Sars-Cov-2 pandemic.

Conclusion: Our data demonstrate the nutritional fragility of Brazilian students, as trends reveal malnutrition with an increase in dietary extremes and a reduction in eutrophy. Significant regional differences and the need to adopt public health policies for each region group are highlighted.

LB7

Hypercalcemia in children: experience from a single center

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Purpose: This study aimed to profile children diagnosed with hypercalcemia of different etiologies at a single center.

Method: We retrospectively reviewed 13 children diagnosed with hypercalcemia of different etiologies.

Results: We describe 13 pediatric cases, aged 4 months to 12 years old (median age: 8 months), diagnosed from 2018 to 2021. Six males and seven females were included, with varied clinical presentations across departments. The most common etiology was malignant tumors (6/13), including one parathyroid carcinoma, one neuroblastoma, three leukemias, and one ovarian malignant tumor. Genetic disorders were the second most common cause (5/13), including glycogen storage disease type I, hypophosphatasia caused by ALPL gene mutation, idiopathic infantile hypercalcemia (IIH) caused by CYP24A1 gene mutation, hypocalciuric hypercalcemia caused by CaSR gene mutation, and infantile hypercalcemia caused by SLC34A1 gene mutation. Except for one child with parathyroid carcinoma, all had high serum calcium levels and normal or lower serum parathyroid hormone (PTH) levels.

Conclusions: Hypercalcemia is a rare condition in childhood. The etiology of hypercalcemia in children can differ by age and include a broad differential diagnosis. All forms of hypercalcemia should be interpreted according to the serum PTH level. The vast majority of hypercalcemia that occurs in childhood is PTH-independent and is attributed to genetic disorders in infants and malignant tumors in older children and adolescents. As untreated hypercalcemia can have a profound impact on a child's growth and development, it is important to have a prompt diagnosis and intervention.

LB8

Mutant MCM8 induces apoptosis and S Phase Arrest in Premature Ovarian Insufficiency

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Keywords: Primary ovarian insufficiency; Microsomal maintenance complex 8; Cell apoptosis; Cell cycle; PI3K/AKT

Background: Primary ovarian insufficiency (POI) with a chromosome karyotype of 46,XX in children, compared to adults, is difficult to diagnose and often seek medical attention due to delayed puberty or short stature. We have reported the two novel pathogenic mutations p.C242R and p.S445*of MCM8 gene in a pedigree of POI, characterized by a gradual decline of ovarian function in childhood.

Purpose: To explore the effects of MCM8 mutations on DNA damage repair, apoptosis, and cell cycle function, and clarifying the signal pathway mechanism related to POI induced by Mutant MCM8.

Methods: Construction overexpression plasmids of compound mutant C242R-S445* of MCM8 gene in Hela cells. Screening differential interacting proteins by immunoprecipitation (CoIP) combined with mass spectrometry (LC-MS/MS). Differential interaction genes were screened through Cut&tag-mRNA-seq cross-linking analysis. The expression of meiotic homologous recombinant repair proteins, the apoptosis and cell cycle proteins were detected by Western blotting. The flow cytometry was used to detect the cell cycle and cell apoptosis. Positive and negative COIP were used to verify MCM8 differential protein interaction.

Results: The delayed recovery of expression of meiotic repair proteins RAD51 and DMC1 suggests that the C242R-S445* mutation interferes with the meiotic homologous recombination repair pathway of DMC1-RAD51.

Forward and reverse COIP validation confirmed that the interaction between mutant MCM8 and MCM6 is enhanced during the DNA repair phase. During the DNA repair phase, the G1 phase was significantly decreased, the S phase was significantly increased, the expression of CyclinD1 was downregulated, while the expression of CyclinA2 and CyclinB1 was sustained, suggesting that the S phase was stagnant. The downregulation of Bax and Capase3 expression was delayed compared with wild type, indicating the persistence of apoptosis.

Cut&tag-mRNA-seq cross-linking analysis revealed the PI3K/AKT pathway may be inhibited. The genes involved in signal pathways such as PI3K/AKT/Bcl-2 is related to the mechanism of cell apoptosis, and PI3K/AKT/Cyclins is related to cell cycle.

Conclusion: Mutant MCM8 interferes with the meiotic recombination repair DMC1-RAD51 pathway, delaying DNA damage responses, which interacts with MCM6 to block the S phase of the cell cycle, and continuously activate the Bcl-2/Bax/Caspase 3 mitochondrial apoptosis pathway. It is speculated that mutant MCM8 interferes with the PI3K/AKT pathway, inducing cell cycle arrest and apoptosis.

LB9

Clinical Characteristics and Long-Term Management for Patients with Vitamin D-dependent Rickets Type II: A Retrospective Study in Saudi Arabia

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Background: Hereditary Vitamin D-Resistant Rickets (HVDRR) is a rare autosomal recessive disorder caused by mutations in the vitamin D receptor (VDR) resulting in end organ resistant to 1a,25-dihydroxyvitamin D, [1,25(OH)2D]. Majority of HVDRR has Elevated 1, 25(OH)2D which is a hallmark for diagnosis of this disease. High doses of vitamin D, oral calcium and most importantly IV calcium infusion are the mode of therapy in HVDRR.

Aim of study: To evaluate the clinical characteristics, molecular genetics etiology and long term outcome of the largest group of patients with Hereditary Vitamin D-dependent rickets (HVDRR) in Saudi Arabia

Methods: We conducted a retrospective chart review and patient interview to collect the clinical, biochemical and genetic data for all Vitamin D dependent rickets type 2 patients who are currently receiving treatment at King Faisal Specialist Hospital.

Results: We had a total of 42 patients with 57% female and 42 % male, 7 patient treated with high does of oral calcium while 35 of them treated with IV calcium. The median age at presentation is 15.5 months. Alopecia found in 97.61 %, 21.42% presented with bowing legs, 14.28% delayed walking, 9.52% seizure and 2.38% presented with respiratory failure while family history of the disease was positive in 71.42% of total patients.

The molecular genetic test for VDR gene showed 4 common mutations (p.Y295* c.885C>A, p.R30* c.88 C>T, p.I268T c.803 T>C, p.V346M c.1036G>A)

Conclusion: We are describing the largest cohort of patients with HVDDR, their clinical biochemical and genetic data. We noticed their good response to IV calcium, also we identified the commonest genetic mutation in our HVDDR patients.

LB10

FTO-mediated m6A modification of BDNF enhances GnRH expression during puberty onset via activating PI3K/AKT signaling

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Background: The etiology of central precocious puberty (CPP) still remains unknown. The abnormal expression of Fat mass and obesity-associated (FTO)-mediated N6-methyladenosine (m6A) has been confirmed to play the crucial roles in CPP. This study aimed to explore the mechanism of FTO-mediated m6A modification of brain-derived neurotrophic factor (BDNF) on CPP with puberty onset.

Methods: The qRT-PCR and immunofluorescence were carried out to confirm the expression and location of BDNF at different development stages in female rats. The levels of BDNF in peripheral serum was detected by ELISA. Methylated RNA immunoprecipitation sequence (MeRIP-seq), Dual luciferase reporter and RNA stability assays confirmed the interaction between BDNF and FTO. FTO-mediated m6A modification of BDNF on PI3K/AKT pathway were detected by Western blotting.

Results: In female rats, the level of BDNF in hypothalamus increased gradually with puberty. BDNF and GnRH were colocalized in the hypothalamic arcuate nucleus (ARC). Peripheral serum BDNF increased abnormally in girls with CPP. Overexpressing or knockdown BDNF in GT1-7 cells showed that BDNF positively regulate the expression of GnRH. MeRIP-seq analysis showed that m6A methylation of BDNF decreased significantly in pubertal female rats' hypothalamus. Dual luciferase reporter gene test confirmed that FTO could regulated m6A demethylation of BDNF and promoted BDNF expression. And FTO could enhance the stability of BDNF by the m6A modification. Up-regulating FTO expression could activate the BDNF/PI3K/AKT signaling pathway in GT1-7 cells and female rats' hypothalamus.

Conclusion: This study revealed that FTO-mediated m6A modification of BDNF could enhance GnRH expression and accelerates puberty onset by activating PI3K/AKT pathway.

LB12

Dysregulated adipose tissue expansion and impaired adipogenesis in Prader-Willi syndrome children before obesity-onset

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Objective: Prader-Willi syndrome (PWS) is a rare genetic imprinting disorder resulting from the expression loss of genes on the paternally inherited chromosome 15q11-13. Early-onset life-thriving obesity represents the PWS clinical hallmarks. The non-coding RNA gene SNORD116 within the minimal PWS genetic lesion plays a critical role in the pathogenesis of the syndrome. Despite advancements in understanding the genetic basis for PWS, the pathophysiology of obesity development in PWS remains largely uncharacterized. Here, we investigated the signatures of adipose tissue development and expansion pathways and associated adipose biology in PWS children without obesity-onset at an early stage, mainly from the perspective of the adipogenesis process, and further elucidated the underlying molecular mechanisms.

Methods: We collected inguinal white adipose tissues (ingWATs) from phase 1 PWS and healthy children with normal weight. Adipose morphology and histological characteristics were assessed. Adipose stromal vascular fractions (SVFs) were isolated and used to determine the capacity and function of white and beige adipogenic differentiation. High-throughput RNA-sequencing

(RNA-seq) was performed in adipose-derived mesenchymal stem cells (AdMSCs) to analyze transcriptome signatures in PWS subjects. Transient repression of SNORD116 was conducted to evaluate its functional relevance in adipogenesis.

Results: In phase 1 PWS children, impaired white adipose tissue (WAT) development and unusual fat expansion occurred long before obesity onset, which was characterized by the massive enlargement of adipocytes accompanied by increased apoptosis. White and beige adipogenesis programs were impaired and differentiated adipocyte functions were disturbed in PWS-derived SVFs, which were consistent with the results of RNA-seq analysis of PWS AdMSCs. We also experimentally validated disrupted beige adipogenesis in adipocytes with transient SNORD116 downregulation. The transcript and protein levels of PPARγ, the adipogenesis master regulator, were significantly lower in PWS than in control AdMSCs as well as in SNORD116 deficient AdMSCs/adipocytes than in scramble (Scr) cells, resulting in the inhibited adipogenic program.

Conclusions: Imbalance in the WAT expansion pathway and developmental disruption are primary defects in PWS displaying aberrant adipocyte hypertrophy and impaired adipogenesis process, in which SNORD116 deficiency plays a part. Our findings suggest that dysregulated adiposity specificity existing at an early phase is a potential pathological mechanism exacerbating hyperphagic obesity onset in PWS. This mechanistic evidence on adipose biology in young PWS patients expands knowledge regarding the pathogenesis of PWS obesity and may aid in developing a new therapeutic strategy targeting disturbed adipogenesis and driving WAT plasticity to combat abnormal adiposity and associated metabolic disorders for PWS patients.

LB13

Low-Dose Liraglutide-Induced Acute Kidney Injury and Hepatocellular Disorder in an Adolescent Patient

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Background: Liraglutide (SAXENDA®) is a glucagon-like peptide 1 (GLP-1) receptor agonist approved as an adjunct for chronic weight management in combination with a reduced-calorie diet and increased physical activity. Previous case reports have suggested an association between liraglutide use and acute kidney injury in adults, particularly at maintenance doses of 1.2 mg/day or higher. However, there is less data on the impact of liraglutide in the adolescent population.

Case Presentation: We present a case of a 17-year-old adolescent who was admitted to the hospital with symptoms of mild vomiting, abdominal pain, anorexia, and low urine output persisting for three days. Laboratory tests revealed elevated levels of serum creatinine (1.92 mg/dL) and uric acid (11 mg/dL). Additionally, the patient exhibited elevated liver enzyme levels (AST 187 U/L, ALT 230 U/L), hyperbilirubinemia (2.15 mg/dL), and elevated LDH levels (650 U/L). He had been receiving liraglutide treatment for morbid obesity class 3 (BMI 50), at a minimal dosage of 0.6 mg/day for the preceding three months and experienced significant weight loss of over 20 kg during that period. The dose was not increased due to significant loss of appetite and successful weight loss with that low dose. Notably, the patient reported experiencing changes in mood, particularly melancholy.

Treatment and Outcome: The patient's treatment involved discontinuing liraglutide, implementing a low-salt and low-potassium diet, rehydration, and administering of proton pump inhibitors and antiemetics. After four days of hospitalization, the patient was discharged with restored kidney function, and improved hepatocellular function. Follow-up evaluation after 2 weeks revealed normalization of liver enzymes, improved appetite, and resolution of the depressive mood.

Discussion and Conclusion: The Naranjo adverse drug reaction probability scale indicated a probable relationship (score of 5) between the patient's acute kidney injury, hepatocellular disorder, and liraglutide use. Thus, this is the first documented case of acute interstitial nephritis with a hepatocellular disorder induced by the lowest dose of liraglutide in real life setting in the adolescent population.

Healthcare providers should be aware of the potential complication of liraglutide use, even at low doses, which can lead to acute kidney injury and hepatocellular disorders in adolescents. Patients should be educated about the importance of reporting any unusual weight loss or prolonged gastrointestinal or urinary symptoms. Further prospective real-life research is warranted to enhance our understanding of the risks and benefits associated with liraglutide treatment in adolescents.

LB14

Prevalence and risk factors of bone problems in children with supratentorial midline Low Grade Glioma

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Introduction: Children with cancer are at increased risk of endocrine complications, especially children with a brain tumor. One of these late effects includes bone disorders (ranging from low bone mineral density (BMD) to osteoporosis). Children with a suprasellar Low Grade Glioma (LGG) may be especially at risk for bone problems due to exposure to multiple treatment modalities, hypothalamic dysfunction and/or decreased mobility in combination with vision loss. We aimed to identify the prevalence and risk factors for bone problems in children with suprasellar LGG to guide clinical decision making.

Methods: A retrospective study was performed in children aged ≤ 18 years at diagnosis of a suprasellar or thalamic LGG between 1-1-2003 and 1-1-2021. Optic pathway gliomas without involvement of the optic chiasm were excluded. Bone problems were defined as presence of vertebral fractures, any fractures not related to (the intensity of) trauma, treatment with bisphosphonates, very low BMD as measured by DXA scanning or by Bone Health Index using digital X-ray radiogrammetry (Z score below -2 SDS) or spine collapse on MRI scan or X-ray of the spine.

Results: In total, 139 children were included with a median age at diagnosis of 4.7 years and median follow-up time of 7.6 years. 'Any' bone problem occurred in 25.2% (35/139) of the children. Diencephalic syndrome history, blindness, hypothalamic syndrome, thyroid-stimulating hormone deficiency, growth hormone deficiency, adrenocorticotropic hormone deficiency, hypogonadism, and glucocorticoid over-exposure were associated with bone problems. No independent risk factor could be identified for bone problems by multivariate analysis.

Conclusion: Bone problems are prevalent in children with suprasellar LGG and the results from this study may even be an underestimation. The origin of bone problems appears to be multifactorial in these children. Given this high prevalence, bone health must be a point of awareness in the care and follow-up in children with suprasellar LGG.

LB15

Metabolic Status in children with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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Objective: To summarize the metabolic status in children with classic congenital adrenal hyperplasia(CAH) due to 21-hydroxylase deficiency (21OHD).

Methods: Children with classic 21OHD from Pediatric Endocrinology Clinics at the First affiliated hospital of Sun Yat-Sen University from January 1990 to February 2023 were included in the study. The prevalence of overweight/obesity, dyslipidemia [high triglyceride (TG), high cholesterol (TC), low high-density lipoprotein cholesterol (HDL), high non-high-density lipoprotein cholesterol (nHDL), high and low density lipoprotein cholesterol (LDL)], and abnormal glucose metabolism [hyperglycemia, hyperinsulinemia and insulin resistance] were investigated.

Results: (1) BMI: A total of 379 children were included. Overweight/obesity was observed in 50.40% and obesity in 25.07% of the children at 1 or more visits, with higher prevalence in SW form than SV form(57.92% vs 43.37%) (P=0.005). The prevalence of obesity increased significantly from the age of 4 and peaked at the age of 8(5.49% -25.58%). (2) Dyslipidemia: A total of 291 children were included, 64.60% of whom were found with dyslipidemia at 1 or more visits, with the rank (from high to low) was high TG (36.08%), high TC (31.27%), low HDL (30.93%), high nHDL (29.21%) and high LDL(25.43%). Overweight/obesity was a risk factor for high TG (OR: 1.992, 95%CI: 1.210, 3.280) and low HDL (OR: 1.802, 95%CI: 1.057, 3.075). (3) Abnormal glucose metabolism: A total of 379 children were included. The prevalence of fasting hyperglycemia, hyperinsulinemia and insulin resistance was 1.32%, 21.40% and 21.03%, respectively. Overweight/obesity (OR: 7.083, 95%CI: 3.417, 14.683) and dose of hydrocortisone of 15-17mg/m^2/d (OR: 5.351, 95%CI: 2.592, 11.047) were the risk factors for hyperinsulinemia, while male (OR: 0.437, 95%CI: 0.217, 0.881) was protective against hyperinsulinemia. For insulin resistance, the risk factors were obesity/overweight (OR: 5,870, 95%CI: 2.902, 11.872) and relatively high-dose hydrocortisone 15-17mg/m^2/d (OR: 5.136, 95%CI: 2.518, 10.478). The prevalence of hyperinsulinemia and insulin resistance was parallel with age, peak at the age of 13 (38.71% and 35.48%, respectively). Conclusion: Children with CAH 21OHD had high risk of metabolic disorders increasing with ages. Higher incidence of hyperinsulinemia was found in female. Obesity/overweight was a risk factor for dyslipidemia, insulin resistance and hyperinsulinemia. Dose of relatively higher dose of hydrocortisone 15-17 mg/m^2 /d was a risk factor for insulin resistance and hyperinsulinemia.

LB16

Associations Between Serum Levels of Thyroid Function and Per- and Polyfluoroalkyl Compounds Concentrations in Central Precocious Puberty in Girls

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Background: Exposure to per- and polyfluoroalkyl substances (PFASs) may interfere with thyroid function in the general population and disturb the timing of puberty onset.

Objectives: We investigated the possible relationship between PFASs and thyroid hormone (THs) exposure in girls with central precocious puberty (CPP).

Methods: In a prospective study initially established for assessing CPP, 627 serum samples were collected with (n = 226) and without (n = 401) CPP. The concentrations of 25 PFASs, thyroxin (T4), 3,5,3'-triiodothyronine (T3), and 3,3',5'-triiodothyronine (rT3) were measured. We used logistic regression to examine the association of THs with the odds of having CPP and multiple linear regression to analyze the associations between THs and various PFASs in the CPP and control groups.

Results: The levels of T4 in the CPP group were significantly lower than those in the control group, and the levels of T3 and rT3 were significantly higher than those in the control group. After adjusting for confounders, T3 concentrations were associated with 1.526-fold increased odds of having CPP [odds ratio (OR) = 1.526, 95% confidence interval (CI):1.216–1.914]. In the CPP cohort, perfluoroheptanoic acid (PFHpA), perfluoro (2-ethoxyethane) sulphonic acid (PFEESA), and fluorotelomer phosphate diester (6:2/8:2 diPAP) were inversely associated with T3; perfluorobutanoic acid (PFBA) was inversely associated with T4, and PFEESA and 6:2/8:2 diPAP positively associated with T4; PFBA was positively associated with rT3, and perfluorooctane sulfonic acid (PFOS) was inversely associated with rT. In the control cohort, perfluorobutanesulfonic acid (PFBS) was positively associated with T3, and PFEESA and 6:2/8:2 diPAP were inversely associated with T3, and these PFASs had an adverse association with T4. Perfluorohexanoic acid (PFHxA) was positively associated with rT3, and 6:2/8:2 diPAP was negatively associated with rT3.

Conclusion: In this study, different measurements of PFASs and THs were observed in the CPP and control groups. Discrepancies in exposure to PFASs were associated with THs in the CPP cohort and healthy girls. Further research is necessary to investigate the mechanism by which PFASs affect the timing of puberty onset and thyroid function.

LB17

The Majority of Children with Pediatric Growth Hormone Deficiency Treated With Lonapegsomatropin for Up To 6 Years Met or Exceeded Average Parental Height SDS: Final Results of enliGHten

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Introduction: Lonapegsomatropin (SKYTROFA, TransCon hGH), a prodrug of somatropin administered once-weekly, is approved for the treatment of pediatric growth hormone deficiency (GHD) by the Food and Drug Administration and European Commission. In the pivotal 52-week phase 3 heiGHt trial and 26-week fliGHt trial (enrolled treatment-naïve and treatment-experienced participants, respectively), lonapegsomatropin demonstrated safety and efficacy in children with GHD. The final results of long-term safety and efficacy in the open-label extension trial enliGHten are reported here.

Methods: The primary objectives of enliGHten were to evaluate the long-term safety and efficacy of treatment with lonapegsomatropin. enliGHten enrolled 298 participants from heiGHt and fliGHt. Results are reported through the participants' final visit (study end date: December 31, 2022), including the subset (n=81) that completed lonapegsomatropin treatment because it was determined by the investigator that treatment for pediatric GHD was no longer necessary (referred to as "treatment completers").

Results: By study end, there were 81 participants who had completed treatment with lonapegsomatropin for pediatric GHD as determined by investigator judgement as no longer necessary. Of these participants, 59.3% met or exceeded average parental height SDS. The difference between height SDS at last visit and average parental height SDS mean (SD) was 0.08 (0.69), and the mean (SD) height SDS was -0.36 (0.74) at last visit. Treatment completers had a mean age of 16.5 years at last visit (range, 13-18.6 years), their mean duration of treatment was 3.2 years (maximum duration of 5.3 years), and a mean (SD) lonapegsomatropin dose at last visit of 0.15 mg hGH/kg/week (range 0.04-0.27 mg hGH/kg/week). Consistent with these results, 53.4% of the total 298 participants had met or exceeded average parental height SDS by the end of the trial, despite the majority having not yet completed treatment for pediatric GHD at study end date. The mean treatment duration with lonapegsomatropin for all 298 participants through heiGHt, fliGHt and enliGHten trials was 4.1 years (maximum duration 6 years). The safety profile remained consistent with prior observations with no new signals.

Conclusion: Long-term safety was demonstrated in participants treated with lonapegsomatropin for pediatric GHD for up to 6 years. Furthermore, the majority of all participants, including those who by study end date had completed treatment with lonapegsomatropin, met or exceeded average parental height SDS without a mean dose increase over time.

LB18

A Novel Variant of *NR2F2* Associated with Non-syndromic 46,XY DSD

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Differences of sex development (DSD) are congenital conditions with discordance between chromosomal, gonadal and/or anatomic sex. DSD can be syndromic or non-syndromic based on the presence or absence of somatic anomalies, respectively. Variants in several genes have been identified in association with errors of testis determination and male genital differentiation. However, despite technological advances, a genetic diagnosis is not achieved in nearly 50% of individuals presenting with 46,XY DSD.

NR2F2 (nuclear receptor subfamily 2 group F member 2) encodes an orphan nuclear receptor, COUP-TFII (chicken ovalbumin upstream promoter transcription factor II). Variants in *NR2F2* have been reported in XX individuals with the development of testicular tissue and abnormalities in the heart, the diaphragm and the eyelid.[1] This study describes a 2-year-old 46,XY boy presenting with micropenis, middle hypospadias and inguinal testes without associated somatic anomalies. Hormonal profile shows age-appropriate levels of luteinizing hormone (0.4 IU/L, normal <1.5), follicle-stimulating hormone (1.2 IU/L, normal <5), hCG-stimulated testosterone (705 ng/dL, normal 660 ± 410) and anti-Müllerian hormone (41 ng/mL, normal 13-167). Abdominopelvic ultrasonography was unremarkable with no Müllerian structures. Whole exome sequencing revealed a novel *de novo* heterozygous missense variant in *NR2F2*, NM_021005.4:c.737G>A resulting in p.Arg246His. The variant is absent in ancestry-matched populations and the gnomAD database (http://gnomad.broadinstitute.org/). It is located within a highly conserved region of the ligand-binding domain (LBD) and is predicted to be potentially damaging. The mutation, however, does not impact the nuclear localization or the stability of the protein. It has been shown that mutating specific residues in LBD can substantially reduce the COUP-TFII transcriptional activity.[2] Consistent with this, we observe that NR2F2$^{\mathrm{Arg246His}}$ showed a significant loss of inhibitory effect on the NR5A1-mediated activation of LH-β and INSL3 promoters, while maintaining the binding between the two proteins. Taken together, our results support the pathogenicity of the p.Arg246His variant in 46,XY DSD and expand the small but growing list of genes that are associated with both 46,XX and 46,XY DSD.

Reference

1. Bashamboo A, *et al.* Am J Hum Genet. 2018;102:487–493.
2. Kruse SW, *et al.* Plos Bio. 2008;6:e227.

LB19

Identification of a novel homozygous mutation in LEPR gene associated with severe early-onset pediatric obesity in two sisters from Central Brazil

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Introduction: Early-onset severe obesity (before five years of age) without intellectual deficit, dysmorphisms, or malformations raises the hypothesis of monogenic obesity. The leptin receptor (Lepr) pathway is essential for food intake regulation, energy expenditure, and body weight. Mutations in leptin and the Lepr have been shown to cause early-onset severe obesity in mice and humans.

Objective: To report the clinical and molecular investigation of 2 sisters with severe obesity starting in the first year of life

Case Report: MEGS and AVGS, second and third daughters of 3 offspring, the older brother being of normal weight. Non-obese, consanguineous parents who are cousins of third-degree. The patients are 5 and 6 years old, with severe obesity that started during the exclusive breastfeeding phase, reaching a maximal Z-BMI of 8.86 and 7.82, respectively. The two sisters present: hyperphagia, increased abdominal circumference, acanthosis nigricans, arterial hypertension, dyslipidemia, increased insulin, and HOMA IR. MEGS evolved with varus deformity of the lower limbs leading to gait impairment. Whole-exome sequencing (WES) followed by target gene panel analysis was performed, which identified the homozygous variant NM_002303.5:c.1603+3A>G in the LEPR gene in both sisters.

Discussion: The variant found in the sisters was identified in a homozygous state in the LEPR gene in the splice region (strand+, exon 11). This gene is intolerant of loss of function (pLI: 0.99), and the severity of the variant was predicted to be harmful. It was not reported in the GnomAD and ExAC public databases. The deleterious nature of the mutation is consistent with the clinical conditions of hyperphagia, rapid weight gain, and extreme obesity observed in both sisters. Furthermore, in addition to dietary measures and physical activity stimulation, treatment with the new medication Setmelanotide, a melanocortin-4 receptor (MC4R) agonist, may be efficient and will be carried out as soon as it is available in our country.

Conclusion: WES, followed by target gene panel analysis, efficiently identified a homozygous mutation in a consanguineous case of early-onset severe obesity. Although cases of monogenic obesity represent a small portion of patients with childhood obesity, it is essential to recognize its existence and consider the clinical and therapeutic implications associated with such genetic conditions. Early identification, genetic counseling, and clinical and therapeutic approach directed according to molecular diagnosis prove fundamental for a practical approach to patients and genetic counseling.

LB20

Turner Syndrome: Skin, Liver, Eyes, Dental and ENT assessments should be improved

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Introduction: Turner syndrome (TS) association with multi-organ system comorbidities highlights the need for effective implementation of follow-up guidelines. We aimed to assess 1/ the adequacy of care with international guidelines published in 2007 and 2017 and to describe the phenotype of patients; 2/ the effectiveness of our transition program.

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Methods: In this multicenter retrospective descriptive cohort study, we collected growth and pubertal parameters, associated comorbidities, treatment, and karyotype in patients diagnosed at age <18 years between 1993 and 2022. We assessed age-appropriate recommendation follow-up (children, adolescents and adults) according to the 2007 guidelines if the last visit was before 2017 (18 recommendations) and the 2017 guidelines if the last visit was after 2017 (19 recommendations).

Results: We included 68 patients followed at Lausanne University Hospital (n=64) and at Neuchatel Regional Hospital (n=4). 2.9% of patients underwent all recommended investigations. Overall, 68.9 ± 22.5% and 78.5 ± 20.6% of the recommendations were followed, before and after 2017, respectively. The recommendations with the highest implementation rate were height, weight, BMI (100%), and cardiac (range: 80 to 100%) and renal (range: 90 to 100%) imaging. The recommendations with the lowest implementation rate were Ear, Nose and Throat (ENT) (56.5%), skin (38.5%), dental (23.1%), ophthalmological (10%), and cholestasis (0 to 29%) assessments, depending on age and time of visit. In children (n=13), the overall mean proportion of recommendations followed was 75.5 ± 19.1%. In adolescents (n=22), we found no difference between overall followed recommendations for patients last seen before 2017 compared to patients last seen after 2017 (76.6 ± 15.1% vs. 80.9 ± 18.3%, p=0.306). In contrast, in adults (n=33), the mean proportion of followed recommendations was lower before than after 2017: 63.5 ± 25.8% vs. 78.7 ± 23.4%, p=0.039.

Conclusion: Growth parameters, cardiac assessment and renal ultrasound are well followed up. However, efforts should be made for dental, ENT, ophthalmological, skin and cholestasis assessments. Adequacy of follow-up improved with the quality of transition to adult care.

Poster Category 2

Adrenals and HPA Axis

P2-3

Glucocorticoid induced adrenal insufficiency evaluated by the low dose short corticotropin test in children

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Background and Aims: The low dose short corticotropin test (LCT) is the most frequently used test to diagnose glucocorticoid-induced adrenal insufficiency (GAI) in children. Result of the LCT must be interpreted with caution since stimulated peak cortisol (PC) thresholds depend on the assay and time of sampling. We evaluated the prevalence of GAI by the LCT using both 20 and 30 minutes sampling and cortisol measurements by the most recent Roche Elecsys Cortisol II assay in children who had been treated with high dose oral (>20 mg/m² hydrocortisone converted dose) synthetic glucocorticoids for at least 4 weeks (HDSG). In addition, we investigated the relationship between PC and age, BMI SDS, basal cortisol (BC) at testing and time since stopping glucocorticoid treatment.

Methods: Clinical and laboratory data on 28 children, who underwent a LCT using 1 µg /m² Synacthen between 08.00 and 9.00 h AM in fasting condition between 01-2016 and 08-2022, were retrieved. Cortisol was measured by the Cobas 8000 e801/Roche Diagnostics assay (intra-assay CV of 1.9-2.8%). Both a PC <160 µg/L and a PC <135µg/L were used for the definition of GAI.

Results: In all children, the LCT was performed at least 4 weeks after stopping glucocorticoid treatment: in 5/28 for asthma, in 6/28 for bronchopulmonary dysplasia, in 2/28 for rheumatic arthritis. PC was observed at 20 minutes in 2/28 (7.1%) and at 30 minutes in 25/28 (89.3%) children. In total, 10/28 (35.7%) had a BC < 60 µg/L, while 13/28 (46.4%) had a PC <160 µg/L and 7/28 (25%) had a PC <135µg/L. Mean PC was not different between boys and girls (169 µg/L vs 160µg/L, P = 0.782) or between the studied diseases. PC correlated significantly with BC (r = 0.502, P = 0.007). PC did not correlate significantly with age, BMI z-score at testing and time since stopping glucocorticoid treatment. A BC >120µg/L predicted a PC >160 µg/L, while all children with a BC >65 µg/L had a PC >135µg/L.

Conclusion: Almost half of the HDSG treated children had GAI when using the commonly used PC cut-off, compared to only a quarter when using the newly proposed lower cut-off for the Elecsys Cortisol II assay. Considering a GAI by a PC <135 µg/L, LCT might not be of additional value in children presenting with a basal cortisol >65µg/L after stopping glucocorticoid treatment, irrespective of their underlying disease and age.

P2-4

Newborn screening for 21 OH Congenital adrenal hyperplasia in Italy: a 14 years population study

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Introduction: Early identification of classic 21OH-Congenital Adrenal Hyperplasia (21OH-CAH) through newborn screening (NBS) is crucial to prevent adrenal crises, especially in males.

Today 21 OH-CAH NBS is performed in 5/21 regions of Italy. This study aims to report the results of 21OH-CAH NBS in Italy from 2006 to 2019.

Methods: All patients underwent a dried blood spot (DBS) test for 17OH-progesterone (17OHP) within the first 48-72 hours of life. According to different regional protocols, for the preterm newborns, different thresholds for 17OHP and specific protocols for retesting were utilized, mainly based on gestational ages or birth weight. In 1/5 region of Italy, the second-tier test with Tandem Mass MS/MS was utilized from 2018. The analysis included the number of newborns screened, the sensitivity of NBS for SW-CAH, the number of positive cases, the recall rate (RR) and predictive positive value (PPV), the number of false negatives (FN), age at blood sampling, number of cases suspected before NBS results.

Results: A total of 2,933,074 newborns were screened, and 166 pts (78M,88F) were diagnosed with classic 21OH-CAH, resulting in an incidence rate of 1:17,669 newborns. The Salt Wasting (SW) CAH was the most common form identified (125 pts, 80%), with 100% of NBS sensitivity. The mean age at blood sampling in true positive cases was 9±18 days of life. In 46/166 (28%) cases, the diagnosis was suspected before the NBS Results: in 35 females due to genital ambiguity, in another 4 females, and in 7 males due to prenatal diagnosis. Overall, the mean RR was 0.77; the mean PPV was 1.02. Three FN cases (2M) with simple virilizing 21OH-CAH were diagnosed in infancy. In the region where 2nd tier was available, the recall rate in the last 2 years was 0.17, with a PPV of 4.3.

Discussion: The results of this study demonstrate the effectiveness of newborn screening for the early detection of SW 21OH-CAH. The mean age at blood sampling suggests that timely reporting of screening results is crucial to ensure early diagnosis and treatment. The recall rate and PPV could be dramatically improved by implementing 2nd tier-test protocols. The data analyzed in this study provide valuable insights into the epidemiology of CAH and may provide useful information to guide Italian public health interventions aimed at improving the health outcomes of infants with CAH.

P2-42

Exploring the Experiences of Parents of Children with Congenital Adrenal Hyperplasia: a study in Developing Country

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Keywords: Congenital Adrenal Hyperplasia, Parent's experience, Focus Group Discussion

Background: Congenital Adrenal Hyperplasia (CAH) leads to many unseen social burdens for parents, including ambiguous genitalia (in girls), lifelong use of medication, including stress dosing, social and psychological pressure, and stigmatization. This study aimed to investigate various lived experiences of parents caring for their children with CAH in Indonesia.

Methods: We employed a focus group qualitative study. For recruitment, purposive sampling was done on all parents of children with CAH routinely followed at the Diponegoro National Hospital, Semarang, Central Java, Indonesia. We asked three main open questions: 1) What is the main concern of raising a child with CAH? 2) What is the most remarkable experience in raising a child with CAH? 3) What is the biggest obstacle for taking medicine regularly? We recorded, transcribed, and thematically analysed each focus group discussion.

Results: We interviewed parents from 35 families with one or more children diagnosed with CAH (21-hydroxylase deficiency and 11-beta-hydroxylase deficiency). Twenty-four parents of children with the classic salt-wasting CAH. Thirty-two families raised daughters and three raised sons with 46, XY CAH. Thirteen families were raising children below five years old, and six parents had children older than 17 years old (Indonesia's age of consent). Most parents (16/35) had concerns about the future of their daughters, especially about future spouses/married and the possibility of becoming infertile. Five parents had concern about taking care of the children in the future, three parents had concern about medication availability. The other concern were their children's gender identity in the future, early puberty, and masculine and aggressive behaviour. Three parents reported their worries about the history of siblings died due to late diagnosis and salt-wasting crisis. Most of the parents did not report problems with taking medicine regularly; however, the biggest obstacle was taking the medication with suboptimal timing.

Conclusions: Parents with children with CAH in Indonesia experience many concerns, particularly about the future spouses of their children, who will take care in the future, medication availability, behaviour, and gender problems that may result in worries for their children. Comprehensive CAH education will decrease their fears, increase compliance, and help them accept their children's condition.

P2-76

The genotype-phenotype correlations in patients with 21-hydroxylase deficiency in Henan,China and the relationship between the clinically effective dosage of hydrocortisone and CYP21A2 genotype

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Purpose: Identify CYP21A2 gene variants in pediatric patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency from Henan, China, and to analyze genotype-phenotype correlations. We also analyze the relationship between the clinically effective dosage of hydrocortisone and CYP21A2 genotype.

Materials/Methods: A total of 214 21-OHD children were recruited in Henan children's hospital from 2008 to 2023. The patients were categorized into five genotypic groups (group 0,group A,group B,group C and group D) according to their residual CYP21A2 enzymatic activities. The expected phenotype associated with groups 0 or A was salt-wasting (SW) form. Genotype of patients in group B were predicted to result in simple virilizing (SV) form and those of group C were predicted to present as nonclassic (NC) form. The dosage of hydrocortisone was calculated for each genotype group at the age of 1 year and 6 years, respectively (including 153 cases aged 1 year and 92 cases aged 6 years), and analyzed whether there is statistically significant difference in the dosage of hydrocortisone among the groups.

Results: In this study, 214 children were diagnosed with 21-OHD, among whom 161 (75.2%) presented SW form, 48 (22.4%) presented SV form and 5 (2.3%) presented NC form. The most frequent micro-conversion was I2G (35.0%),p.I173N (12.0%),p.Q319* (6.1%),p.R357W (5.6%).Other 25 different types of spontaneous mutations accounted for 8.4% of alleles.Large gene deletions account for 19.7%. Among 214 patients, 8 cases had spontaneous mutations in one allele, while the mutation in the other allele was inherited from the father or mother.

In 214 patients genotype-phenotype correlations measured by positive predictive value (PPV) were as follows: 92.6% in group 0, 93% in group A, 68% in group B, and 50% in group C.

Among 153 children aged 1 year or older, the average dosage of hydrocortisone in Group 0, A, B, and C was 10.33±2.38mg/m^2,10.38±2.56mg/m^2,11.51±2.59mg/m^2,10.56±2.48mg/m^2 respectively. Among 92 children aged 6 years or older, the average dosage of hydrocortisone in group 0, A, B, and C was 11.7±2.47mg/^{m}2,11.48±2.58mg/m^2,11.68±2.62mg/m^2,11.4±2.59mg/m^2 respectively, There is no statistical difference among the groups.

Conclusions: There was a good correlation between genotype and phenotype in group 0 and group A, while the correlation is considerably lower in group B and C. There is no statistical difference between the clinically effective dosage of hydrocortisone and genotype group.

P2-77

Massive adrenocortical carcinoma with right atrium invasion in a two-year old girl with li fraumeni syndrome – possibility of succesful ressection after neoadjuvant chemotherapy

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Background: In Brazil, specially in the south, there is a high prevalence of p53 mutations – 1:300 compared to 1:5000-1:20000 incidence worldwide. (1) As a consequence, adrenocortical carcinoma as a cause of virilization in children is much more common in our practice.

Clinical Case: M.P.O., a 32-month-old girl, was referred to our institution - Hospital de Clínicas de Porto Alegre - in May 2022 due to progressive abdominal swelling, hirsutism, and premature pubarche.

At presentation, M.P.O. had a high BMI (19,8 kg/m^2) with an impression of increased muscle mass, normal height for age (90cm p27), high blood pressure, fine and dark hair across the legs, face, and arms, axillary terminal hair, clitoromegaly, and a Tanner stage of B1P4. It was unclear when the virilization had started, but the patient had a reportedly normal physical examination at birth. During anamnesis, it was revealed that there was a family history of lethal adrenocortical carcinoma.

The laboratorial evaluation showed normal fasting glucose, slightly elevated morning cortisol of 21,3 ug/dL, an inappropriately normal ACTH of 44,2 pg/mL, a normal 24-hour urinary cortisol, an elevated DHEA-S of 6143,4 ug/dL – more than 20 times the reference value for age and sex, elevated androstenedione of 10 ng/dL, a markedly increased testosterone of 343 ng/dL, normal gonadotropins but a discretely elevated estradiol of 28 pg/mL, an aldosterone of 3,66 ng/dL and renin levels of 44,3 mUI/L.

Imaging studies revealed an enormous tumoral mass of 750 cm^3. The patient weighed 15 kg at diagnosis, and the represented 5% of her body weight. The tumor extended from the right adrenal gland towards the inferior cava vein and the right atrium, occupying 50% of this heart cavity, and protruded through the tricuspid valve during diastole.

Initially considered inoperable, the tumor was later resected after six months of chemotherapy involving cisplatin, etoposide, doxorubicin, and mitotane, and a regression in size of almost 70%. Pathology studies confirmed the adrenocortical origin of the tumor.

Genetic analysis showed a pathogenic variant in the TP53 gene c.1010G>A (p.Arg337His) in heterozygosity. The family received adequate genetic counseling.

M.P.O. is currently three years old and continues to receive mitotane treatment, with no signs of disease relapse.

Discussion: This case report discusses the diagnosis and management of a potentially lethal advanced adrenocortical cancer, a cause of virilization of a 2 year-old-girl. The Pediatric Endocrinologist must be aware of this potential diagnosis and its treatment.

P2-78

Massive adrenocortical carcinoma with right atrium invasion in a two-year old girl with Li Fraumeni syndrome – possibility of succesful ressection after neoadjuvant chemotherapy

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Discussion: This case report discusses the diagnosis and management of a potentially lethal advanced adrenocortical cancer, a cause of virilization of a 2 year-old-girl. The Pediatric Endocrinologist must be aware of this potential diagnosis and its treatment.

P2-79

Final Adult Height in Saudi patients with Congenital Adrenal Hyperplasia

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Introduction: Congenital Adrenal Hyperplasia (CAH) is a chronic disease that requires life-long hormonal replacement therapy. Growth of patients with CAH can be affected by this therapy or the hyperandrogenic effect of the disease. In this study, we aimed to assess the potential effect of CAH and its therapy on final height in Saudi affected patients.

Methodology: This is a retrospective cohort study from two tertiary endocrine centres in Riyadh, Saudi Arabia. We included all patients above 19 years of age diagnosed with CAH. Clinical data were collected from patients' medical records and we used SPSS in statistical analysis.

Results: A total of 92 patients were included [54.4% (n=50) female); mean age for males was 25.6 (+/-6.4) year and 26 (+/-6.6) year for females]. Two adult females (46XX) were permanently raised as males in our cohort. CYP21 gene defect was the most common 94.4% (n=85), followed by CYP11 5.4% (n=5), then HSD3 2.2% (n=2). Mean final Height (cm)(SD) in males was 156.3 (9.5) and in females was 148.9 (7.2). Final height of CAH patient compared to Saudi population was -1.69 SD and -1.07 SD in males and females, respectively.

Conclusion: Our CAH adult patients had significant impairment of their final height that could be related to genetic defect or gender or medications side effect. Males were more affected in our cohort. This may require special attention to their growth during childhood to offer an appropriate and early intervention.

P2-80

Cortisol and 11-oxygenated androgens in hair samples from children and adolescents with congenital adrenal hyperplasia

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Background: Children with classical congenital adrenal hyperplasia (CAH) require glucocorticoid replacement. In addition to auxological examinations, laboratory measurements of e.g. 17-hydroxyprogesterone and androstenedione in serum are also necessary to assess the required dosage of hydrocortisone. Another possibility for measuring precursor steroids is hair analysis, which has not yet been carried out in children with this issue. The role of so-called 11-oxygenated steroids in patients with CAH has also been discussed recently.

Objective and Hypothesis: Is the analysis of steorides in hair suitable for the assessment of therapy quality in patients with CAH?

Method: In this prospective study of 26 children and adolescents with CAH, cortisol, 11-ketotestosterone and 11-hydroxyandrostenedione (and other steroids) were measured in hair samples from the occiput. Except for one sample, 3 cm of hair were measured to cover a period of about 3 months. The measurements were carried out by means of LC/MS.

Results: 24 samples (14 girls, 10 boys) could be evaluated, as 2 samples had too little material. Cortisol could be measured in varying concentrations in each hair sample. Only in 6 subjects with the highest cortisol levels of >300 pg/mg could 11-hydroxyandrostenedione also be measured. The median for hair cortisol in the remaining 18 subjects was 16.6 (range 4.8 - 102.9) and 11-hydroxyandrostenedione was not detectable. No difference in the dosage of hydrocortisone was found between the 6 and 18 subjects (13.37 and 13.70 mg/body surface/day, respectively).

Conclusion: Cortisol could be measured in all hair samples. This is plausible because all subjects were treated with hydrocortisone. However, a comparison between the doses of the groups with very high levels of cortisol in hair and average levels of cortisol showed no difference. Thus, the amount of exogenous intake of hydrocortisone cannot be verified by hair samples. The concentration of cortisol in hair of healthy children is about 2-6 pg/mg, depending on BMI, sex and tanner-stage. Thus, subjects with CAH have significantly higher concentrations of cortisol in hair. The association between high cortisol levels and only then measurable 11-hydroxyandrostenedione remains unclear. Furthermore, it should be noted that 11-ketotestosterone could only be detected in one subject. This sample was from an infant with mutations with 0% residual 21-hydroxylase-activity in the neonatal period. 11-ketotestosterone does not seem to be a suitable parameter for therapy adjustment. However, the lack of reference values from healthy controls and the small sample size remain major restrictions for interpretation.

P2-139

A 6-year-old boy with Duchenne Muscular Dystrophy and acute adrenal insufficiency: a case report

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Background: Adrenal crisis is a life-threatening condition caused by either primary adrenal insufficiencyor hypothalamic-pituitary-adrenal (HPA) axis dysfunction, commonly due to chronic use of high-dose glucocorticoids. Clinical presentation, often with gastrointestinal symptoms (weakness, nausea, vomiting,epigastric pain) poses clinical challenges, sometimes leading to an incorrect diagnosis of gastroenteritis.

Material: We present a clinical case of a boy with Duchenne Muscular Dystrophy and acute adrenal insufficiency.

Case Presentation: A 6-year-old boy with a past medical history of Duchenne Muscular Dystrophy (DMD) treated with deflazacort (0.9 mg/kg/day), presented to theEmergency Department with emesis that started hours ago, abdominal pain, weakness and loss of appetitefollowing 10 days of mild diarrhea. His molecular genetic report detected the deletion of exons 46-50 in the Dystrophin gene. During the physical examination the boy was hemodynamically stable, mildly tachycardic(Temperature 36.1°C, SatO2 97%, Heart rate 128/min,Blood pressure 105/73mmHg) and had flushing. He was ambulatory with assistance and presented pseudohypertrophy of the calves and a positive Gower's sign. Laboratory testing revealed elevated transaminases (SGOT 199 U/L, SGPT: 315 U/L) and CK (6000 U/L), hyponatremia (Na 133mmol/l), hyperkalemia (K+5,2mmol/L), hypoglycemia (Glu 45mg/dl) and metabolic acidosis (pH 7.24, HCO3 17mmol/L). The electrocardiogram was normal. The boy's chronic treatment with deflazacort was discontinued five days ago on the parents' own initiative, due to the diarrhea. Based on the clinical status and laboratory findings, the child was diagnosed with acute adrenal insufficiency. Treatment with emergency intravenous stress dosehydrocortisone and fluid replacement with dextrose and sodium was initiated, with immediate clinical and laboratory improvement. The patient was then transferred to a specialized pediatric endocrinology unit, where the parents were educated about hydrocortisonestress dosing plans and the dangers of abruptdiscontinuation of chronic glucocorticoid treatment.

Conclusion: Glucocorticoids are the cornerstone in the treatment of DMD. Deflazacort is a new synthetic glucocorticoid commonly used in children with DMD due to its favorable side effect profile. Considering that its anti-inflammatory potency is approximately 10-20 times higher than prednisolone and 40 times higher than hydrocortisone, its chronic use in therapeutic doses causes secondary adrenal insufficiency and its abrupt cessation can lead to adrenal crisis. It is imperative that all families are educated about stress dosing and recognizing the symptoms of adrenal crisis.

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P2-140

Testicular Adrenal Rest Tumors (TARTs) as presenting symptom of CAH due to CYP11A1deficiency

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Background: TARTs mostly occur in congenital adrenal hyperplasia due to 21-hydroxylase deficiency, but were described in other forms of CAH. Elevated ACTH levels, may play a role in TARTs development. Here we describe the first child with undetected CYP11A1 deficiency who presented with TART.

Case Description: An 11 year old boy noticed left sided scrotal enlargement, without further complaints. Ultrasound showed a hydrocele and in both testis a testicular mass near the mediastinum testis with a heterogenous hypo-isoechogenic aspect, with symmetric focal hyperemia and microcalcifications. TARTS were considered and he was referred to the pediatric endocrinologist.

At the age of 1 year he had a febral convulsion, hypoglycemia and hepatomegaly. Metabolic investigation was normal and hepatic enlargement resolved spontaneously. Puberty started early at the age of 11 years. He had diffuse hyperpigmentation. During illnesses, he often vomited and was more severely ill than other children. Normal male genital development, Tanner stage: P4, G4, testis 12 ml.

Laboratory Results at Age 11 Years: normal sodium and potassium, increased ACTH (798 ng/l), basal cortisol 185 nmol/l, normal renin concentration, low adrenal steroids. ACTH-stimulation test: no increase in cortisol, or other adrenal steroids.

LH and FSH were moderately increased (LH 11,9 U/l, FSH 13,67 U/l) and testosteron was moderately increased for his age (8,16 nmol/l). Karyotype 46XY.

Adrenals were not seen on ultrasound, bone age was 1,5 years advanced.

Whole Exome Sequencing for disorders in sexual development/adrenal disease showed two compound heterozygous variants in CYP11A1. The pathogenic variant c.835del p.(lle279fs) leads to a premature stopcodon in CYP11A1 protein. The second variant c.940G>A p.(Glu314Lys) is a variation with unknown significance but has been described as pathogenic together with the c.835deletion. Both parents are carrier of one of the mutations

The patient is treated with hydrocortisone, ACTH concentration has decreased, on ultrasound TARTS are slightly smaller.

Cytochrome P450 side-chain cleavage enzyme (CYP11A1) facilitates the first step of steroidogenesis. Patients present with adrenal insufficiency and disorder of sex development in 46XY individuals. Milder CYP11A1 deficient patients present with isolated adrenal insufficiency or isolated glucocorticoid deficiency and normal male genital development. On ultrasound, adrenals are invisible or normal in size. Sufficient androgens must have been synthesized for appropriate masculinization and pubertal development. Although fertility may be compromised due to TARTs and due to CYP11A1deficiency.

Conclusion: TARTs can be a presenting symptom of CAH due to CYP11A1 deficiency.

P2-141

Pediatric Cushing Disease: a single center experience

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Introduction: The incidence of Cushing disease (CD) is 0.7-2.4/year per million, andadolescents and children make up 10% of new cases annually. However, thesensitivity and specificity of tests used to diagnose CD in childhood may bepoor, resulting in difficulties in diagnosis and treatment. The aim was to reportpediatric CD patients attending our pituitary referral center for surgery and todescribe their diagnosis, treatment and long-term follow-up.

Materials and Methods: The retrospective study included CD cases between the years 2000-2022. Medical records of the patients were reviewed to evaluate symptoms, clinicalfeatures, treatment and follow-up. The diagnosis of hypercortisolemia wasconfirmed by first-line tests, including loss of cortisol circadian rhythm, and afailure to suppress serum cortisol levels to <1.8 μg/dL during an overnightdexamethasone suppression test (DST) and low-dose DST. Second-line testswere also performed to determine the etiology, including high-dose DST, withcortisol decreasing by 50% compared to basal cortisol and corticotropin-releasing hormone (CRH) stimulation test during which ACTH rose to >35% ofbasal at the 15th and 30th minutes. We compared the basal cortisol result inthe patient group with normal ranges to investigate sensitivity and specificity ofcortisol and ACTH.

Results: The study included 17 patients (Female n=9) diagnosed at a median age of 14.9(8.0-18.2) years. Acne, obesity, hirsuitism, short stature, headache andmenstrual irregularity were the most common features at diagnosis. Tenpatients also had central hypothyroidism at diagnosis and all recovered after surgery without thyroxine replacement. Six patients had hypogonadotropic hypogonadism and three patients had growth hormone deficiency. Fifteenpatients had micro-adenoma and two macro-adenoma. Basal cortisol and ACTHcut-off levels for distinguishing CD patients from controls were 11.7 ug/dL(sensitivity 92.3%, specificity 90.9%) and 38.3 ug/dL (sensitivity 92.3%,specificity 100%), respectively. All cases underwent endonasal trans-sphenoidalsurgery. Remission was achieved in 15 (88%) within one week of surgery. Fourpatients were re-operated including one patient who underwent adrenalectomy.

Discussion: Children and young people with CD have a good prognosis after treatment inexperienced centers, when the hypothalamic-pituitary-adrenal axis heals completely. CD pediatric patients should be referred to multidisciplinary specialist centers managed by pediatric endocrinologists and specialized neurosurgeons. Early diagnosis and specialist management are critical due to the adverse health outcomes from long-term hypercortisolism and morbidity due to complications.

P2-155

A case of Ectopic ACTH in a girl with thymic carcinoid

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Background: Ectopic ACTH-producing tumors rarely occur in children, with <1% of all adolescents with Cushing Syndrome (CS). Many cases of ACTH-secreting ectopic neuroendocrine tumors (NETs) are reported in literature. In most patients, tumors secrete corticotropin-like peptides and/or corticotropin releasing factor (CRF)-like peptide, which stimulate cortisol hyperproduction.

Case Report: A 17-year-old girl presented to our hospital with a history of psychosis, progressive weight loss, recent onset widespread acne, hirsutism, amenorrhea and muscle weakness. Her height was 164 cm (+0.17 SDS), weight 43.6 Kg (-1.81 SDS) and body mass index (BMI) SDS was -2.31. At the physical examination we observed facial plethora and fullness, lower limb edema, "buffalo hump", mild hirsutism and hypertension (BP 140/100 mmHg, > 99° pct). Blood tests showed fasting hyperglycemia (180 mg/dl) with HbA1c 49 mmol/mol and high levels of ACTH and plasma cortisol according to circadian rhythm (at 00.00 am: ACTH 34,1 pg/ml, range 0–42, cortisol 63,84 mcg/ml, range 4–22, at 8.00 a.m.: ACTH: 62,7 pg/ml—cortisol: 84,96 mcg/dl). We performed overnight 1 mg and a high-dose suppression test with 8 mg of dexamethasone, without suppression of adrenal axis (at 8 am: ACTH 179 pg/ml, cortisol 69 mcg/dl). High levels of free urinary cortisol were detected in a 24-h urine collection (>510 mcg/24 h). Moreover, hypokaliemia (K 2.4 mEq/L) and mild anaemia (Hb 9.2 g/dl) were found. Negative NET markers were observed. Ultrasonography and abdominal magnetic resonance imaging (MRI) showed bilateral adrenal gland hyperplasia. Brain MRI showed normal pituitary gland. Total body CT was negative for tumor lesions but vertebral fractures and aseptic necrosis of the femoral head was identified. Pharmacological treatment of hypercortisolism was started using metyrapone therapy 1000 mg/day. After one week of therapy we found normal ACTH and cortisol levels. Gallium-68 labelled somatostatin receptor and FDG PET/CT was performed in order to identify paraneoplastic NET lesion. A small lesion (1.4 cm) was found in thymus. Transthoracic surgery was performed, and pathological examination revealed atypical thymic carcinoid. After surgery, ACTH and cortisol levels were normal, 34 pg/ml and 16.25 ng/dl respectively.

Conclusion: EAS is a rare, often severe condition. Its management for diagnosis and treatment is considered a hard challenge for paediatric endocrinologists. In the future, advances in imaging techniques will improve the identification of small occult NETs and thus allow their removal.

P2-156

Aldosterone deficiency and resistance: The different faces of renal salt loss

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Introduction: Heritable conditions causing aldosterone deficiency (hypoaldosteronism) or target-organ resistance (pseudohypoaldosteronism, PHA) can lead to life-threatening salt-wasting crises in early life. Prompt evaluation and correct interpretation of aldosterone and renin are crucial to guide differential diagnosis and further testing. Here we report on the similarities and differences of two neonates presenting with salt-wasting: Patient (P1) due to PHA type 1A and, Patient 2 (P2) due to aldosterone-synthase deficiency type 2 (ASD).

Case Reports: Both patients were admitted in their first month of life for failure to thrive, dehydration, with features of severe hyponatremia and hyperkalemia. They had normal external genitalia and no hyperpigmentation. Whilst 17-OH-progesterone and ACTH-test were normal, renin was markedly elevated. P1 (female) had substantially elevated serum aldosterone concentrations, while P2 (male) had low-normal aldosterone.

Both patients were initially treated with intravenous NaCl, salbutamol-inhalations, glucose/insulin infusions and fludrocortisone. P1 also received oral and rectal resonium, but was unresponsive to fludrocortisone. Thus, PHA type 1A was suspected in P1 and later on confirmed by genetic testing (heterozygous NR3C2 mutation: c.2306T>C). Further management for P1 consisted of oral resonium (0.3 g/kg/d) and NaCl (5.7 mmolNa/kg/d) with decreasing requirements incrementally.

P2 had a history of neonatal sepsis and developed E.coli sepsis on readmission. He was initially presumed to have acquired hypoaldosteronism secondary to a critical illness. He was discharged on oral NaCl (9 mmolNa/kg/d) and followed-up at a peripheral hospital, where he was weaned off NaCl. He was readmitted at one year of age with severe hyponatremia and hyperkalemia and persistent failure to thrive. Reevaluation revealed a plasma aldosterone/renin ratio < 1pmol/mU (normal reference range 1-72 pmol/mU) and elevated urinary aldosterone-precursors suggestive of ASD. Fludrocortisone and oral sodium were restarted leading to prompt stabilization. Genetic testing confirmed ASD type 2 (homozygous CYP11B2 mutation: c.554C>T).

Conclusion: Salt loss in neonates is an endocrine emergency, requiring tertiary endocrine care. While renin and aldosterone are markedly elevated in patients with PHA, as in our case, aldosterone may remain inappropriately normal in ASD2. Thus, a decreased aldosterone/renin ratio should prompt further investigation to avoid delay in diagnosis and life-saving treatments.

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P2-157

ACTH-independent hypercortisolemia: onset clinical picture in a 10-year-old boy with Carney complex

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Background: "Carney complex" is an autosomal dominant inheritance extremely rare genetic syndrome, usually determined by PRKAR1A (17q22-24) gene mutations. The clinical picture is characterized by speckled skin pigmentation; cardiac, cutaneous and mammary myxomas; schwannomas; endocrinopathies (acromegaly, Cushing syndrome due to primary pigmented nodular adrenocortical disease) and tumors of the endocrine glands.

Case Report: A 10 years-old boy first came to our ambulatory due to severe obesity. Height was 134.2 cm (-0.86 SD), within target height, BMI 27.1 kg/m^2 (+3.05 SDS). On physical examination acanthosis nigricans was observed. Hyperinsulinemia was documented by OGTT. During the first three months of follow-up the statural growth rate was regular but the dietary response was poor. When the patient came back to our observation 10 months after the last visit, there was evidence of worsening of obesity (BMI +3.22 SDS), statural growth failure (growth velocity 0.7 cm/year), hypertension and the occurrence of striae rubrae at the trunk and root of the limbs. Endocrinological causes of obesity associated with statural growth failure have been investigated. The circadian rhythm of cortisol (22 ug/dl at 7 a.m., 23.3 ug/dl at 4 p.m. and 15.5 ug/dl at midnight) and ACTH (persistently <1.5 pg/ml) and cortisoluria (568ug/24hour) were suggestive of ACTH-independent hypercortisolemia. Iatrogenic causes were ruled out. Adrenal ultrasound and CT scan were performed, suspecting the presence of a nodule or hyperplasia of the medial arm of the left adrenal gland. Conversely, MRI showed a significant increase in the global dimensions of the adrenals. For the suspicion of bilateral adrenal hyperplasia, a genetic investigation was performed, which found a mutation in the PRKAR1A gene (c.46C>T p.(Arg16*) of exon 2) pathogenic for ‚Carney complex'. Other related diseases were ruled out. Patient started and well tolerated therapy with Metyrapone, an adrenal steroidogenesis inhibitor, 250 mg daily. The clinical picture has slightly improved (disappearance of striae rubrae, reduction in mean blood pressure, slight weight loss, spontaneous onset of pubertal development), cortisoluria is again within normal limits, but ACTH suppression persists.

Conclusions: Our patient, suffering from "Carney's complex", had onset symptoms related to ACTH-independent hypercortisolemia. No established protocols are currently available for the management of this condition. Bilateral adrenectomy is often the only resolving treatment approach for hypercorisolemia. In our case, a two-years fair clinical-biochemical response to Metyrapone was observed, but it cannot be ruled out that other medical therapies or bilateral adrenectomy will have to be considered.

P2-160

Factors Influencing the Final Height of Congenital Adrenal Hyperplasia Patients

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Introduction: CAH is a common clinical condition with treatment and follow-up challenges. As a result, the adult height of the cases is known to be affected. We aimed to assess the growth and pubertal development of CAH patients and the factors that influence final height.

Method: Between 1980-2022, 41 patients diagnosed with CAH were observed at our clinic. Only cases that attained the final height were retrospectively analyzed. The following factors were assessed: admission complaints, demographic, clinical features, medical/surgical treatments, subsequent clinical course, laboratory and genetic results, bone age, target, and final heights, and long-term follow-up data. The cases were divided into 2 categories at the analytical stage: those with 21 hydroxylase deficiency and those with 11 beta-hydroxylase deficiency.

Results: Thirty-three (80%) of the cases were being followed up on, with the diagnosis of 21 hydroxylase deficiency and 8 (20%) of the cases having 11 beta-hydroxylase deficiency. 56% of the patients had ambiguous genital structures; 7% had macro genitalia; 10% had vomiting, weakness, and inability to gain weight; and 46% had increased hair growth. The consanguineous marriage occurred 51% of the time, and a similar history in the family occurred 34% of the time.

The salt-lasting form was diagnosed in 9 (27%) of the 21 cases with hydroxylase deficiency, the simple-virilizing form in 11 (33%), and the late-onset form in 13 (40%). The age at which puberty started, the height SDS, the final height SDS, and the final height age did not differ statistically between the 2 groups. The height measured at the time of admission had a considerably higher SDS in the 11 beta-hydroxylase group (p:0.013); the target height/height SDS difference was also significantly higher in the 11 beta-hydroxylase group (p:0.004). The height SDS at the onset of puberty negatively correlated with the final height/target height SDS difference (p:0.04/R:-0.497). A negative correlation was discovered between the age of diagnosis and final height (p:0.02/R:-0.369). The final height/target height SDS difference negatively correlated with the target height SDS (p:0.02/R:-0.576), as did the target height/height SDS difference at the time of admission (p:0.03/R:-0.563). In 7(17%) cases, GnRH analog was used due to central puberty praecox.

Conclusion: Patients with CAH should be closely monitored for growth and puberty to achieve a better final height. Late diagnosis, inadequate treatment, and shorter stature at puberty's onset deleteriously impact final stature.

P2-168

Cushing's Disease: an Example of Drug Shortage's Impact in Pediatric Endocrinology

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Cushing's disease (CD) is defined as hypercortisolism secondary to an adrenocorticotropin (ACTH) secreting pituitary adenoma. It is rare in the pediatric age and early diagnosis and treatment are important to prevent long-term complications. In the diagnostic workup, bilateral inferior petrosal sinus sampling (BIPSS) of ACTH after corticotropin-releasing hormone (CRH) stimulation is the gold standard in the differential diagnosis of ACTH-dependent hypercortisolism.

We report the case of a 14-years old female patient who came to our attention for growth failure, rapid weight gain, swelling of the face and hypertrichosis, without a history of recent or prolonged corticosteroid therapy. Hypercortisolism was confirmed by 24-h urinary free cortisol (UFC, repeated twice) and two dexamethasone suppression tests. High levels of basal plasma ACTH measured at 8 am allowed to identify an ACTH-dependent form. To confirm the pituitary etiology we performed a high-dose dexamethasone suppression test with a positive result, showing a decrease of > 70% and > 90% respectively of plasma ACTH and cortisol. She underwent two pituitary MRI which failed to identify any lesion or abnormality. We couldn't perform BIPSS with CRH stimulation because of CRH shortage and therefore we weren't able to localize the tumor and perform pituitary surgery. To treat the hypercortisolism and prevent related complications the patient is being treated with osilodrostat, a suppressor of adrenal steroidogenesis.

In pediatrics, over half of the pituitary adenomas are undetectable in MRI. In these patients, BIPSS after CRH stimulation is the gold standard to localize the tumor but since the production of corticorelin was discontinued in September 2020 we are now unable to perform it. Desmopressin has been used as an alternative but there is no extensive literature on its use in pediatric patients. When unable to localize the tumor, as in our reported case, surgery cannot be performed, and patients must start long term medical treatment with possible adverse effects.

Drug shortage has been increasing in the last years, affecting patient's correct medical care. Similarly to CRH, many other hormonal therapies (such as Growth Hormone Releasing Hormone, GHRH) are now unavailable. We report an example of how drug shortage can negatively impact the diagnostic workup in pediatric endocrinology and influence the therapeutic options. New political propositions are needed to incentivize the production of these less profitable drugs.

P2-169

Von Hippel-Lindau syndrome in a 9-year-old boy

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Background: Von Hippel-Lindau (VHL) syndrome is a rare autosomal dominant genetic disorder characterized by retinal and central nervous system hemangioblastomas, pheochromocytomas and multiple cysts in the pancreas and kidneys, with increased risk of malignant degeneration.

Case Presentation: A 9-year-old boy with uncomplicated premorbid and family history presented with ice-cold hands and profuse night sweating on the head and chest since 1 month. The only pathological findings from the physical status were sinus tachycardia and persistent arterial hypertension up to 160/100 mmHg. The FBC and all biochemical and hormonal tests (TFT, Cortisol, Aldosterone and PTH) were within reference ranges except for elevated plasma Dopamine: 78.8 pg/ml (0-50 pg/ml) and 24-hour urinary Normetanephrines: 16 922 µg/24h (n< 600 µg/24h). The CT scan revealed a well-demarcated, rounded, inhomogeneous tumor formation 47/38 mm in the right adrenal gland and an irregular oval nodular lesion 14/17 mm in the left adrenal gland. A small-sized, 3 mm, low-density round nodule was found in the thyroid gland.

The patient underwent laparoscopic radical right adrenalectomy without surgical intervention on the left adrenal gland. The histological analysis showed alveolar pheochromocytoma with slightly expressed polymorphism and extensive necrosis.

The differential diagnosis included: Multiple endocrine neoplasia type 2A or 2B; Von Hippel-Lindau syndrome; Familial paraganglioma syndrome; Neurofibromatosis type 1 and sporadic PHEOs.

The analysis of 19 genes, associated with hereditary syndromes with CNS and PNS tumors, detected a rare heterozygous pathogenic variant: c.340G>A (p.Gly114Ser) in exon 1 of the VHL gene, encoding the tumor-suppressor protein VHL.

During the first six postoperative months the urinary Normetanephrines remained in the upper part of the normal range, after which they started to rise gradually. At the last visit, one year after the operation, the patient was asymptomatic, normotonic, with normal growth. The 24-hour urinary Normetanephrines were elevated - 1 250 µg/24 (n< 600 µg/24h). The abdominal MRI revealed that the tumor in left adrenal gland had increased to 20/27 mm. MRI suggested that it might be malignant. No renal or pancreatic lesions were detected. Ocular involvement was excluded by fundoscopy. Due to the lack of focal neurologic symptoms CNS imaging was not required. A left adrenalectomy was planned.

Conclusion: The early identification of VHL is important in view of the increased risk of malignancy. The pleiotropic clinical manifestations require a close, lifelong surveillance (especially of the renal, ocular and nervous systems) in order to timely detect and treat the complications.

P2-186

Severe hypertension with hypokalemia in uncompliance child with CAH: Fludrocortisone a cause of HTN

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Introduction: Congenital lipoid adrenal hyperplasia (CLAH) due to mutation in StAR gene, is the most severe form of congenital adrenal hyperplasia (CAH). Affected patient had intracellular cholesterol accumulation in the adrenal glands and tests that manifest clinically in adrenal insufficiency and sex reversal in XY male. Hormonal replacement therapy with physiological doses of glucocorticoids and mineralocorticoids, is the treatment option.

Case Presentation: A 4 year old XX female diagnosed in the neonatal periods with CLAH, based on clinical manifestation of hyperpigmentation and laboratory findings of hyperkalemia, hyponatremia, low cortisol and low 17-hydroxyprogesteron. Genetic testing confirmed the diagnosis of homozygous mutation in exon 3 of StAR gene ,c.201_202delCT (p.leu67fsX3). She was maintained on hydrocortison (15mg/m^2/day) and fludrocortisone 0.1 mg twice daily. The family lost follow up and kept on the same doses till age of 4 years. Later, she was admitted with respiratory distress. During hospitalization found to have hypokalemia, normal sodium, and BP 150/100 (severe hypertension >>95th percentile for systolic and diastolic). Fludrocortisone was stopped, potasuim supplement and anti hypertensive medication (spironolactone & hydralazine) was added. As no respond, she was shifted to metalazone 5mg with improvement in BP. Renal causes was ruled out, and cardiac echo showed mild LV hypertrophy. She was initially discharge on hydrocortison 15 mg/m2/day, K supplement & metalazone for 3 months, then kept only on hydrocortison. Six months later, fludrocortisone 0.05mg was resumed due to electrolytes disturbances, without hypertension (HTN).

Discussion: Fludrocortisone is a synthetic adrenal steroid with high mineralocorticoid activity. It acts on mineralocorticoid receptor, increase transcription of ENac and up-regulate positive regulator of channel that result in Na retention and HTN.

Conclusion: Hormonal replacement therapy with physiological dose of glucocorticoids and fludrocortisone is the option of treatment in CLAH. BP monitoring with Regular follow up and age based dose adjustment is recommended to avoid complications.

References

- Hashemipour M, Ghasemi M, Hovsepian S. A case of congenital lipoid adrenal hyperplasia. Int J Prev Med. 2012;3(7):510-514.
- Sun Y, Zhang JN, Zhao D, et al. Role of the epithelial sodium channel in salt-sensitive hypertension. Acta Pharmacol Sin. 2011;32(6):789-797. doi:10.1038/aps.2011.72.

P2-187

Challenges and barriers of choosing the sex in patients with congenital adrenal hyperplasia: a case report

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Background: Congenital adrenal hyperplasia (CAH) is a disorder, leading to hyperandrogenaemia in the period of organogenesis of external genitalia, resulting in the disorders of sex development(DSD) in 46XX patients where external and internal genitalia do not correspond to each other.

The aim of current work is to show the barriers and challenges in a 46XX patient in choosing the sex for up-bringing the child.

Case Presentation: Two children in a family were diagnosed with CAH after birth with 46XX (senior-child) and 46XY (younger-child) karyotypes. The younger child has obviously normal male external and internal genitalia. The senior child has female internal and male (empty scrotum) external genitalia. The child was admitted to the hospital at 2 months old with the multicystic kidney disease and was referred to endocrinologist with hyperkalemia and weight loss. Genetic analysis was performed, CYP21A2-gene mutations were found. The treatment was started with poor compliance. The parents insisted on keeping the male sex. At the age of 5 years the child was diagnosed with Mediterranean Fever (two MEFV-gene compound-heterozygous mutations, M694V/V726A). Due to poor treatment compliance the central precocious puberty (CPP) developed at the age of 5years, breast, uterus and ovaries enlargement were revealed in contrast with the enlarged penis and pubic hair(Tanner 3-4). The bone age was accelerated and corresponded to 14 years. Parents were pushing the surgeons to do hystero-, ovaries- and breast-ectomy, but were unsuccessful. Incompliance to the treatment was documented at the inpatient clinic, the parents understood that increasing the adrenal androgens would not play a role in the sex choosing, they starting the adequate treatment for both CAH (hydrocortisone+fludrocortis one) and CPP (triptorelin injections).

Conclusion: Hyperandrogenaemia in CAH fetus prenatally can lead to ambiguous or reverse external genitalia development, which has a psychological implication for the child and the family. The choosing of the sex for upbringing the child is challenging and has many medical and social barriers also due to lack of legal regulations.

Healthcare professionals should find the optimal treatment with no harm on the patient’s health condition, to consider the parents’ opinion and not to ignore the right of patient’s choice.

P2-188

7-year-old girl as compound heterozygote of non-classic congenital adrenal hyperplasia

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Background: Deficiency of 21-hydroxylase (CYP21A2) is responsible of 90-95% of all cases of congenital adrenal hyperplasia (CAH). CYP21A2 converts 17OHprogesterone into 11deoxycortisol and is encoded by the CYP21A2 gene on chromosome 6p21.3, within the class III region of the highly polymorphic HLA histocompatibility complex. CAH refers to a group of autosomal recessive disorders. Nonclassic CAH (NCAH) is milder and more common, however it may not be identified until childhood or early adulthood. Clinical features in late childhood include premature adrenarche, acne and accelerated bone age. Adolescent and adult females present with acne, hirsutism and menstrual irregularity. The frequency of NCAH is ethnic-specific, with the prevalence being even higher among Mediterraneans, Hispanics, and Eastern European Jews (1/1000-1/100).

Objective: We report an 7-year-old girl with precocious adrenarche, who was investigated for CAH.

Case Presentation: An 7-year-old girl was admitted as the first clinical feature of CAH, for evaluation of pubic hair. Clinical examination showed precocious adrenarche, Tanner stage pubic hair III, without any secondary sex characteristics maturation. The past medical history includes multiple respiratory infections. All tests for early puberty were negative (synacthen test, bone age, hormonal investigations) except for the U/S, which revealed adrenal hyreplasia. Genetic analysis was performed using whole-exome sequencing.

Results: Molecular genetic testing confirmed compound heterozygous mutations in the CYP21A2 gene: p.P453S (c.1357C>T) (maternal mutation) and p.P30L (c.89C>T) (paternal mutation) at exons 10 and 1 respectively. Diagnosis of compound heterozygote of NCAH was established and hydrocortisone therapy was initiated.

Conclusion: Approximately two-thirds of patients with NCAH are compound heterozygotes. Hundreds of mutations of CYP21A2 have been described, with p.P453S, p.P30L among 12 most common for the nonclassic phenotype. As NCAH presents with a wide range of clinical variants the patient phenotype cannot be predicted based on the mutations of the CYP21A2 gene, as NCAH can present with a wide range of clinical variants.

P2-189

A rare case of a newborn with congenital adrenal hyperplasia, osteogenesis imperfect and cow's milk allergy

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Background: Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a rare pediatric disorder. The classic form occurs in 1:15,000 births worldwide. Osteogenesis imperfecta is a rare bone disease occurring in 1 in 15,000 to 20,000 births. Cow's milk allergy (CMA) is of the commonest food allergies in early life. Our case presents the co existence of the abovementioned entities in a patient.

Case Report: A newborn female was born at term to consanguineous parents after an uncomplicated pregnancy. The clinical examination revealed atypical external genitalia suggestive to masculinization. The diagnosis of congenital adrenal hyperplasia (CAH) was considered and had to be excluded to prevent acute adrenal crisis. Cortisol levels were low at baseline as were and after ACTH stimulation test. The diagnosis of primary CAH was confirmed with genetic testing, which documented homozygous pR316X/pR316X classic form of CAH due to 21-hydroxylase deficiency with salt loss.

Additionally, during the first month of life, the patient was admitted to the emergency department with symptoms of vomiting, bloody diarrhea and electrolyte disturbances. After restoring the electrolyte imbalance and ruled out pyloric stenosis, cow milk intolerance was considered due to family history (father allergic to cow's milk). The baby was commence to hydrolyzed formula and the symptoms where resolved, thus supporting the diagnosis of cow's milk allergy.

Moreover, due to blue sclera and the family medical history (the father had multiple hospitalizations due to bone fractures and he received osteogenesis imperfecta treatment without ever being genetically tested) a genetic panel for osteogenesis imperfecta was send. It tested positive, disclosing that the patient was heterozygous for COL1A1 c. 903+1G>T, as also her father.

The medication on discharge was hydrocortisone, fludrocortisone and sodium chloride, extensively hydrolyzed formula and a high dose of Vitamin D.

Conclusion: This coexistence of three conditions in one patient is rare and emphasizes the need for vigilant clinical assessment. Future research could explore the possible interplay between the three conditions and their effect on the patient's outcome. A multidisciplinary approach - involving in our patient endocrinologists, gastroenterologists, bone expert and geneticists- is essential for managing patients with rare and complex conditions.

P2-190

Evaluation of two cases with 46,XX and 46,XY karyotypes diagnosed with 17α-hydroxylase deficiency

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Introduction: 17α-hydroxylase deficiency (17OHD) is a rare form of congenital adrenal insufficiency characterized with decreased cortisol and sex steroid biosynthesis, overproduction of ACTH, and increased mineralocorticoids. The overproduction of corticosterone hinders the symptoms of glucocorticoid deficiency and causes sodium retention, hypertension, and hypokalemia in severe cases. Affected 46,XX and 46,XY individuals are phenotypically female in the severe 17OHD.

CASE 1: A 15-year-old girl was referred for the absence of puberty and headache. The previous and family history was nonsignificant except parents being first-degree cousins. On physical examination,her height:162.2 cm(0.05 SDS), weight:43.8 kg(-2.02 SDS), BMI:16.65 kg/m2 (-2.42 SDS). Blood pressure was 147/98 mmHg. The patient was prepubertal and had a typical female genitalia. The endocrinological evaluation revealed; ACTH:563 pg/mL(N:7.2-63), FSH:70 IU/L (N:3.5-12.5), LH:14 IU/L (N:2.4-12.6), progesterone:10.8 ng/mL (N:0.20-27), E2:<5pg/mL, T.testosterone:<2.5 ng/dL, AMH:1.03 ng/mL (N:0.62-7.8),17OH progesterone:0.16 ng/mL (N:0.47-4.32), morning cortisol:0.7 mcg/dL (N:4.8-19.5), DHEA-S:5 μg/dL (N:65-368), 1-4 androstenedione:0.028 ng/dL (N:0-4.71), renin:0.38 ng/mL, Na:143 mEq/L, K:4 mEq/L.Uterus was seen in ultrasonography.Karyotype resulted 46,XX.

CASE 2: An 11-year-old girl was referred for hyperpigmentation in the skin folds and the absence of uterus in ultrasonography, while she was on chemotherapy for lymphoma.

The patient's parents were first-degree cousins.

On physical examination, her height:150.6cm(0.51 SDS), body weight:45kg (0.63 SDS), BMI: 19.84 kg/m^2 (0.55 SDS). blood pressure was 123/77 mmHg. The patient was prepubertal and had a typical female genitalia. The endocrinological evaluation revealed;ACTH:199 pg/mL(N:7.2-635), FSH:41 IU/L(N:3.5-12.5), LH:32 IU/L(N:2.4-12.6), progesterone:6.61 ng/mL(N:0.20-27), E2:<5 pg/mL(N:30.9-90.4), T.testosterone:<2.5 ng/dL, AMH:9.40 ng/mL(N:0.62-7.8), 17OH progesterone:<0.01ng/mL(N:0.47-4.32), morning cortisol:0.5 mcg/dL(N:4.8-19.5), DHEA-S:1.94 μg/dL(N:65-368), 1-4 androstenedione:undetectable, renin:<1.1 ng/mL(N:<5.9), aldosterone: <3.7 ng/dL Na:136 mEq/L, K:3.6 mEq/L. Mullerian structures were not seen in ultrasonography, and a structure that may belong to the testis was detected in the inguinal canal and intra-abdominal area. Karyotype resulted 46,XY. The psychiatric evaluation revealed a female gender identity. The diagnosis of 17OHDwas confirmed by molecular analysis. In addition to hydrocortisone treatment, antihypertensive treatment was started in the first patient, and gonadectomy, E2 replacement therapy and blood pressure monitoring was planned for the second patient. Conclusion:In these two cases with 46,XX and 46,XY karyotypes, 17OHD was identified in the differential diagnosis of hypergonadotropic hypogonadism. The absence of or obscure hypertension and electrolyte imbalance may lead to a delay in diagnosis even in severe cases with 17OHD.

P2-191

Should we routinely assess hypothalamo-pituitary-adrenal axis in pediatric patients with Prader-Willi Syndrome?

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Background: It was reported recently that central adrenal insufficiency (CAI) in pediatric patients (pts) with Prader-Willi Syndrome (PWS), presented in up to 60% of them, could be a potential cause of sudden death. Moreover it has been suggested that CAI could be aggravated by rhGH recombinant human growth hormone (rhGH) treatment.

Objective: To prevent both over- and undertreatment with hydrocortisone, we assessed the prevalence of CAI in a large multicenter cohort of pediatric patients with PWS analysing adrenal response in Low-Dose ACTH Test (LDAT) or/and in Glugacon Stimulation Test (GST).

Methods: Forty-six pts with PWS were included into the study. Thirty-three of them were treated with rhGH, with median dose 0.21 mg/kg/week. LDAT with 1 μg tetracosactrin i.v. was performed in 33 pts. Serum cortisol and plasma ACTH at baseline and cortisol response after stimulation were measured. Serum cortisol at baseline and after stimulation was measured in GST (0.1 mg/kg i.m.) in 2 pts. Both tests were performed in 11 pts. Tests started at 8.00 a.m. All hormones were measured using radioimmunoassays. A serum cortisol response > 181.2 ng/ml (500 nmol/l) in LDAT and > 199.3 ng/ml (550 nmol/l) in GST was considered a normal response. Additionally, either delta of cortisol response (the difference between the baseline and its highest value) > 90 ng/ml or doubling/triplication of baseline cortisol indicates normal adrenal reserve.

Results: Three GSTs were not diagnostic (no hypoglycemia). The LDAT results suggested CAI in 4 pts, but in 2/4 CAI was excluded in GST. The GST suggested CAI only in one patient, but it was excluded in LDAT. Therefore CAI was diagnosed in 2/46 pts (4.3%), one treated and one untreated with rhGH, with the highest cortisol values 162 and 175 ng/dl, but only in one test. However, in one of them delta cortisol response was > 90 ng/ml and more than tripled from baseline. So finally CAI was diagnosed in one pt with PWS treated with rhGH (2.2%).

Conclusion: Our data do not confirm a necessity of the routine diagnostics towards CAI in PWS pts. We present low occurrence of CAI in pediatric pts with PWS. Moreover, either LDAT or GST are not sensitive enough in diagnosing CAI in PWS and a suspicion of CAI in one of them should be confirmed in another. Treatment with rhGH in PWS pts rather does not increase CAI incidence.

P2-192

Neonatal CAH screening in patients with rare causes of inherited primary adrenal insufficiency

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Background and Objective: 21alpha-hydroxylase deficiency congenital adrenal hyperplasia (21OHD-CAH) is the most common etiology of inherited primary adrenal insufficiency (PAI) in children. Neonatal CAH screening is important for early diagnosis of salt-wasting 21OHD and other virilizing CAH (11beta-hydroxylase, 3beta-hydroxysteroid dehydrogenase deficiencies) and for avoiding mortality, especially in salt-wasting CAH. Neonatal CAH screening has become nationwide since the beginning of 2022 in Turkey. Nevertheless, neonatal CAH screening is negative in newborns with symptomatic adrenal insufficiency due to rare non-CAH PAI and congenital central adrenal insufficiency. Here clinical data and neonatal CAH screening results of 5 newborn babies with non-CAH PAI are presented.

Patients and Results: Patients (n=5) were presented with hyperpigmentation (n=5), hypoglycemia (n=2), hyponatremia (n=2), hyperkalemia (n=1), respiratory distress syndrome (n=1) between 3rd hour to 2 months of life. All of them had negative neonatal CAH screening with low 17hydroxyprogesterone (0.05-0.85 ng/mL). After critical blood samples were taken, glucocorticoid therapy was started in all patients. Fludrocortisone was also added in two of the patients. In the molecular analysis, biallelic mutations were found in the MC2R (n=3; 2 homozygous, 1 compound heterozygous), MRAP1 (n=1) and StAR (n=1) genes (Table).

Conclusion: A negative neonatal CAH screening cannot exclude the diagnosis of non-CAH PAI even in severely symptomatic newborns. All newborns with symptoms and signs of adrenal insufficiency should be investigated further and treated with glucocorticoids to avoid poor clinical outcomes.

	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**
1st step 17OHP	0,16 ng/ml	0,85 ng/ml	0,13 ng/ml	0.05 ng/ml	0.05 ng/ml
presenting time	Postnatal 1t h day	At 2.5 months of age	Postnatal 1th hour and On the 6th day	postnatal 3rd hour and at 2 months of age	postnatal 1th day and on the 6th day
symptom	Darkening of skin color	hyponatremia (118 meq/L), hyperkalemia/12 meq/L) Darkening of skin color	RDS and hyponatremia (122 meq/L) darkening of skin color	hypoglycemia and darkening of skin color	hypoglycemia and darkening of skin color
etiology	MRAP1 homoz. c.106+1del	STAR homoz. p.Leu157Pro	MC2R homoz. c.560del	MC2R comp.hetero. c560del/c.702del	MC2R homoz. c.560del

P2-193

Patient with Carney complex syndrome due to PRKAR1A mutation

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Introduction: Carney Complex is a rare genetic disorder inherited in an autosomal dominant manner or may occur sporadically due to de novo mutations. It is characterized by the presence of cardiac myxomas, psammomatous melanotic schwannomas, skin pigmentation (blue nevi, lentigines) and multiple endocrine and non- endocrine tumors. It is caused by inactivating mutations or large deletions of the PRKAR1A gene. Management of the syndrome involves ongoing surveillance and treatment of clinical manifestations and complications.

Aim: Clinical presentation, laboratory values, molecular genetic testing, treatment and monitoring of a patient with Carney complex, first diagnosed with adrenal Cushing's syndrome due to primary pigmented nodular adrenocortical disease (PPNAD).

Patient and Methods: The patient was referred at the age of 82/12 years due to rapid weight gain the last 4 months. Her past medical history was insignificant, but her father had a testicular seminoma surgically removed years ago. Her physical examination showed central obesity (BMI>97 percentile), hypertension, buffalo hump, moon facies and red striae at thighs. On biochemical workup, 24h urinary free cortisol (UFC) levels were elevated and serum ACTH levels were undetectable. Moreover, an overnight 1 mg dexamethasone suppression test failed to suppress morning serum cortisol levels. The child was put on felodipine and CT and MRI imaging of retroperitoneum revealed mild bilateral adrenal thickening, mostly of the left gland.

Treatment and follow up: The patient underwent left adrenalectomy. The pathology analysis revealed PPNAD. A remission phase of Cushing's followed with loss of body weight, improvement of growth rate, normal evolution of adolescence. Furthermore, antihypertensive therapy was withdrawn as she was normotensive. Due to the pandemic, she was not consistent with her medical appointments and at the age of 105/12 years, she appeared with weight gain, blue nevi as well as skin and oral mucosa hyperpigmentation. Recurrence of Cushing Syndrome was not confirmed. At that point, a Whole Exome Sequencing of the patient and her parents took place, and revealed a heterozygous paternal origin mutation (pathogenic variant p.Arg97Stop) in the PRKAR1A gene. Thyroid gland and internal genitalia ultrasound imaging were normal. At the age of 114/12 years, with progressive weight gain and fall in growth rate, Liddle tests took place which confirmed recurrence of Cushing syndrome. Right adrenalectomy is planned.

Conclusion: PPNAD is combined with Carney Complex syndrome at a rate of 60%. Early detection and genetic identification of the syndrome allows timely diagnosis and treatment of multiple evolving clinical manifestations.

P2-202

Rare Association of 11 Beta Hydroxylase Deficiency and Gitelman Syndrome and Overlapping Symptoms

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11 Beta Hydroxylase Deficiency and Gittelman Syndrome are two rare autosomal recessive diseases. Our patient,whose brother had 11 beta Hydroxylase Deficiency, was diagnosed at the antenatal period. We detected hypomagnesemia,hypokalemia, hypocalciuria and metabolic alkalosis at the age of 3 years and 8 months, after vomiting and diarrhea. In our patient, a homozygous mutation was detected in the SLC12A3 gene at the c.1049C>T (p. Ser350Leu) (rs7785585043) location. There is a relationship with Gittelman Syndrome in the literature, the clinical and laboratory findings of our patient, whom we followed up with the diagnosis of 11β-OHD deficiency, which did not coincide with this disease, became clear. Although serum and urine biochemical parameters and clinical findings are guiding in Gittelman Syndrome, genetic testing is important in cases with additional disease in which clinical and laboratory findings may be confused, as in our patient with 11 beta hydroxylase deficiency. The coexistence of these two rare diseases is presented for the first time in the literature.

P2-203

A male infant with X- linked congenital adrenal hypoplasia and Xp 21 contiguous gene deletion syndrome- case report

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Background: The Xp21 contiguous gen deletion syndrome is a rare disorder which is characterized by complex glycerol kinase deficiency, congenital adrenal hypoplasia, intellectual disability and Duchenne muscular dystrophy. It is caused by partial deletion of Xp 21. On Xp21 several genes are located contiguously, such as NR0B1/DAX1, dystrofin gen and gene for glycerol kinase, and the clinical features depend on the size of the deletion. The major clinical manifestations are: electrolyte imbalance and hyperpigmentation of skin, psychomotor retardation, lethargy, convulsions, muscle weakness and hypotonia. We present the case of 8-day old patient with this rare disease.

Case Report: A 8-day old male newborn was admitted to our clinic for vomiting, poor feeding, weight loss and scrotal hyperpigementation. He was born at 37 weeks of gestation from uncomplicated pregnancy by spontaneus vaginal delivery. Birth lenght was 47cm (3rd percentile). Birth weight was 2610 g (10th percentile). There was no family history of endocrine disorders or consanguinity. Essential finding at presentation showed dehydrated neonate with blood pressure 52/34 mmHg, bilateral cryptorchidism and scrotal hyperpigementation. Laboratory findings showed hypoglicaemia (1,4mmol/l), hyponatremia (122 mmol/l), hyperkalemia (6,1mmol/l), extremely elevated adenocorticotropic hormone (ACTH 6870 pg/ml), low cortisol (13 ng/ml), abnormaly low aldosteron (1,0 ng/ml), high plasma renin concentration (500 mIU/ml) and normal range of 17-hydroxyprogesteron. An ultrasound of adrenals was demonstrated small for age adrenal glands. Based on the biochemical features of hyponatremia, hyperkalemia, hypoglycemia, low cortisol, low aldosterone, high ACTH, he was diagnosed to have primary adrenal insufficiency. Hydrocortisone and fluorohydrocortisone treatments were started. He was well until six months. He regularly came for endocrinologist checks-ups and his supstituion was good. At the age of 6 months, he became hypotonic and he had hypertransaminasemia, high creatine phosphokinase (9516 U/l) and high triglyceride (7,1 mmol/l). Combining this evidence of adrenal hypofunction with highly elevated creatine phosphokinase levels and hypertriglyceridemia, the Xp21 contiguous gen deletion syndrome was suspected. Neonate underwent genetic investigations. Microarray analysis showed the Xp deletion (Xp 21.2-21.3), which include NR0B1, GK, and DMD genes.

Conclusions: The Xp21 contiguous gen deletion sydrome is a rare disorder in our population which requires multidisciplinary team approach. Pediatricans should consider Xp 21 syndrome in infants with congenital adrenal hypoplasia, hypotonia, increased levels of creatine phosphokinase, transaminases and triglycerides to be able to prevent and treat the possible complications.

P2-212

A rare case of Aldosterone synthase deficiency presenting with Hypertension

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Introduction: Aldosterone synthase deficiency (ASD), also known as Corticosterone methyloxidase deficiency, is a rare autosomal recessive disorder characterized by severe hyperkalemia, salt loss, vomiting, severe dehydration and failure to thrive. It is caused by inactivating mutations of the *CYP11B2* gene.

We herein report the first confirmed Egyptian infant who had clinical and hormonal features of aldosterone synthase deficiency. Unexpectedly, our patient had hypertension at diagnosis.

Case Summary: A 4-month-old boy born to consanguineous parents with a birth weight of 3.700 Kg, presented with faltering growth noticed since the age of 2 months. He had history of recurrent vomiting and poor feeding, and no history of polyuria or polydipsia. His weight was 4.5 KG (-3SD), length 51 cm (-4.3SD), penile length 3 cm, and palpable testes. Despite being dehydrated, his blood pressure was between the 95th and 97th percentiles for age.

His laboratory investigations showed hyponatremia, hyperkalemia, and metabolic acidosis. His random blood sugar, and renal functions were normal. Congenital adrenal hyperplasia was excluded with normal levels of 17-hydroxyprogesterone 1.04 ng/ml (0.34-4.7), ACTH 8am 4.32 pg/ml (7.2-63), and cortisol 8 am 20.97 ug/dl. Pseudohypoaldosteronism was suspected due to the elevated blood pressure, however, renin, aldosterone were done showing hyperreninemic hypoaldosteronism. He had elevated spot Na 58 mEq/L, and Cl 30 mEq/L in urine, with low urine K 6.2 mEq/L and a transtubular potassium gradient of 2. Ultrasonography of the kidneys and adrenal glands were normal. These findings suggested a diagnosis of aldosterone synthase deficiency, and treatment with fludrocortisone, sodium chloride 3%, and oral bicarbonate was started. In addition, therapy with angiotensin-converting enzyme inhibitor was transiently required initially to control elevated blood pressure. A novel homozygous pathogenic variant was identified by genetic analysis in *CYP11B2* (c.1012C>T, p.Gln338Ter) confirming the diagnosis of congenital hypoaldosteronism due to corticosterone methyloxidase II deficiency.

Conclusion: Although a rare cause of hyperreninemic hypoaldosteronism, aldosterone synthase deficiency should be suspected in infants presenting with salt-wasting. It is a life-threatening disease, if left untreated; however, it has a good prognosis when adequate fludrocortisone replacement is given. Hypertension has been rarely reported and is postulated to be caused by the high levels of renin and angiotensin II as potent vasoconstrictors.

P2-213

Pseudohypoaldosteronism in congenital anomaly of the kidneys and urinary tract – Case presentation

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Introduction: Pseudohypoaldosteronism (PHA) is a clinical syndrome characterized by multiorgan or isolated renal tubular resistance to the effects of aldosterone, resulting in hyperkalemia, metabolic acidosis, and normal to high serum aldosterone levels. PHA may be primary (hereditary) or secondary (acquired). Primary forms are subclassified into two: PHA type 1 (salt-wasting) and PHA type 2 (salt-retaining). Secondary forms are typically associated with severe urinary tract infections (UTIs), often combined with obstructive congenital anomalies of kidneys and urinary tract (CAKUT). Secondary PHA are mostly seen in the first year of life, mimicking clinically PHA type 1. The electrolyte and acid-base changes are transient and usually determine with healing of the underlying urinary tract disturbance. The unrecognized PHA could lead to life-threatening hyperkalemia with severe dehydration and cardiopulmonary arrest.

Case Presentation: We report a 2-year old boy with pseudohypoaldosteronism and CAKUT

Till the age of 4 months the boy was admitted at The Clinic of Pediatrics of UMHAT – Pleven twice in life-threatening condition with dehydration, severe hyponatriemia (132-123 mmol/L), extreme hyperkalemia (6,3-8,4 mmol/L), metabolic acidosis (pH 7,29-7,18; BE -18,5) and acute kidney failure. He was undernourished with severe hypotrophy to marasmus. At first hospitalization salt-wasting form of Congenital adrenal hyperplasia (CAH) was excluded and appropriate feeding with hydrolysed formula was started. UTI with Klebsiella pneumoniae from urine culture was proven. Imaging testing was performed and an obstructive CAKUT (posterior urethral valves with bilateral megaureters and hydronephrosis) was detected. Because of the persistent electrolyte disturbances at second admission aldosterone and plasma renin were measured (renin 467,4 mU/L, aldosterone >2 770 pmol/L). Secondary PHA was diagnosed and continuing per oral sodium chloride and bicarbonate supplementation with excellent laboratory results was introduced. Later a stepwise operative correction of the CAKUT was started.

Conclusion: Secondary PHA is a rare clinical condition, but it should be considered in infants with salt wasting and hyperkalemia. In such of cases an early screening for CAKUT should be performed.

P2-214

APECED and COVID 19: Two Case Reports

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Introduction: Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is a rare autoimmune disease caused by a loss-of-function mutation in the autoimmune regulator gene (AIRE). AIRE gene mutation disrupts the negative selection of self-reactive T cells in the thymus, causing autoimmune reactions in endocrine and non-endocrine tissues. Impairment in T cell function is also associated with susceptibility to specific infections along with autoimmune diseases. Here, two cases who were diagnosed with APECED after COVID-19 infection and died with COVID-19 MIS-C while diagnosed with APECED will be presented.

Case 1: 5.5-year-old female patient was consulted to our clinic because of the detection of hyponatremia, hypoglycemia and hyperkalemia in the tests taken during the follow-up of the pediatric in-patient clinicdue to urinary tract infection. It was learned that she had an infection, had hyponatremia, hyperkalemia and hypoglycemia during the infection, and it was associated with vomiting during the infection. In physical examination; anthropometric values were normal. In the laboratory examination; glucose:62mg/dl, sodium:129mEq/L, potassium:5.53mEq/L, ACTH:942pg/mL and cortisol:5.3µg/dL. With the diagnosis of primary adrenal insufficiency, hydrocortisone treatment and fludrocortisone treatment was started. Other autoimmune diseases (celiac, autoimmune thyroiditis, diabetes autoantibodies, autoimmune hepatitis and hypoparathyroidism) were screened for autoimmune adrenalitis and it was negative. CES analysis result: AIRE, NM_004006.2, c.133-127_ c.539-182del, Exon 2-4 deletion was found to be homozygous.

Case 2: 12.5-year-old male patient who was diagnosed with hypoparathyroidism in another center and had a previously unidentified IVS3-3C>G(c.464-3C>G) homozygous mutation in AIRE gene was referred to our clinic. From his history, when he applied with the complaints of thrush in the mouth, weakness, at the age of eight; ıt was learned that calcitriol treatment was started with the diagnosis of hypoparathyroidism. In physical examination; body weight 35.9kg(-1.86SDS), height 140cm(-2.65SDS), diffuse vitiligo, photophobia, 8ml testicles. The case was admitted for further screening. Hashimoto's thyroiditis-euthyroidism phase (no goiter/nodules), primary adrenal insufficiency (Cortisol:8.1µg/dl ACTH:568pg/ml), autoimmune hemolytic anemia (Coombs positive), autoimmune asplenia (spleen not observed on USG, non-marking on scintigraphy, functioning spleen), autoimmune hypophysitis (infundibulum thick/pituitary heterogeneous) and growth hormone deficiency were detected. Hydrocortisone, growth hormone therapy, penicillin prophylaxis, and a preventive vaccination program were started. During his follow-up, he died with COVID -19 infection and MISC.

Conclusion: Here, two cases with APECED Syndrome, one of whom had a COVID-19 infection and one recovered without any problems and the other died, are presented to draw attention to the precautions to be taken in terms of the follow-up of these cases.

P2-215

Pseudocushing. an exceptional patology in pediatrics

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Introduction: PseudoCushing is an unusual pathology. Among adults several cases have been published, however, in paediatrics it is unusual.

Objective: Description of a PseudoCushing case from a patient admitted in a hospital and results from a study to discard secondary hypercortisolism due to stress.

Patients and Methods: 13 years old patient that it is admitted in hospital due to vomits and abdominal pain. A Hypercortisolism study was performed due to the presence of cutaneous striaes.

Personal History: Ileo-caecal invagination and prophylactic appendicectomy when 2 years old. Controlled by general paediatrics due to recurrent vomits (several hospital admissions).

Physical Exploration: Normal phenotype. Weight: 69 kg (p90-p97), Height: 168.1 cm (p90). Blood pressure: 117/77 mm Hg. Cutaneous striaes of unusual colour on the back.

There was not other signs of Hypercortisolism. Normal growth speed. During hospital admission, no medication was provided, apart from serum therapy and paracetamol.

Prospective Methodology: With the current exceptional process and the possibility that these symptoms were carried out by a stress situation, a prospective study was performed to discard hypercortisolism in acute hospital admitted patients. After the 2nd day of hospital stay tests of 1st level: 24h urinary free cortisol (UFC), Night Salivary Cortisol (NSC) (23-24H) and blood analytics at 8 AM (Glycaemia, cortisol y ACTH) were performed.

Results: COMPLEMENTARY STUDIES DONE DURING HOSPITALIZATION.

Complementary explorations: Glucose: 104 mg/dL; normal biochemistry, HbA1c: 4.8 %

24hUFC: 1st sample: 464 µg/24 h; 2nd sample: 428 µg/24h.

(Normal values (1-100 µg/24 h)

Blood Analytics: 1st sample: Cortisol: 37,3 µg/dL (normal values: 4.5-25 µg/dl), ACTH 45 pg/mL (normal values: 5-49 pg/ml) 2nd sample: Cortisol 26,2 µg/dL, ACTH: 45 pg/mL

NSC (23 h): 1st sample: 1.15 mcg/dl; 2nd sample: 0.73 mcg/dl (normal values <0.2 µgr/dl)

Suppression test with Dexamethasone: ACTH: non-detectable, Cortisol: 2 mcg/dl

Hypothalamus-hypophysis MRI: Normal morphology and density.

ANALYTICS AFTER 1 WEEK OF BEING RELEASED:

- UFC: 22 mcg/24 hours
- Night Salivary Cortisol (23h): non-detectable
- Night blood Cortisol: 1 mcg/dl

After the disappearance of Hypercortisoluria in several determinations hypercortisolism is discarded. After one year of the release the patient is asymptomatic.

Prospective: 5 patients have been valued and in none of them Pseudo-Cushing has been objectify.

Comments: Pseudo-Cushing is rare in paediatrics, but the acknowledgement of this entity can avoid erroneous diagnostics and treatments. Normal growth speed and weight gain can orient us towards previously mentioned diagnostic.

P2-216

Non classic congenital adrenal hyperplasia caused by mutations in CYP21A2

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Background: Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive genetic defects in cortisol synthesis caused by the deficiency of 21-hydroxylase which convert 17-hydroxyprogesterone to 11-deoxycortisol. A variety of mutations in one or more genes encoding enzymes essential for cortisol synthesis leads to a spectrum of disorders and disease severity. In general, complete or nearly complete enzymatic defects result in overt adrenal insufficiency, and are conventionally referred to as "classic" CAH. In milder forms of the disease, also termed "late-onset" or "non-classic" CAH (NCCAH), partial enzymatic defects are overcome by ACTH elevation. These patients have compensated cortisol and aldosterone production. Among genotypic mutations that cause NCCAH are p.P453S and p.P30L. p.P30L is 1 of the 8 most common. Clinical features may include premature pubarche, medication-resistant cystic acne and accelerated growth with tall stature as children. However, these children may enter puberty early, with early epiphyseal closure, leading to short stature as an adult.

Case Presentation: We report the clinical case of a 7-year-old girl which was compound heterozygote of 21-hydroxylase. Her parents were heterozygotes for NCCAH with the protein p.P453S (maternal mutation) and p.P30L (paternal mutation). Clinical examination revealed pubic hair (Tanner stage III) and the ultrasound revealed adrenal hyperplasia.

Conclusion: NCCAH is a relatively common disease, and it should be suspected and excluded in all women with PCOS-like phenotype, including hirsutism, acne, and menstrual abnormalities.

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P2-217

Primary hypoaldosteronism due to aldosterone synthase deficiency in a small for gestational age born infant

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Keywords: Primary hypoaldosteronism, aldosterone synthase deficiency, salt-wasting, failure to thrive, *CYP11B2* gene mutation

Introduction: Aldosterone synthase deficiency is a rare autosomal recessive inherited disorder. The patients carry mutations in the *CYP11B2* gene. It is primary hypoaldosteronism presented in early childhood with electrolyte abnormalities (hyponatremia, hyperkalemia, and metabolic acidosis), vomiting, salt-wasting, failure to thrive and impaired growth.

Patient and Methods: A 2-month-old female infant, born in term (40th gestational week), but small for gestational age (SGA) (birth weight -2.10 SDS and birth length -2.20 SDS), presented with failure to thrive and poor weight gain (-2.71 SDS), vomiting and moderate dehydration. The diagnostic assessment included a clinical examination, biochemical and hormonal investigations, followed by the imaging study and molecular analyses.

Results: The laboratory analyses revealed hyperkalemia (8.6 mmol/l), hyponatremia (128 mmol/l), and metabolic acidosis (pH 7.26, HCO3 16.8 mmol/l, BE -9.5 mmol/l), with elevated rennin (5293.00 ng/l) and low aldosterone concentration (28.6 ng/l). The targeted massive parallel exon sequencing analysis revealed a homozygous pathogenic variant, (c.554C>T; p. Thr185Ile) in exon 3 of the *CYP11B2* gene. Both parents are heterozygous carriers of the same variant. The parenteral rehydration and mineralocorticoid replacement treatment resolved the electrolyte imbalances and gradually increased weight gain.

Conclusions: Herein we present an SGA born infant with a rare isolated hyperreninemic hypoaldosteronism due to aldosterone synthase deficiency. The detected pathogenic variant in the *CYP11B2* gene in our patient is common for patients with hypoaldosteronism from the Southern Balkan region. Adequate and timely mannered diagnostic assessment and monitoring in these patients are not only necessary for the therapeutic approach, but also lifesaving.

P2-218

Early manifestation of primary adrenal insufficiency in patients with X-linked adrenoleukodystrophy: clinical cases description

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Keywords: Primary adrenal insufficiency, X-linked adrenoleukodystrophy, early manifestation

Background: The primary adrenal insufficiency (PAI) in patients with X-linked adrenoleukodystrophy (X-ALD) is known to develop commonly after three years of life and there are little cases with an early manifestation described. Here we report cases of early PAI manifestation in X-ALD patients.

Clinical cases description: Three patients with genetically confirmed X-ALD were referred to our institute.

The patient A, 7 years old, had a loss of acquired skills, hypotension and fatigue in 1.3 years. In 1.5 years he was diagnosed with X-ALD due to positive family history (cerebral form of X-ALD (cALD) in patient's brother). Blood examination showed elevated ACTH (914.4 pg/ml) and low serum cortisol (164.7 nmol/l) and PAI was diagnosed at 1.5 years. The combined hormonal replacement therapy (HRT) was started.

The patient B, 13 years, was also diagnosed with PAI (ACTH 333 pg/ml) and X-ALD in 1.5 years due to positive family history (cALD in patient's brother) without any sign of PAI. The HRT with hydrocortisone was initiated; fludrocortisone was added to the therapy at 2.6 years when the mineralocorticiod deficiency was diagnosed.

The patient C, 13 years, was noted to have an increasing weakness, vomiting, seizures during the infectious diseases, hyperpigmentation of the skin at 1.5 years. The PAI was diagnosed at 3 years (ACTH 1250 pg/ml, cortisol 9 nmol/l) and HRT with hydrocortisone had been prescribed. Fludrocortisone was added to the therapy at 4.3 years.

At the abstract publication time patients A and C have an isolated PAI as a form of X-ALD. Patient B was diagnosed with cALD at 4.5 years and undergone gene therapy with autologous CD34+ cells transduced with the elivaldogene tavalentivec during the BlueBirdBio trial of gene therapy in X-ALD patients. No data of disease progression received.

Conclusion: It is important to examine all male patients with PAI regardless of the manifestation age to exclude X-ALD. It is necessary to examine all male patients for the presence of PAI regardless of the diagnosis age of X-ALD.

P2-219

Osteoporosis as the first sign of Cushing disease - a case report

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We present the case of a 16.5-year-old short, thin boy with Cushing disease. The first symptom of the disease was spinal pain and vertebral fractures attributed to osteoporosis.

The patient was admitted to the clinic due to severe back pain. On dual X-ray absorptiometry (DXA), the Z-score TBLH was: -1.9, Z-score Spine: -4.2. The X-ray and magnetic resonance imaging (MRI) revealed multilevel fractures of the thoracolumbar vertebrae. The causes of this condition initially remained unknown. The boy was during puberty but short and thin (height: 162 cm, <3 percentile, BMI: 18.1 kg/m2).

In March 2021, at the age of 15.5 years, the boy was diagnosed with autoimmune hepatitis. For this reason, oral steroid therapy with deflazacort (Calcort) was introduced at an initial dose of 24 mg in the morning + 18 mg in the afternoon, which was gradually reduced. Spinal pain appeared as early as day 5 of steroid therapy, which argued against pharmacotherapy-related osteoporosis.

From the age of 11, the boy's growth rate slowed down and at that time he presented short stature - therefore a hormonal diagnosis was performed (during the administered steroid therapy). Growth hormone deficiency, hypothyroidism and coeliac disease were excluded as causes of short stature. An pituitary gland MRI examination described a poorly demarcated area measuring approximately 2 x 3.5 x 5 mm in the anterior part of the glandular lobe.

The MRI examination was repeated after 5 months - the previously observed area was faintly visible. During the endocrine check-up, attention was drawn to the "rigid" rhythm of ACTH and cortisol secretion (despite the cessation of steroid treatment over the past few months). A dexamethasone inhibition test was therefore performed, the results of which indicated Cushing disease, however, no ion, lipid and blood count abnormalities were observed in the patient.

Due to the raised suspicion of Cushing disease, in March 2022 the patient underwent a bilateral inferior petrosal sinus sampling. ACTH-dependent hypercorticosolaemia of pituitary origin was confirmed. The boy was qualified for transsphenoidal surgery of the pituitary adenoma. Postoperative histopathological examination revealed features of a corticotroph-rich pituitary adenoma.

Conclusion: The case we present is an atypical presentation of Cushing disease, in which the first symptom – apart from short stature - was osteoporosis. Traits characteristic for the disease - such as striae, abnormal fat distribution or typical features in laboratory tests including ionic, lipid or blood count disturbances were not found.

P2-220

A Case of Adrenal Suppression Secondary to Intranasal Betamethasone

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Introduction: A 5 month old boy is admitted to his local hospital with increased work of breathing secondary to a viral upper respiratory tract infection. The admitting team found pubic hair on examination, with otherwise normal infant genitalia, prompting a screen for precocious puberty. A low random cortisol was found at 15nmol/L. Following this, he had an inadequate response to a Synacthen test (peak Cortisol 190 nmol/L) demonstrating adrenal insufficiency. Awaiting results of further investigations, the infant developed bronchiolitis requiring local admission and then transfer to a tertiary unit for escalation of treatment.

Background: The infant was born at term and required a neonatal admission for respiratory distress. There were no antenatal concerns or family history of note. He had no dysmorphic features. However, there was difficulty passing a nasogastric tube and on ENT review he was diagnosed with pryifrom aperture stenosis. He was commenced on intranasal Betamethasone, 1 drop to each nostril BD from day 5 of life, which were continued on discharge.

Management: On admission to the tertiary hospital, in view of his failed Synacthen test and due to clinical deterioration, he was commenced on stress Hydrocortisone. On examination the infant was noted to have a markedly cushingoid appearance with hirsutism and pubic hair tanner stage 2. His testicular volume was pre pubertal with normal penile appearance for infancy.

Regarding his investigation results; ACTH was low at <2ng/L. Remaining pituitary hormones, adrenal androgens and urine steroid profile were all normal. An MRI brain showed a normal pituitary gland and an ultrasound abdomen showed no adrenal abnormality.

Adrenal Suppression secondary to long-term topical steroid treatment for nasal stenosis was diagnosed and Betamethasone were stopped. He was commenced on a gradual weaning Hydrocortisone regime over six weeks. A repeat Synacthen test post weaning steroids showed a satisfactory response and therefore resolved adrenal suppression.

Conclusion: This case supports the findings that all exogenous steroids put patients at risk of adrenal suppression and reinforces the recommendation that if glucocorticoids have been used for 3 weeks or longer, then an assessment of the integrity of the HPA axis should be performed.

These parents had not been made aware of the potential side effects of glucocorticoids and had not attributed the growth of pubic hair to his nasal treatment signifying the importance of patient/parent education and awareness of adrenal insufficiency risk with glucocorticoids.

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P2-221

Diabetes insipidus as first manifestation of congenital malformation of the neurocranium

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Central diabetes insipidus (CDI) at neonatal age may occur in the setting of intracranial abnormalities that affect the hypothalamus-pituitary system. These conditions are characterized by defective production, transport or secretion of antidiuretic hormone (ADH). This results in inappropriately low ADH levels in the setting of increased plasma osmolality.

We present the case of an infant born by C-section at 38 weeks of gestation, with bilateral cheilognatopalatoschisis, naso-maxillary hypoplasia and microcephaly.

The cranio-cerebral CT performed at 35 days of life reveals agenesis of the anterior knee and the middle 1/3 of the corpus callosum, possibly with the presence of the spenium of the corpus callosum, agenesis of the frontal horns of the lateral ventricle, hypoplasia of the third ventricle and cleft lip and palate. Blood tests reveal severe hypernatremia, suspecting central diabetes insipidus due to malformations of the middle floor of the neurocranium. Treatment with Minirin (Desmopresin) 30 micrograms daily is introduced with favorable evolution.

The patient is hospitalized at the age of 6 months for the surgical intervention for cheilognatopalatoshisis, which was carried out without problems. During the hospitalization in the plastic surgery clinic, the patient has a convulsive episode in the conditions of severe hypernatremia (163.61 mmol/L) associated with hyperchloremia (135.45 mmol/L), hypokalemia (3.09 mmol/L), which is why he is transferred to the department of intensive care, where he received 30 micrograms twice a day with subsequent favorable evolution.

The baby boy is discharged in good general condition, with a recommendation for treatment with Minirin 30 micrograms twice a day and ionogram monitoring.

CDI is a complex disease, due to the destruction of supraoptic and paraventricular neurons by germ cell tumors, surgical or accidental trauma, brain malformations, infections and rare genetic conditions.

Bone, growth plate and mineral metabolism

P2-51

Primary hyperparathyroidism in a pediatric patient with tuberous sclerosis

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Introduction: Tuberous sclerosis (TS) is a rare, autosomal dominant, multisystem disease with a frequency of 1:6,000-10,000. It is caused by variants in the genes encoding hamartin (TSC 1) and tuberin (TSC 2) that normally act as inhibitors of the mTOR signaling cascade that regulates cell proliferation and migration, angiogenesis, and cell metabolism.

The most frequent clinical presentation includes hypochromic macules, angiofibromas, hamartomas in the central nervous system (CNS), renal tumors, and cardiac rhabdomyomas among others.

There are few communications of neuroendocrine tumors in TS and their association with primary hyperparathyroidism is very rare, with only 4 cases reported, 2 of them in pediatric patients.

Case Report: An 11.5 years old male patient with history of TS confirmed by clinical criteria at 3 years of age (hypochromic macules, hamartoma in the CNS, and mother and sister with TS) was consulted to endocrinology department for the laboratory finding of hypercalcemia.

During anamnesis, he referred headache, nicturia and behavioral disorders with self and hetero-aggression. He had weight and height in 50 percentile, peripubertal, blood pressure in 90 percentile and normal EKG.

Within diagnostic studies it was requested: -biochemical profile: elevated calcemia (11.3 mg/dl), low phosphatemia (3.3 mg/dl), inadequate elevated PTH for calcemia (49 pg/ml), low 25(OH) D (12.8 ng/ml), normal ALP (296 IU/L), normal renal function, hypercalciuria (436 mg/day: 13 mg/k/day) and low tubular phosphorus reabsorption (86%).

-imaging studies: generalized mild osteopenia, absence of periodontal lamina dura and diploe thickening, total body less head densitometry: Z score -2.2 SDS and normal renal ultrasound.

Clinical case was consistent with symptomatic primary hyperparathyroidism.

Parathyroid ultrasound showed an 8 mm hypoechoic image behind the left thyroid lobe and Sestamibi and Technetium 99 scan with late uptake and thyroid suppression confirmed hyperfunctioning of both superior parathyroid glands.

Surgery was performed with identification of both enlarged upper parathyroids and pathology was compatible with hyperplasia.

He presented transient post-surgical hypoparathyroidism and during follow up he normalized biochemical profile in 3 weeks.

Conclusions: Primary hyperparathyroidism is very infrequent in pediatrics. Its association with TS is extremely rare. The suspected pathophysiological mechanism could be related with the abnormal proliferation of the parathyroid cells mediated by the lack of inhibition of the mTOR pathway.

We suggest evaluating symptoms associated with hypercalcemia and eventual phosphocalcic profile in patients with TS.

P2-52

Patient with ABCD syndrome (Abnormal Calcium, Calcinosis, Creatinine in Down syndrome), a rare cause of pediatric hypercalcemia

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Introduction: ABCD syndrome is characterized by hypercalcemia, hypercalciuria, nephrocalcinosis, and renal impairment, generally under 4 years old. This is a rare cause of pediatric hypercalcemia with only 7 cases published, but it is believed to be underdiagnosed.

The suspected mechanism would be associated with overexpression of transient receptor potential channels (TRP) that modulate intestinal absorption of calcium, since TRP-M2 is encoded on chromosome 21. Dietary calcium restriction would be the treatment of choice.

Clinical Case: A 4-year-old male with DS, postviral lung disease, cordal paralysis with tracheostomy and feeding by nasogastric tube, was consulted to endocrinology for hypercalcemia and hyperphosphatemia

He consulted the emergency room for vomiting, diarrhea and fever. He was in fair condition with general pallor. His laboratory showed anemia, impaired renal function (creatinine 3.3 mg/dl, urea 70 mg/dl), normal electrolyte panel, hypercalcemia (11.8 mg/dl), hyperphosphatemia (10 mg/dl), low PTH (4.7 pg/ml), and normal 25 (OH) vitamin D (47.4 ng/ml). Calciuria/creatininuria was elevated (0.8) and renal ultrasound showed bilateral nephrocalcinosis.

He was admitted for diagnosis, ruling out oncological and infectious diseases. ABCD syndrome was suspected and he started treatment with hyperhydration, furosemide, sevelamer, aluminum hydroxide, and decreased milk intake (he was receiving 1500 ml of 15% formula per day due to poor weight gain).

Renal biopsy was performed to rule out another associated renal component, and reported calcium deposits and tubulointerstitial inflammatory involvement.

Despite the adequate initial response to treatment, he required 2 new hospitalizations due to hypercalcemia (up to 13.7 mg/dl) and, for this reason, he started methylprednisone 1 mg/kg/day with little response.

Dairy intake was progressively reduced to an extensively hydrolyzed formula and a formula with a low calcium and phosphorus content without vitamin D, with a total of 196 mg/day of calcium.

He presented good response to dietary calcium restriction (calcemia 10.2 mg/dl, phosphatemia 3.6 mg/dl and creatinine 1.8 mg/dl) that allowed progressive decrease in methylprednisone until suspension.

Conclusions: ABCD syndrome is a very rare cause of pediatric hypercalcemia. In our patient, this diagnosis was confirmed by clinical evolution and results of the renal biopsy.

In patients with DS, the endocrinologist should consider the possibility of this condition, maintain an age-appropriate calcium intake, and perform a phosphocalcic profile and renal ultrasound in those with compatible symptoms or high calcium intake.

P2-53

Case report of an 18-month child with profound osteopenia, hypotonia, respiratory distress and RSV bronchiolitis, on a background of vitamin D dependent rickets type 1 (VDDRI): Acute management and 6 months follow-up

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Aim: Case report of an 18-month-old child with a background of vitamin D dependent rickets type 1(VDDR1)], due to a mutation of CYP27B1 (c.1319_1325dup and c.335C>T: compound heterozygote).

Methods: Presentation of the case and the management of hypocalcemia as well as the complications of follow-up.

Results: The patient presented at the A&Es of the 2nd Department of Pediatrics, National and Kapodistrian University of Athens (NKUA), “P. & A. Kyriakou” Children’s Hospital, with hypotonia and respiratory distress. The possibility of the diagnosis preceded presentation in the A&Es for about 2 months and the patient was receiving calcium supplementation (750mg/d), phosphate (500mg/d) and calcitriol (250 mcg/day, 27 mcg/kg/d). The patient showcased respiratory distress due to RSV bronchiolitis, that was aggravated by the osteopenia of the thoracic cage. The initial laboratory evaluation showcased hypocalcemia (Ca 7,7 mg/dl), ALP 1859 U/L, hyperparathyroidism (PTH 1004 pg/ml), 25(OH) Vitamine D 82 ng/ml and 1,25 (OH)2 Vitamine D 67,2pg/ml. Following specialist consultation, a skeletal survey was performed that showed extended rickets and significant osteopenia. The patient was started on alphacalcidol (calcitriol is unavailable in Greece) on progressively increasing doses, increased calcium and phosphate supplementation and respiratory support with bronchodilators and oxygen. Oxygen supplementation continued following discharge. During hospitalization the patient showed persistent "hungry bone-like" syndrome, due to redistribution of calcium in the bones. Trough calcium concentrations were 6.4 mg/dl and repetitive gluconic calcium boluses were required as well as gradual increase of alphacalcidol, so the required doses to stabilize calcium at 8,4 mg/dl, were alphacaclidol 4000 ng/d (481ng/kg/d), [usual treatment range: 20-60ng/kg/d]. At 6 months post discharge, the patient is still receiving calcium supplementation (100mg/kg/d) and alphacalcidol (400ng/kg/d), x-ray findings and anthropometry are improving and the hypotonia has improved (the patient is now standing unsupported), while oxygen supplementation is no longer required.

Conclusion: VDDR1 is a rare condition that following recognition requires appropriate treatment with alphacalcidol or calcitriol and regular follow-up, due to the possibility of developing profound osteopenia, failure to grow and failure to achieve developmental motor milestones, as well as the potential to aggravate the morbidity of infections of the respiratory tract.

P2-54

Over four generations of adult-form HPP diagnosed from an asymptomatic child with low ALP levels

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Background: Hypophosphatasia (HPP) is an inherited bone disorder caused by *ALPL* gene mutations. It is classified into 6 clinical types (perinatal lethal form, prenatal benign form, infantile form, childhood form, adult form, and odontohypophosphatasia). Severe types show autosomal recessive inheritance, and mild types show autosomal recessive or autosomal dominant inheritance. The adult form is asymptomatic in childhood. Treatment includes ALP enzyme replacement therapy, but there are no clear treatment-initiation criteria for asymptomatic HPP.

Case: A 3-year-old girl with normal growth and development. She was born at 38 weeks of gestation with a birth weight of 2162 g and length of 48.0 cm. She was admitted to NICU due to low birth weight, had no symptoms of respiratory distress or convulsions, and her physical and radiographic findings were unremarkable. HPP was suspected because blood tests showed low ALP of 57-88 U/L (reference value: 186-564 U/L) during hospitalization, and her low ALP level persisted after discharge from NICU. After obtaining informed consent for genetic analysis from her parents, Sanger sequencing analysis for the *ALPL* gene in her and her parents revealed the heterozygous missense variant c.1354G>A in the patient and her father. Furthermore, her paternal grandmother had experienced body pain after the age of 50, and her great-grandmother had severe osteoporosis and a history of three fractures after the age of 70. Because of the sequence of events, informed consent was obtained from each individual, and analysis of the *ALPL* gene identified the same mutationsin her paternal grandmother and great-grandmother, respectively. Her only sibling, an older brother, had ALP of 287 IU/L at age of 3 years old and was considered to be unaffected.

Discussion: *ALPL* gene c.1354G>A mutation has been reported to be a perinatal lethal form as a compound heterozygous mutation with c.331G>A, and a heterozygous form of this mutation has been reported as adult-type HPP with a dominant-negative effect.

This case is also considered to involve the adult-type HPP based on the symptoms of the family.

Conclusion: We identified *ALPL* mutations in adult-form HPP inherited over four generations.

We report this case because we consider it to be a valuable familial case in which differences in natural history and individual symptoms in adult-form HPP can be simultaneously observed.

We did not administer enzyme replacement therapy in this case, but we will follow-up the patient cautiously to promptly identify future manifestations.

P2-55

Three Years of Burosumab Treatment in a Child with Cutaneous Skeletal Hypophosphatemia Syndrome: A case report

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Cutaneous skeletal hypophosphatemia syndrome (CSHS) is a rare mosaic disorder caused by somatic gain-of-function RAS mutations. It is characterized by segmental epidermal nevi and fibroblast growth factor-23 (FGF23) mediated hypophosphatemic rickets. These patients also have dysplastic cortical skeletal lesions.

We describe an Emirati child with CSHS whose hypophosphatemic rickets and dysplastic skeletal lesions failed to heal due to poor adherence to conventional oral phosphate supplements and alfacalcidol treatment. The diagnosis of CSHN with FGF23-mediated hypophosphataemic rickets was made in our patient due to increased urinary phosphate excretion and hypophosphatemia in the face of normal serum PTH levels and inappropriately elevated plasma FGF23 levels. The whole-exome sequence on cells from nevoid skin biopsy revealed a somatic missense variant c.182A>G p.(Gin61Arg) (chr11:533874;hg19) in the HRAS gene (OMIM *190020; chromosome 11p15.5).

Burosumab, a fully human immunoglobulin G1 monoclonal antibody to FGF23, has been approved for treating children with X-linked hypophosphatemia (XLH), a multisystem disorder caused by increased expression of FGF23. Treatment of our patient with Burosumab for 36 months resulted in normalization of her serum inorganic phosphate and alkaline phosphatase levels, healing of rickets, improvement in her linear growth, symptoms of myopathy, and quality of life.

In summary, we report the successful long-term treatment of hypophosphatemic rickets in CSHS with Burosumab over 36 months. Burosumab showed promising efficacy and safety profile in our patient, without any side effects. This success may help in the approval of this targeted therapy for CSHS.

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Table 1. Fasting serum PO4 and ALK over 36 months of Burosumab treatment

Week	Fasting Serum PO4 (3.4-5.5mg/dl)	ALK (< 269 U/L)
0	2.6	638
4	6.1	376
8	5.6	341
12	5.3	320
16	5.8	289
20	5	295
24	5.1	267
28	5.2	273
32	4.8	295
36	5.0	295
40	5.0	300
48	5.2	273
60	5.4	286
72	5.0	300
84	5.3	298
96	4.9	295
108	5.5	302
120	4.8	277
132	5.2	289
144	5.1	291
156	5.2	301

P2-56

Mosaic Disorders of FGF23 Excess: A case of Cutaneous Skeletal Hypophosphatemia Syndrome (CSHS) associated with thyroid medullary carcinoma

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Pathologically elevated serum levels of fibroblast growth factor-23 (FGF23), a bone-secreted hormone that regulates phosphorus homeostasis, result in renal phosphate wasting leading to rickets or osteomalacia. Patterns leading to FGF23 excess are still unknown. Recently, FGF23 elevated rickets has been associated with epidermal nevus syndrome, designating the cutaneous skeletal hypophosphatemia syndrome (CSHS). The clinical picture is not completely defined as, to date, only about fifty CSHS patients have been reported, all harbouring gain-of-function somatic mutations in *HRAS* or *NRAS* genes. RAS/MAPK signaling pathway is a key regulator of FGF23 production and the various clinical manifestations underscore its ubiquitous nature. We describe the first CSHS case molecularly confirmed, who developed a thyroid medullary carcinoma.

The patient is an 11-year-old boy. At birth a large pigmented skin lesion involving the right hemisome was found. Dermatological evaluation diagnosed an extensive epidermal nevus, for which he underwent surgical treatment and laser therapy. Brain MRI and abdominal ultrasound were normal. At the age of two, he presented bilateral flatfoot and valgus knee, which progressively worsened. He was referred to our Pediatric Endocrinology Unit at 4 years old: from blood chemistry tests a picture of hypophosphatemic rickets emerged, so treatment with oral phosphate and calcitriol was started; growth was within the family target. Sequencing of genes associated with hypophosphatemic rickets and with RASopathies on DNA from blood was negative. Due to poor clinical response to standard rickets therapy, at the age of five he underwent bilateral femoral hemiepiphysiodesis surgery. At the age of seven he underwent total thyroidectomy because of a medullary carcinoma diagnosis. At 10 years old he started therapy with human monoclonal antibody burosumab, showing a particular good response, indeed he needs drug administration every 2-3 months. Based on the clinical picture, we repeated sequencing of the RAS/MAPK pathway genes on DNA from epidermal nevus biopsy and detected the pathogenic missense variant NM_005343.4:c.182A>G p.(Gln61Arg) in the *HRAS* gene, with an allele frequency of 35%. The *HRAS* variant was detected in DNA from urinary cells (at 4%), but not in saliva, confirming the mosaic and the CSHS diagnosis.

In conclusion, in case of FGF23 increased hypophosphatemic rickets it is important to evaluate the presence of other particular clinical features and take into consideration a mosaic disorder of the RAS/MAPK signaling pathway. To reach the correct diagnosis allows to establish the more effective treatment and follow-up.

P2-57

Heterozygous mutations in SETD5 are associated with bone fragility

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Background: SET domain-containing 5 (SETD5) is an uncharacterized member of the protein lysine methyltransferase family, a group best known for its ability to methylate their substrate and, by that, regulate gene expression. Heterozygous pathogenic variants in SETD5 are known to cause neurodevelopmental delay. We present two children with pathogenic variants in SETD5 and vertebral fractures with low bone mass.

Individual 1: This 15-year old male of Caucasian and Chinese origin first presented with delayed speech, irregular sleep, learning difficulties and aggression during the first years of life. After a fall at the playground at the age of 8 years he was referred to the pediatric bone clinic, where x-rays showed mild scoliosis and vertebral wedge fractures at T11, L2 and L3. Bone densitometry (DXA) revealed reduced lumbar spine bone mineral apparent density (BMAD) with a Z-score of -2,3, a subtotal BMD for height Z-score of -2,5 and subtotal BMC for height of -3,1. Notable skeletal features were hyperflexibility of elbows, thumbs and wrists alongside bilateral clubfoot and pes cavus. Whole exome sequencing revealed a pathogenic heterozygous SETD5 variant c.1498C>T (p.Gln500*het) in exon 13. Since he fulfilled the criteria for paediatric osteopororis, therapy with zoledronic acid was established.

Individual 2: This 13-year old male of Latin American origin was born preterm at a gestational age of 25 weeks with bronchopulmonary dysplasia, bronchomalacia, larnygomalacia, bilateral inguinal hernia and unilateral renal hypoplasia. Brain MRI identified bilateral cerebellar hypoplasia. Aged 5, he had a febrile seizure. At the age of 13 years, he presented with persisting sternal pain with no evidence of trauma. Radiographs showed fissures of the sternum. Aged 14, following trivial fall, radiographs showed multiple vertebral fractures and anterior wedging of T6-T7 and possible fractures of T6 and T9 with suspected microfractures affecting the upper platforms of T5, T6 and T10. The DXA scan showed a low lumbar spine BMD with a Z-score of -1,9. As the criteria for pediatric osteoporosis was fulfilled, therapy with zoledronic acid was established. Whole exome sequencing revealed a pathogenic heterozygous c.1082G>A (p.Arg361Gln) variant in exon 11 of SETD5.

Conclusion: The combination of SETD5-associated neurodevelopmental delay and low bone mass has only recently been described. Our two cases corroborate this association. Neither of the patient had other risk factors for bone fragility nor was there a family history of fractures. We explore mechanism of action to ascertain how SETD5 affects bone metabolism and results in bone fragility.

P2-58

Kenny Caffey syndrome 2; expanding the clinical spectrum

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Background: Kenny–Caffey syndrome 2 (KCS 2) is a rare cause of hypoparathyroidism, characterized by proportionate short stature, cortical thickening and medullary stenosis of tubular long bones, delayed closure of anterior fontanel and eye abnormalities.

Objective: We report the case of a 4-years'-old boy, who presented with the characteristic, and newly identified clinical, biochemical, radiological and genetic abnormalities of the syndrome.

Results: The toddler presented for short stature investigation. He is the second child of the family, born after an otherwise full-term uneventful pregnancy. On the third day of life, he presented with respiratory distress, attributed to birth asphyxia. On revisiting his personal history several episodes of hypocalcemia were reported, requiring repeated hospital admissions. He firstly presented with an episode of neonatal seizures, attributed to central nervous system (CNS) infection, with concurrent hypomagnesemia, and hypocalcemia. Normocalcemia was achieved with parenteral calcium gluconate, and maintained with oral elemental calcium and cholecalciferol, or alfacalcidol. Parents are clinically unaffected, and there is no family history of short stature or hypoparathyroidism. On examination his height and weight were below the 3rd centile (89,5cm;-4.11SD, 15,7kg;-3SD, respectively). He had noticeable dysmorphic features, including prominent forehead, small palpebral fissures, low set ears, long philtrum, thin upper lip, pectus excavatum, and genu valgus. Although the closure of anterior fontanel was delayed until the age of 2-years, developmental milestones were achieved at expected ages. Skeletal survey revealed cortical thickening, and medullary stenosis of the long bones.

The biochemical evaluation showed hypocalcemia (7.9mg/dl), high normal phosphorous (5.4mg/dl) and inappropriately low normal parathyroid hormone (PTH) (20.4pg/ml). To rule out other causes of short stature, routine investigations were performed, revealing on CNS MRI small pituitary gland and empty sella, and low IGF-1. Nocturnal levels of growth hormone were normal (21.2ng/ml). Cortisol, and thyroid function tests were within normal range. Comprehensive cardiovascular, and ophthalmological evaluation was negative for any pathology. Based on the aforementioned clinical, biochemical and radiological features KCS2 was suspected.

Molecular Analysis: Molecular genetic analysis was carried out employing Whole Exome Sequencing, followed by Sanger sequencing of the pathogenic variant detected. Genetic testing revealed heterozygosity for the FAM111A gene with *de novo* pathogenic variant c.1706G>A,p.Arg569His. This variant has been reported in KCS2. Pathogenic variants related to patient's pituitary morphology were not identified.

Conclusion: To our knowledge this is the first time KCS2 is associated with low levels of IGF-1, and pituitary abnormalities on the MRI of the hypothalamic-pituitary region.

P2-59

Serum levels of carboxylated and undercarboxylated osteocalcin in non-obese children with Prader-Willi syndrome

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Introduction: Prader-Willi syndrome (PWS) is a rare congenital neurodevelopmental disorder characterized by hyperphagia, growth hormone (GH) deficiency, short stature, and low bone mineral density. The mechanisms concerning bone metabolism disturbances in these patients are still unclear. An important role in the process of bone formation is played by osteocalcin (OC), the most abundant non-collagen protein of the bone matrix. OC has three potential gamma-carboxyglutamic acid residues that are responsible for the binding of OC to hydroxyapatite. In the circulation, carboxylated (Gla-OC) and undercarboxylated (Glu-OC) forms of OC are present. The aim of this study was to analyze both forms of osteocalcin in non-obese children with PWS in comparison with normal-weight controls.

Patients and Methods: The study consisted of eighteen children (aged 1-12 years) with PWS during treatment with growth hormone (GH) and dietary intervention. The control group consisted of eighteen healthy, normal-weight children (BMI z-score <-1+1>). We determined the levels of OC, Gla-OC, Glu-OC, insulin-like growth factor-I (IGF-I) and IGF-binding protein 3 (IGFBP3) by ELISA kits. Anthropometric measurement (body weight, height, body mass index - BMI) and dietary intake (energy and macronutrients intake) were assessed in all studied children. This study was approved by the Ethics Committee at the Institute of Mother and Child.

Results: The daily energy intake in children with PWS was lower by about 30% ($p<0.001$) compared with the controls. Daily dietary protein intake was similar in both studied groups, but carbohydrate and fat intakes were significantly lower in the patient group than in the controls ($p<0.001$). Similar values of BMI were observed in both studied groups of children. The concentration of OC was significantly lower in patients in comparison with the controls ($p=0.02$). The values of Gla-OC were higher ($p=0.008$), but the values of Glu-OC were lower ($p=0.001$) in patients with PWS than healthy children. Positive correlation was found between Gla-OC and IGF-I/t-IGFBP3 ratio ($r=0.433$; $p<0.05$) in patient group.

Conclusions: An altered profile of OC forms was found in non-obese children with Prader-Willi syndrome during treatment with GH and reduced energy intake. These changes may be related to disorders of bone metabolism in patients with PWS.

P2-116

Some of the clinical characteristics of osteogenesis imperfecta in children

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Osteogenesis imperfecta, also known as “brittle or glassy bone disease”, is a connective tissue disease that occurs as a result of quantitative and qualitative changes in type 1 collagen. The disease is transmitted in an autosomal dominant way and the incidence is 1:20,000.

The Aim: of the study was to evaluate the clinical characteristics and treatment of children diagnosed with osteogenesis imperfecta in children.

Materials and Methods: 10 patients diagnosed with Osteogenesis imperfecta were examined in the pediatric department of teaching and therapeutic clinic of the Azerbaijan Medical Univercity during 2020-2023 years. 3 of the patients were boys and 7 were girls. Patients were between 5-14 years old, the average age was 11.2 years. The diagnosis was made on the basis of clinical, X-ray and laboratory examinations.

Results: As a result of the study, bone fractures and bone deformations, which are the main symptoms of osteogenesis imperfecta, were found in each of 10 children. Of the bone fractures, 6 (50%) were femur, 2 (16.7%) humerus, 2 (16.7%) elbow, 1 (10%) shin (8.3%) and 1 (8.3%) shaft. 5 out of 10 children (50%) had blue colored sclera from other symptoms of the disease, 2 (20%) had spinal deformations, 3 (30%) had hypermobile joints, 4 (40%) had dentinogenesis imperfecta, 4 (40%) short stature was noted. Minimal valvular regurgitation was detected in 1 patient (10%) as a result of echocardiography examination. Cases of hearing loss that may occur in old age have not been identified in any patient. All patient was treated with pamidronate. Any bone fractures in the children was not ovserved after treatment and improved densitometry indicators.

P2-117

Pediatric onset hypophosphatasia: a case report

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A 8 years and 7 months old male presented with short stature related to his target height. No history of bones fractures. The patient was 120.7 cm (- 1.77 SDS). Physical exam demonstrated peculiar facies, relative macrocephaly, delayed tooth eruption and pectus carinatum. He referred during the clinical evaluation diffuse bone pain and weakness, mostly exacerbated by sport activity. A first diagnostic investigation had already been made showing low serum alkaline phosphatase activity (124 U/L, 140-400).

Taking into account of all these clinical elements, we performed laboratory investigations aimed to evaluate calcium-phosphate metabolism. We found out a low serum ALP value for age and gender (125 U/L, n.v. 140-400), and elevated vitamin B6 level (38.2 mg/dl, 3.6-18). Blood calcium, phosphate, parathormone and vitamin D levels were normal.

Due to these findings, targeted NGS for hypophosphatasia was performed. A mutation in ALPL gene was detected (c.1183A>G heterozygote) already classified as a pathogenetic variant. After the diagnosis was made, a DEXA scan was carried out and reported a normal Z score for age and gender. The leg radiographs didn't identify any specific radiographic abnormality of hyphosphatasia.

Hyphosphatasia has a wide possibility of clinical manifestations and this can obstacle the diagnosis, particularly when the symptoms, as in our case, are chronic pain and bone impairment (1). However, a calcium-phosphate metabolism's study including the measure of ALP serum level, and a mutations analysis of ALPL gene allowed here a rapid diagnosis.

Considering the pediatric onset, our patient is eligible to be treated with Asfotase alfa (Strensiq), a human recombinant ALP therapy recently approved, which showed clinical improvements and skeletal healing during the trials' phase 2 (2).

At the moment, we are discussing the risk-benefit balance about using a new therapeutic tool, whose long and short-term results are limited, in a context of disabling symptoms but nuanced osteo-articular involvement, given the early diagnosis.

P2-118

Evaluation of the frequency of decreased bone mineral density and the impact of selected auxological and hormonal factors on bone mass among children with endocrine disorders

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Introduction: Bone mineral density (BMD) is affected not only by genetic and enviromental causes, but various hormonal factors. It seems reasonable to seek for dependencies between BMD and paediatric endocrinopathies.

The aim of the study was to assess the frequency of decreased BMD in children with several endocrinological disorders and evaluate the influence of selected auxological and hormonal parameters on their BMD.

Materials and Methods: The participants of the study were children diagnosed at our Clinic over the last three years. In each patient additional total body less head (TBLH) and lumbar spine (Spine) DXA examination was carried out, as well as calcium, phosphates, vitamin D, PTH, osteocalcin, crosslaps concentrations were assessed.

Basing on the height and body mass of each child, HSDS and BMISDS were calculated and the advancement of puberty was estimated according to the Tanner scale. In most patients TSH, FT4, FT3, IGF-1 (expressed as IGF-1 SDS) were marked and bone age (BA) was graded. The DXA examination was performed among all children.

Results: The analysis consisted of 148 children (73 girls and 75 boys) aged (mean±SD): 11.85 ± 3.34 SD, including 66 patients with short stature and 43 children with obesity.

Throughout the group, reduced BMD (Z-Score <-1.0) was found in 53.3% children (based on TBLH) and 37.1% (based on Spine), with the highest frequency of decreased BMD observed in the short-stature group (88% according to TBLH i 53.7% according to Spine).

A significant positive correlation was found between Z-score TBLH and: HSDS (r=+0.70), BMISDS (r=+0.64) and IGF-1 SDS (r=+0.49) as well as Z-score spine and: HSDS (r=+0.56), BMISDS (r=+0.55), IGF-1 SDS (r=+0.43).

Vitamin D deficiency was found in 104 (69.8%) children (<20 ng/dl - in 44, 20-30 ng/ml - in 60 cases), but suprisingly there was a negative correlation between vitamin D levels and: Z-score TBHL (r=-0.43) and Z-score Spine (r=-0.33). A negative correlation was noted for these parameters in respect to the BA delay severity.

Conclusions: A high incidence of cases with reduced BMD is observed in children with endocrinopathies. It seems that deficient and excess in both height and body mass affect BDM. In children with short stature, these disorders may be additionally associated with reduced IGF-1 levels.

On the other hand, in some cases the possibility of overdiagnosing reduced BMD may rise due to the lack of automatic BMD adjustment in the software of the densitometer for anthropometric measurements and BA.

P2-119

A rare case of hypocalcemia: was it better when it got worse?

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XY, 14 years old, was born at term, birth weight 4900 g, length 54 cm. No problems reported in the early years of life.

Due to recurrent abdominal pain for several years associated with dyspepsia, at 13 years he performed blood tests, with evidence of hypocalcemia (6.1 mg/dl) and hyperphosphatemia (8.6 mg/dl). For this reason, he was admitted to our ward: the weight was Kg 67.1 (1.8 SDS), height 168 cm (1.5 SDS), pubertal stage 4, objective examination in the norm. The exams performed in the department highlighted primary hypoparathyroidism with the associated blood abnormalities (total and ionized hypocalcemia, hyperphosphatemia, hypomagnesemia, mild hypercalciuria, hyper phosphaturia, 25 OH D3 and alkaline phosphatase in the limits, PTH below the norm). The ECG holter ruled out conduction disturbances (QTc 450 msec). The brain NMR documented Fahr syndrome. Renal ultrasound ruled out nephrocalcinosis. No abnormalities of chromosome 22, he had mutation activating the CaSR gene. Bone densitometry was normal. Parents have normal PTH and calcium values.

He had intravenous therapy with calcium associated with calcitriol and magnesium per os, without meaningful change the blood picture, but with the appearance of hypercalciuria. The vitamin and calcium and magnesium intake by mouth were reduced to the doses indicated by the literature for the treatment of hypoparathyroidism, Now the values of calcium and magnesium remain below the norm (Ca 8 mg/dl, P 7 md/dl), but he refers tetany, myalgia (CK higher than normal), asthenia, abdominal pain, nausea. QTc is < 500 msec. For the appearance of nephrocalcinosis, he started therapy with thiazide diuretic. In practice, he felt better when the tests were worse.

P2-120

Identification of 2 new heterozygous ACAN variants in a 3-years-old boy with short stature who presented with advanced bone age: a case report

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Aggrecan, encoded by the ACAN gene, is the main proteoglycan component in the extracellular cartilage matrix. A heterozygous ACAN mutation has been reported as a major cause of idiopathic short stature, it causes an accelerated bone age maturation and premature growth cessation. Recently, the effectiveness of GH treatment for achieving an appropriate adult height has been reported in several cases with ACAN mutations.

We report the case of a 3 years and 2 months old boy, with height of 88 cm (SDS -2.5) and weight of 15 kg (0 SDS). He is the only son and he was born to non consanguineous parents. He was born at 39 weeks through cesarean delivery because of mother's narrowed pelvis and with a birth weight of 3.5 kg. He presented with frontal bossing, a broad chest, a low posterior hairline and a short neck, Tanner stage 1. The mother's and father's heights were 143 cm (-3 SDS) and 173 cm (-0.5 SDS) respectively. The patient's bone age was 2 years more advanced than his chronological age using the standard Greulich-Pyle method. Pelvic and knees x-ray imaging did reveal a bilateral ostechondral defects, enlargement of the proximal tibial and distal femoral metaphyses, irregular femoral epiphysis and patellar contours. The patient's mother had short stature, and early-onset lumbar disc herniation, patellofemoral dysplasia, degenerative chondral involvement of the patella, and degenerative bone remodeling of the trochlea, were all confirmed with MRI in her 23 age. ACAN mutation was suspected. Exome sequencing of a targeted growth panel (ECCTV3 Short Stature Comprhensive Panel : 286 genes) revealed 2 new heterozygous ACAN vatriants : c.7127G>A (p.Arg2376His) and c.386G>A (p.Gly129Glu) in the boy. No endocrine abnormalities were detected except a probable partial GHD (GH peac in Glucagon stimulation test realised at 3 years and 7 months age: 6.79 ng/ml with normal pituitary MRI). rhGH treatement had been started at a dose of 1mg/m^2 since 8 months. His height velocity ranged from 6 to 7.5 cm/year.

Short stature is generally associated with a delayed bone age, and this case suggests that ACAN mutations may be the most likely etiology of short stature associated with an advanced bone age and should warrant early treatment. The response of GH treatment should be further examined with long-term outcomes.

P2-121

Clinical findings in three Japanese patients with N-acetylneuraminic acid synthetase-congenital disorder of glycosylation (NANS-CDG)

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Background: N-acetylneuraminic acid synthetase-congenital disorder of glycosylation (NANS-CDG) is a recently established rare autosomal recessive disease caused by pathogenic variants in NANS involved in the biosynthesis of N-acetylneuraminic acid (the most common member of sialic acids). Sialic acids are ubiquitously distributed in the body including the brain and skeletal system, and are required for the development and function of multiple organs/tissues. Consistent with this, NANS-CDG leads to Camera-Genevieve type spondyloepimetaphyseal dysplasia (SEMD) associated with infantile-onset intellectual developmental disability (IDD) as well as other various clinical features.

Patients: Patient 1 exhibited a unique constellation of clinical features including marked hydrocephalus, SEMD, and thrombocytopenia which is comparable to that of an infant reported by Faye-Peterson *et al.*, whereas patients 2 and 3 showed Camera-Genevieve type SMED with IDD. Growth pattern analysis in patients 1-3 revealed mildly decreased birth lengths and low-normal birth weights, and severely compromised postnatal heights. Roentgenographic examinations revealed SEMD with remarkable age-dependent evolution. Skeletal hallmarks in the neonatal period included a mildly narrow thorax, mild platyspondyly with multiple coronal clefts, broad ilia with short greater sciatic notches and horizontal acetabula, and stubby long bones. In childhood, platyspondyly became more conspicuous along with development of vertebral endplate irregularities. The long bones became overtubulated together with metaphyseal flaring and subphyseal longitudinal striations with age.

Molecular Studies: We performed whole exome sequencing using genomic DNA of patients 1-3 and their parents, and revealed compound heterozygous *NANS* variants of c.207del:p.(Arg69Serfs*57) and c.979_981dup:p.(Ile327dup) in patient 1, a homozygous *NANS* variant of c.979_981dup:p.(Ile327dup) in patient 2, and compound heterozygous *NANS* variants of c.133–12T>A, leading to aberrant splicing, and c.607T>C:p.(Tyr203His) in patient 3.

Glycosylation Studies: We examined the N-glycosylation status of transferrin and the O-glycosylation status of apolipoprotein C-III by mass spectrometry. Despite the presence of *NANS* variants, both glycosylation patterns were normal in patients 1-3. Blood total sialic acid values were at a low-normal range, whereas urine N-acetylmannosamine (the substrate for NANS) values were obviously increased in patients 1-3.

Conclusion: The results, together with previously reported data, imply that (1) NANS plays an important role in postnatal growth and fetal brain development; (2) SMED is recognizable at birth and shows remarkable postnatal evolution; (3) NANS-CDG is associated with low-normal serum sialic acid, obviously elevated urine N-acetylmannosamine, and normal N- and O-glycosylation of serum proteins; and (4) NANS-CDG is divided into classic Camera-Genevieve type and more severe Faye-Peterson type.

P2-122

A Rare Case of Skeletal Dysplasia: Homozygous Mutation in ACAN Gene

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Spondylo-epimetaphyseal dysplasia -ACAN (SEMD- ACAN) is a rare form of osteo-chondrodysplasia that represents a group of vertebral, epiphyseal, and metaphyseal dysplasia. This genetic condition is caused by biallelic loss-of-function mutations in the ACAN gene, which encodes for aggrecan, an essential component of the extracellular matrix in cartilage. Biallelic loss-of-function mutations in this gene result in a range of characteristic symptoms, including disproportionate short stature, rough facial features, midface hypoplasia, macrocephaly, thoracic deformity, mesomelia, and brachydactyly. In this case report, we present the fourth report of SEMD-ACAN in two siblings.

The proband, a 9-year-old girl, presented with severe growth retardation. She was born at term with a normal weight (1.84 SDS) but severe short stature (41 cm; -3.54 SDS) to healthy consanguineous Turkish parents. Her mother had severe (-2.74 SDS) and her father had moderate (-2.3 SDS) short stature. On physical examination, the proband's weight was -1.25 SDS, height was -4.6 SDS, and she was prepubertal. She had midface hypoplasia, low-set ears, a short neck, short limbs, and truncal obesity. Biochemical and hormonal tests were all normal. In skeletal survey; moderate platyspondily, thoracolomber scoliosis, and lumbar lordosis, and bilateral femoro-acetabular narrowing were noted. The proband had disproportionate short stature with advanced bone age (10 years). In genetic analyses, we detected a homozygous ACAN variation (c.512C>T; p. Ala171Val) with next-generation sequencing (NGS). Segregation analysis revealed that the parents were both heterozygous and the proband's male sibling with a similar clinical presentation was homozygous for this variant. In literature, heterozygous form of this variant was reported in 15 year-old boy with severe short stature with advance bone age, and dysmorphic features (mild midfacial hypoplasia, frontal bossing, a broad chest, and a short neck).

SEMD-ACAN is a rare genetic condition that affects bone growth and development and can result in a variety of physical and developmental abnormalities. Diagnosis of SEMD-ACAN is typically made through clinical evaluation and genetic testing. Skeletal radiography, bone age assessment, and biochemical tests may also be used to support the diagnosis. Management typically involves addressing symptoms such as short stature and skeletal abnormalities. This case report highlights the importance of considering genetic testing in cases of severe growth retardation and other characteristic symptoms associated with SEMD-ACAN.

P2-123

Hypophosphatasia: a pediatric patient treated with asfotase alfa

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We describe a 5 years-old patient referred to our centre for dysmorphic features and delayed psychomotor development.

Negative family history, second child, full-term birth, eutocic delivery, regular growth parameters at birth and neonatal adaptation. Autonomous walking at 20 months with clumsiness; first words at 2 years with dysarthria and dysphagia. Brain MRI and array-CGH were normal.

At the neurological examination: perioral hypotonia, sialorrhea, praxic difficulties. At 4 yrs he developed seizures. The EEG showed paroxycal anomalies in the fronto-centro-temporal zones. A diagnosis of focal idiopathic epilepsy was made and therapy with levetiracetam was proposed.

At the first evaluation in our centre he showed amimic face, telecanthus, buccal hypotonia, absence of 4 deciduous teeth (he lost the upper central incisors at 2.5 yrs, lower right incisor at 3.5 yrs, upper right canine at 4.9 yrs); enamel dysplasia, prognathism; normal stature, ligamentous hyperlaxity, truncal hypotonia, kyphotic attitude; valgus knees; flat feet; dyspraxia and motor clumsiness. A blood sample showed: alkaline phosphatase (ALP) 81 U/L (normal values:150-315), confirmed in a second blood sample, PEA 58 mmol/ml (normal values: 4-10), B6 vitamin 580 nmol/L (normal values: 29.5-99).

A condition of HPP was suspected. Analisis of ALPL gene showed a missense heterozygous mutation c.1172G>A, pathogenetic, compatible with AD-HPP. Renal ultrasound, fundus oculi and skeleton X-ray were normal. Subsequently he lost left upper canine.

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At the age of 6, because of motor clumsiness, dysarthria, hypotonia, premature tooth loss and epilepsy, although without skeletal involvement, he started therapy with asfotase alfa, which he continued for 3 years. He showed reduction of seizures after the beginning of therapy (seizures disappeared at 7 years), improvement in tone, muscle strength, clumsiness, speech, swallowing; physiological eruption of permanent teeth. The 6 minutes walking test, repeated every six months, showed an improvement in greater distance traveled without falls. He developed side effects in injection sites of therapy: erythematous-edematous lesions with lipodystrophic evolution.

Hypophosphatasia is caused by mutations in the gene encoding non-tissue-specific ALP. Biochemical marker is low serum ALP activity, with defective bone and/or tooth mineralization. The serum levels of ALP vary by age with lower values in adults.

The severity is variable from fetal death, without mineralization of the skeleton, to isolate dental pathology in adults. Inheritance can be AR (severe forms) or AD (milder). Early recognition is important because asfotase alfa therapy can avoid the onset of functional limitations in adulthood.

P2-124

Clinical case: a misleading family history

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A 17-year-old girl comes to our attention for a second opinion due to reduced bone mineralization. She has a family history of osteogenesis imperfecta: her mother and younger sister have a COL1A1 mutation. The girl never had any fractures, but considering the familiarity it was carried out a DEXA, showing a Z-score of -1.9 SDS at the femoral level and -2 SDS at the lumbar level; no fractures visible in the spine X-ray. The genetic analysis of COL1A1 was carried out, which came out negative. Prophylaxis with calcium 500 mg/day and vitamin D 440 IU/day was started.

On the day of our first evaluation, the girl shows us her blood tests of calcium-phosphorus metabolism carried out a few months earlier. The results are within the normal limits except for PTH exceeding the normal values (9.4 pmol/L with normal values 1.6-6.9) and calcium, which is at the upper limits (11 mg/dL), with 25OH-vitamin D 29.7 ng/mL. We therefore suggest to stop the prophylaxis with calcium and vitamin D and to repeat the tests after 15 days: serum calcium remains unchanged and PTH tends to the upper normal limits (carried out in a different laboratory, 73.2 pg/mL with normal values 15-88), with calcium to creatinine ratio 0.14 mg/mg.

An ultrasound of the thyroid and parathyroids is then performed, showing an 11x6 mm nodule with poor intrinsic vascular signal at the lower pole of the left thyroid lobe, compatible with a parathyroid adenoma. We decide to carry out a Tc99/sestaMIBI parathyroid scan, which shows a focal radiopharmaceutical uptake consistent with the hyperactivity of the left inferior parathyroid.

Also, all the tests to rule out MEN1, MEN2A and MEN4 result negative: blood pressure monitoring, urinary catecholamine dosage, calcitonin, chromogranin, prolactin, fasting glucose, insulin, abdomen ultrasound and MEN1, RET and CDKN1B gene analysis.

The patient is currently a candidate for elective parathyroidectomy.

In pediatric patients, primary hyperparathyroidism must be taken into account as a rare cause of reduced bone mineralization: an excess of PTH leads to an increased bone resorption. In these cases it is essential to perform an ultrasound of the thyroid and parathyroids and Tc99/sestaMIBI parathyroid scan for early identification and treatment of parathyroid adenomas.

P2-125

Unusual presentation of polyostotic fibrous dysplasia in two unrelated patients

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Background: Fibrous dysplasia (FD) is rare disease that affects skeletal system characterized mostly by abnormal bone formation. The newly formed disorganized mass includes fibrous tissue with poorly organized immature trabeculae. FD is a highly incapacitating condition where fractures, deformities and consecutive functional impairment could occur as mono, olygo or polyostotic form. Aside from predominantly asymmetric skeletal involvement, extra-skeletal manifestations could appear as well. Postzygotic somatic mutation of GNAS1 gene early in embryogenesis is responsible for the disease; however, only in some cases the mutation was detected due to the variable degree of tissue mosaicism. Activating mutation of GNAS1 gene that encodes Ga subunit of G protein, leads to overexpression of adenylyl cyclase and disorganized fibrous development.

Case Report: We present two unrelated male patients with FD with variable presentation of the disease. The first sign of the disease in the first patient was neonatal conjugated hyperbilirubinemia and hepatomegaly, associated with elevated transaminases and hepatic biopsy showing hepatocyte necrosis, consecutive inflammation and bile cholestasis. During the neonatal period, a huge hyperpigmentation was noticed along the right side of the body (arm, leg, thorax). Hepatic dysfunction resolved spontaneously. The second child showed calvarial tumefaction in infancy, mainly on supraorbital region. The initial diferential diagnosis of osteosarcoma was excluded by biopsy that showed cystic fibrotic lesions. Fibrotic tissue expanded along all bones on the skull and made significant pressure on the brain tissue.

Both children experienced multiple fractures of the long bones, predominantly femur and humerus starting early in infancy. Irregular ossification was noticed along skeletal system, both with roentgen graph and scintigraphy. Bone biopsy during operation was performed in both, showing abundance of fibrotic cystic lesions and small patches of immature bone. The mutation of

GNAS1 gene was found only in the second patient. Growth disorders, precocious puberty or any other endocrine dysfunction were not present in both patients.

Discussion and Conclusion: Clinical presentation of FD mostly include trias of symptoms –endocrine dysfunctions, mostly precocious puberty, hyperpigmentation and fractures. Unusual manifestations occur depending on the affected cell lineage during embryogenesis. Therefore, a spectrum of non-endocrine clinical signs of almost every organ and tissue emerge and have to be considered as a part of the disease. Since there are no specific markers for the disease, clinical assessment is critical for establishing the diagnosis, even in patients without hormone disturbances.

P2-170

Vitamin D deficiency in pediatric population and influence on PTH levels

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Transversal study. Patients from 0 to 17 years of age who had undergone an analytical determination of 25OHD during the year 2021 in our hospital were collected. The following were contrasted: 25OHD, PTH, total calcium, age, sex, reason for requesting analysis, time of year and country of origin. 25OHD ranges: normal >30 ng/mL, suboptimal 20-30 ng/mL and deficit <20 ng/mL; and normal PTH: 9-60 pg/mL.

Results: 1: Prevalence of vitamin D deficiency:

2453 patients are included, 23.8% with normal 25OHD, 35.5% with suboptimal levels and 40.7% with deficit. The main causes of request for laboratory tests were endocrinological pathology, request in the context of another laboratory test, and changes in diet or weight.

56.5% are women and 43.5% men, with no significant differences in 25OHD levels (p>0.05). In the group of infants (0-2 years), 31.1% show deficits; however, in the group of adolescents (12-17 years old) this percentage increases significantly to 45.5% (p=0.01). In addition, in the first four-month period of the year, after the winter months, only 15.7% presented normal levels of 25OHD, in the second four-month period it rose to 29.1% and after the summer months, in the third four-month period, it reached 34.7% (p=0.01).

72.5% are Spanish, 13% from the Maghreb and the remaining 14.5% from other areas. A greater deficit of 250HD was observed in patients from non-European countries, presenting deficits in 62.7% (p=0.002), and the difference increasing significantly in patients from the Maghreb, with 68.8%. deficit (p=0.001).

1. Vitamin D and PTH:

599 patients are included. 24.3% with normal 25OHD, 36.3% with suboptimal levels and 39.4% with deficit.

In the group of patients with normal 25OHD, PTH is elevated in 25.8%. In the group with suboptimal levels in 36%, and in the deficit group it reaches 44%. In addition, significant differences are observed by age groups: in 20% of infants with 25OHD deficiency, increased PTH is observed; however, in the group of adolescents with deficiency, an increase in PTH was observed in 40.7% of them.

Conclusions: The pediatric patients studied show a relevant and more prevalent vitamin D deficiency in winter, in adolescence and in children from non-European countries. This leads us to consider the need for vitamin D supplementation in winter for high-risk pediatric patients

A relationship is observed between vitamin D deficiency and increased PTH levels, probably related to secondary hyperparathyroidism, being more evident in adolescents.

P2-171

An Infantile Hypophosphatasia with Novel Mutation in *ALPL* Gene: A Case Report

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Background: Hypophosphatasia (HPP) is a rare inherited disease of bone metabolism caused by inactivating mutations in the *ALPL* gene encoding tissue non-specific alkaline phosphatase (TNSAP). Infantile HPP is characterized by early onset abnormal skeletal mineralization with hypercalcemia and low alkaline phosphatase (ALP). It has been rarely reported from Thailand, resulting in limited disease awareness. We reported an infantile HPP Thai patient who presented with poor weight gain and hypercalcemia. Mutation analysis confirmed a novel compound heterozygous mutation of the *ALPL* gene in this patient.

Methods: The index patient's and parents' genomic DNA was extracted from the peripheral blood leukocytes. The exon 2-12 of the ALPL gene and exon-intron boundaries were amplified for direct sequencing.

Results: A 7-month-old male infant presented with hypotonia, feeding difficulty, constipation, and failure to thrive. He was born to non-consanguineous parents at term gestation with a birth weight of 3035 g. Physical examination showed underweight (weight 3870 g.), short stature (length 58 cm), microcephaly (head circumference 38.5 cm) with enlargement of the anterior fontanelle and widening sutures, small thorax, and marked hypotonia. Hypercalcemia with low parathyroid hormone (Ca 14.0 mg/dL (normal range, NR 8.5-11), P 3.6 mg/dL (NR 4.8-8.4), urine Ca/Cr 0.44 mg/mg (NR <0.6), PTH 7.74 pg/mL (NR 15-65)) were documented. His serum ALP was markedly low (16 IU/L (NR 150-420)), suggesting hypophosphatasia. Bone radiographs demonstrated generalized de-ossification of the skull, spine, and long bones with metaphyseal irregularity and thin ribs. After obtaining informed consent, the *ALPL* gene was sequenced, and both paternally inherited c.650delTinsCTAA and maternally inherited c.707A>G mutations were found in the patient. The later c.707A>G mutation is not in the public databases. Low calcium formula was prescribed to control his calcium levels. Unfortunately, Asfotase alfa, an enzyme replacement therapy (ERT) for HPP, was not given since it was unavailable in Thailand. Because of the underdeveloped ribcage and respiratory muscle hypotonia, he could not maintain his airway. He became ventilator dependent with recurrent pneumonia, resulting in respiratory failure and death at one year and four months old.

Conclusions: We reported an infantile HPP patient with a novel compound heterozygous mutation of the *ALPL* gene. Hypercalcemia with abnormal bone mineralization and low ALP are clues for diagnosis. This HPP type had been categorized as lethal until the era of Asfotase alfa. However, the availability of this ERT is still a considerable barrier to rescuing these patients.

P2-172

Hyperplastic Callus Formation in an Infant with Type I Osteogenesis Imperfecta: A Case Report

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Introduction: Osteogenesis imperfecta (OI) is a rare heterozygous disorder of collagen production. It is characterized by low bone mass, bone fragility, blue sclera, and progressive hearing loss. Expanded Sillence Classification divides OI into 7 types with Type I OI as the mildest and commonest form. Hyperplastic callus (HC) is a rare but characteristic complication in patients with OI type V. We report a infant with Type I OI with hyperplastic callus.

Case: A 2-month-old baby girl born via caesarean section at 37 weeks with birth weight of 2.43 kg. After birth, she had bilateral incomplete Moro's, short limbs with lower limb bowing and blue sclera.

Antenatally, mother had seronegative antiphospholipid syndrome secondary to systemic lupus erythematosus and Vitamin D deficiency. Antenatal scan showed shortened lower limbs.

Serum investigations revealed hemoglobin 18.2 g/dL, total white cell count 19.7 x 109/L, and platelet 494 x 109/L. Renal profile was normal. Other investigations were calcium 2.14 mmol/L, magnesium 0.71 mmol/L, inorganic phosphate 2.36 mmol/L, total protein 66 g/L, albumin 35 g/L, alkaline phosphatase (ALP) 157U/L, alanine transaminase (ALT) 24 U/L, and bilirubin 75 μmol/L. Her intact parathyroid hormone (iPTH) 5.97 pmol/L and vitamin D level 71.13 nmol/L were within normal reference range.

She sustained closed fractures of proximal left humerus, bilateral clavicles, upper third of left ulna, midshaft left femur, proximal third of left tibia, midshaft right femur and multiple ribs bilaterally.

U-Slab was applied for the left humerus and removed 6 weeks later. On repeat X-rays, the child developed HC over each fracture site.

Whole exome sequencing (WES) test revealed pathogenic heterozygous variant identified in COL1A1, c.1273G>A, p. Gly425Ser COL1A1 which is associated with autosomal dominant OI, type I.

She received intravenous Pamidronate at 7 weeks and at 3 months of life.

Conclusion: Hyperplastic callus is a well-described but mysterious feature of osteogenesis imperfecta. In a review of 47 cases of HC in the published literature there was no special tendency as to scleral colour. Although HC occurred more frequently with severe bone fragility, it was also seen with mild bone fragility. Thus, in patients with HC and OI, genetic studies to determine type should be done where available to facilitate counselling.

P2-173

Caval calcium infusion is the best solution for patients with hereditary vitamin D resistant rickets (HVDRR)

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Abstract: Hereditary vitamin D-resistant rickets (HVDRR) is an autosomal recessive disorder characterized by end organ resistance to 1α,25-dihydroxyvitamin D3 (1,25D3). The syndrome is recognized by severe early onset rickets with bowing of the lower extremities, short stature, often alopecia and severe hypocalcemia.

Objectives: To study the effectiveness of our designed protocol of continuous high dose intracaval calcium infusion for the treatment of HVDRR.

Patients and Methods: We studied 12 patients with HVDRR, four of them had alopecia. Age of starting treatment protocol ranged from 2 -12 years. Daily infusions ranging from 1-2.2 g elemental calcium with oral phosphate from 1-2 g and oral calcium from 3.2–4.2 g elemental calcium were given for a period of 8-18 months. Followed by maintenance on oral calcium equivalent to 6.2 - 8g elemental calcium per day with oral phosphate 1-2 g. Measurements of serum calcium, phosphate and serum alkaline phosphatase were obtained before, during and after

the calcium infusions. Urea and electrolytes, serum parathyroid hormone and vitamin D metabolites were measured prior to calcium infusion, then repeated monthly. Kidney ultrasound was done every 6-months. Skeletal X-ray was done before, 6 and 12 months of treatment.

Results: The daily intra-caval infusions of calcium with oral phosphate and calcium resulted in marvelous clinical, biochemical and radiological responses with normalization of calcium, phosphate, alkaline phosphatase and parathyroid hormone in 8-24 months with improvement in height slandered deviation. The patients showed no radiological evidence of nephrocalcinosis on follow up.

Conclusion: The use of intra-caval calcium infusions followed by high dose oral calcium with oral phosphate is an effective method for treatment of HVDR.

P2-174

HIgh variability of phenotypic expression of the same genotype in X linked hypophosphatemic rickets (XLH)

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X-linked hypophosphataemia (XLH) is a dominant disorder caused by mutations in PHEX (located at Xp22.1), associated with rickets, lower limb deformities, pain, poor mineralization of the teeth and disproportionate short stature in children. The characteristics and severity of XLH vary between patients. Early diagnosis and specific treatment is usually decisive to improve short and long term patient outcomes.

We describe the variability of phenotype in two sisters carrying the same PHEX genotype and similar therapeutic history.

Anita starts walking at 12 months. She subsequently presents a progressive severe varus lower limbs. In the family history the mother has had a surgically corrected varus lower limbs with good response but residual bone and joint pain. The laboratory exams lead to the diagnosis of hypophosphatemic hyperphosphaturic rickets both in doughter and mother suspecting an X-linked trasmission (XLH).

At the age of two, Anita initiate appropriate oral medical therapy with calcitriol and phosphate. The genetic analysis don't find the classic mutation of the PHEX gene, but a deletion of exon 1 and 2 of the gene, also present in the mother. When the girl is two years old, her sister Giulia is born. She comes to endocrinological attention at 12 months without signs of rickets, the screening blood test show an hyperphosphaturic hypophosphataemia and specific oral medical therapy is immediately started.

During her growth, the eldest daughter Anita presents a worsening varus lower limbs, that needs numerous orthopedic surgeries with partial benefit. Giulia, instead, presents only a slight varus corrected with physiotherapy.

In 2019, Giulia satisfies the clinical and radiological criteria and starts monoclonal therapy with Burosumab with adequate biochemical response but poor response in height growth due to little residual growth plates. Anita shows, at the time, the fusion of the growth plates and continues oral medical therapy. Anita reaches a definitive height of 148 cm, with an important disproportion due to a still important varus that has poorly responded also to orthopedic interventions. Giulia a height of 153 cm, both below the parental target, despite the small difference in the beginning of the therapy.

Our family case underlines the high variability of XLH genotype-phenotype correlation, considering the mother and two sister therapeutic and clinical history. Moreover, our case report highlights the importance of a careful family history in the early diagnosis of genetic diseases which allows for earlier therapeutic intervention and a better clinical prognosis.

P2-175

Kenny Caffey Syndrome; a Rare Diagnosis in Saudi Arabia

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Introduction: Kenny-Caffey syndrome is a rare syndrome which is a primary bone dysplasia syndrome consisting of growth retardation with proportionately short stature, cortical thickening and medullary stenosis of the long bones, hypocalcemia from congenital hypoparathyroidism, and facial dysmorphism such as a prominent forehead, microphthalmia, and micrognathia. We report 13 years old with Kenny caffe syndrome who found to have a family history of the same presentation.

Case Report: Our case presented to the emergency department of a tertiary hospital in Saudi Arabia, with two days history of painful recurrent upper limb spasms and perioral tingling sensation, which was not triggered by proceeding infection, medication use or herbal ingestion.

Patient had similar episode 2 weeks back, sought medical advice and with normal labs and self-resolution of symptoms, patient was reassured and discharged home.

He was not on restricted diet or restricted sun exposure and not known to have any medical illness.

Patient has two elder siblings with symptomatic hypocalcemia on calcium supplements, but with no definite diagnosis.

He was well, on examination, with subtle dysmorphic features in form of micrognathia and prominent forehead. Height 140 cm (below 3rd centile); weight 35 kg (3rd centile). He had positive chvostek's and trousseau's signs.

Initial labs showed: (Adj Ca 1.43 mmol/L, Phosphorus 2.72mmol/L, Albumin 41 g/L, Magnesium 0.75 mmol/L, PTH0.752 pmol/L). He was treated by IV followed by oral Calcium supplements as well as active Vit D formula.

Discussion: His clinical and biochemical picture was going with familial isolated hypoparathyroidism and no apparent clinical features suggestive of a syndrome related hypo-parathyroid apart from subtle dysmorphism. Gene panel identified a FAM 111A gene mutation of Kenney Caffey syndrome as well as in the other symptomatic members of the family. A diagnosis that is extremely rare in this part of the world.

Conclusion: A careful history taking and proper physical examination can guide reaching to a rare diagnosis with the great help of advanced genetic tests.

P2-176

A patient-centred and multi-stakeholder co-designed, mixed methods, observational, prospective study protocol: Example of the adolescent experience of treatment for X-linked hypophosphatemia (XLH)

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Background: XLH is a rare, genetic, life-long disease caused by PHEX pathogenic variants. It is associated with progressive accumulation of musculoskeletal features and symptoms that evolve across the patient's lifetime if untreated. Although the disease is well characterised in children and adults, there are limited data describing the health outcomes and experiences of adolescents, particularly at end of skeletal growth (EOSG), a crucial phase during transition to adulthood.

To explore these unmet needs, a collaborative, patient-centric, mixed-methods protocol was developed to assess functionality and health-related QoL (HRQoL) in adolescents with XLH at EOSG, as well as caregiver perspectives.

Methods: My XLH (NCT05181839) is a 12-month, multicentre, non-interventional, observational, prospective study using a mixed-methods approach. Research questions and methodology were informed and designed collaboratively by patient-centred outcome research specialists, adolescents with XLH, caregivers, expert European physicians, and specialist technology providers.

Descriptive analyses of quantitative (baseline characteristics via medical records, XLH symptoms via app, physical activity via wearable device and HRQoL via EQ-5D questionnaire) and qualitative data (interviews) will assess the experiences of adolescents and caregivers in the pre-index (before EOSG) and post-index (after EOSG) periods. Targets of 30 adolescents and 15 caregivers were considered sufficient to reflect diversity of opinions and experiences.

The study setting is specialist centres in the United Kingdom, France, the Netherlands, Germany and Spain that treat adolescents with XLH with burosumab, an anti-fibroblast growth factor-23 monoclonal antibody therapy.

The target population is adolescents aged 12–17 years with a genetically confirmed diagnosis of XLH treated with burosumab for ≥12 months and confirmed by their physician as approaching EOSG. Adolescents who are non-adherent to treatment (missing ≥2 injections of burosumab in the previous 6 months) and those scheduled for orthopaedic surgery during the study will be excluded.

Data will be collected for 4 weeks before and 26 weeks after EOSG. Analyses will be conducted to describe characteristics, symptoms, activities, and experiences of adolescents during treatment pre- and post-EOSG (with comparisons over time between patients continuing and discontinuing treatment post-index). Caregivers will be interviewed about their experiences and support needs of adolescents.

Results: Recruitment started on 24 November 2021. As of 18 April 2023, 24 patients have been enrolled. Enrolment is due to be completed by end December 2023. Data analysis is planned to commence in 2024.

Conclusion: Our multistakeholder, mixed-methods research design in a rare disease offers an inclusive approach to better understand patient and caregiver experience.

P2-209

Diagnostic and Management Challenges in X linked hypophosphatemic rickets:-A case series

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Introduction: X Linked hypoposphatemic rickets (XLH) is a rare genetic disorder characterized by variable clinical features. It is often misdiagnosed with other types of rickets. A novel effective treatment is currently available. We report four cases of XLH who presented to our centre over a period of five years and describe their clinical presentation, diagnostic, treatment challenge and outcome.

Case 1: The child presented with short stature and progressive genu valgus deformity from the age of 18 months. She is born to first degree cousin parents. Mother is 142 cm tall but had no skeletal deformities. The patient was diagnosed with vitamin D deficiency and had surgery for deformity correction. At 5 years of age, she was diagnosed with hypophosphatemic rickets. She had a normal PTH and active vitamin D with high FGF23. Genetic testing confirmed mutation in PHEX gene. She was initially started on conventional treatment, then shifted to Burosumab which resulted in normalizing serum phosphate and improving her rickets score and stature.

Case 2: She presented with severe bowing of legs from the age of 14 months. She had a progressive genu varum deformity with rachitic rosary and wrist widening. She had classical biochemical features of XLH with high FGF23. She was genetically confirmed to be having a heterozygous mutation of PHEX gene. She was started on conventional treatment with oral phosphate and 1-alpha calcidiol at 2year of age. Her response is suboptimal with improvement of phosphate level but persistence of ricketic changes and deformity.

Case 3:18-month-old boy was referred for low phosphate levels detected during a febrile illness. He was born by Caeserean section as mother had deformed bones. The child had delayed motor milestones with abnormal head shape. At presentation, he had no bone deformities. Genetic testing confirmed a homozygous mutation variant of PHEX gene. He was started on Burosumab.

Case 4: A 39-year-old woman presented to our clinic as mother of patient case 3 (A). She was diagnosed as osteogenesis imperfecta and underwent multiple bilateral femoral and tibial corrective osteotomies. She is 131 cm tall. She lost all her teeth and is using a fixed denture. Genetic testing a showed a heterozygous mutation of PHEX mutation.

Conclusion: XLH has a variable presentation and can be misdiagnosed leading to deterioration of the bone condition and deformity. High index of suspicion is important for proper diagnosis and effective treatment.

Diabetes and insulin

P2-29

The effect of COVID-19 pandemic restrictions on the frequency of diabetic ketoacidosis at the time of diagnosis in children with type 1 diabetes

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Objective: The aim of this study was to investigate the effect of COVID-19 pandemic restrictions on the frequency of diabetic ketoacidosis (DKA) at the time of diagnosis in children with type 1 diabetes (T1D).

Method: The medical records of children with T1D who were diagnosed between 16.03.2018 and 16.03.2022 in pediatric endocrinology clinics in Elazig province in Turkey were retrospectively reviewed for the presence of DKA at the time of diagnosis (pH<7.3 or HCO_3 <18 mmol/L), severe DKA (pH<7.1 or HCO_3 <5 mmol/L). The two-year period before and after 16.03.2020, when the pandemic restrictions started in our country, was compared.

Results: In the pre-pandemic and post-pandemic period, 82 children, 46 (56.1%) were boys, and 106 children, 50 (47.2%) were boys, were diagnosed with T1D. When the periods were compared, DKA frequencies were 48/82 (58.5%) and 67/106 (63.6%) (p=0.515), respectively; severe DKA frequencies were 11/82 (13.4%) and 21/106 (19.6%)(p=0.247), respectively.

Conclusion: In this group of children with T1D, COVID-19 pandemic restrictions did not make a difference in the frequency of DKA and severe DKA at the time of diagnosis.

P2-30

Long-term follow-up for the first neonatal diabetes mellitus (NDM) due to KCNJ11 gene mutation who were successfully transferred from insulin to oral sulfonylurea in the Arabian Gulf

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Introduction: NDM is a rare disease diagnosed in the first 12 months of life. It is either transient or permanent. Early recognition of mutation in KCNJ11 and ABCC8, which account for approximately 40% of NDM, is essential to consider oral sulfonylurea for responsiveness mutations.

Aim: To study the efficacy and safety of oral sulfonylurea in a long-term follow-up (15 years) for the first successful switch from insulin to oral sulfonylurea in a patient with KCNJ11 gene mutation(R201H) in the Arabian Gulf.

Method: This is a long-term follow-up study of 15 years for the first case of successful transfer from insulin to oral sulfonylurea in the Arabian Gulf at the age of 3 years of life in 2007 after being diagnosed with a mutation in the KCNJ11 gene (R201H). Data were retrospectively collected from clinic visit records for the glycemic control, sulfonylurea dose, side effect, diabetes complication, growth, development, and neurological feature.

Result: Over the 15 years, the patient was on an oral sulfonylurea (glibenclamide) alone at a dose of 0.1-0.3 mg/kg/day, except in the last visit, due to limited supply, the patient switched to gliclazide MR equivalent dose. During that period, she showed excellent glycemic control; her HbA1c level was in the range of 5.8%-6.7% over the 15 years of glibenclamide therapy (Fig1), except recently when an adult physician saw her in a periphery clinic who shifted her to insulin therapy and discontinued glibenclamide after which her HbA1c increased to 8.9 %. Fortunately, her mother returned, the patient resumed glibenclamide, discontinued insulin therapy, and then her HbA1c dropped to 6.8%.

The patient doesn't show diabetes complications except for a mild increase in LDL due to familial dyslipidemia. The patient reached complete puberty. Her final height is 151 cm on the 25 % of the Saudi growth chart (mid-parental height was 154 cm), BMI was 28.4 kg/m^2. She has good academic college performance and normal neurological exam.

Conclusion: Oral sulfonylurea is effective in maintaining excellent glycemic control over the long term in a patient with KCNJ11 gene mutation (R201H), and it is well tolerated without side effects. Awareness about NDM among adult physicians is a priority for the best outcome for this group of patients.

Reference: Successful transfer from insulin to oral sulfonylurea in a 3-year-old girl with a mutation in the KCNJ11 gene. Ann Saudi Med 2010; 30(2): 162-164.

PMID: 20220270 DOI: 10.4103/0256-4947.60526.

(figure cannot be inserted).

P2-60

The effect of health literacy of caregiver parents of children and adolescents with Type 1 Diabetes on glycemic control

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Introduction: T1DM is a serious cause of morbidity and mortality owing to its chronic microvascular and macrovascular complications. Therefore, it is important to determine the factors that may affect the follow-up for diabetes. Some studies conducted on adults with diabetes have suggested that health literacy is an important parameter in the follow-up of diabetes. However, few studies have examined the literacy level of parents of children with type 1 diabetes and its effect on diabetes control. This study aimed to evaluate the level of health literacy of caregiver parents of children and adolescents with type 1 diabetes and the relationship between health literacy and glycemic control.

Method: Sociodemographic data form and Turkey Health Literacy Scale (TSOY-32) were filled in online by the caregiver parents of diabetics aged 1-18 years, who have been followed up with the diagnosis of T1DM in Hitit University Erol Olçok Training and research hospital and Muğla Training and research hospital Pediatric Endocrinology outpatient clinics for at least 1 year. Formula and index calculations of the TSOY scale (insufficient health literacy 0-25; Problematic/Limited health literacy >25-33; Adequate health literacy >33-42; Excellent health literacy >42-50) were arranged in four groups. The metabolic control status of the patients and their scale scores were compared.

Results: One hundred thirty parents with a mean age of 39.1±6.4 years participated in the study. The proportion of mothers among the participating parents was 85%. The mean age of diabetics was 11.6±4.1 years and the mean diabetes age was 4.8±3.8 years. The mean TSOY-32 index score was 34.5 (16-50). 10% (n=13) of the participants were inadequate, 31.5% (n=41) limited-problematic, 36.9% (n=48) adequate, 21.5% (n=28) had excellent health literacy. No correlation was found between the index score and age of the parents, educational status, and hba1c. However, there was a negative correlation between the index score and severe hypoglycemia and the number of hospital admissions due to hypoglycemia (r=-0.285 and -0.245; p= 0.01 and 0.06, respectively).

Discussion: Contrary to the literature, no relationship was found between glycemic control and health literacy levels in our study. This may be due to the fact that the scale used in our study is different from the scales used in studies suggesting a relationship between health literacy and glycemic control, and that it is a subjective scale based on self-assessment.

P2-61

Non-immune diabetes. A case of rare genetic insulin resistance syndrome: Rabson Mendenhall Syndrome

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Background: Rabson-Mendenhall syndrome is an extremely rare, autosomal recessive, severe insulin resistance syndrome that results from a mutation in the insulin receptor (INSR) gene. Currently, no more than 55 identified cases have been described in the world. Below is a clinical case with a newly diagnosed Rabson-Mendenhall syndrome in a girl in the Republic of Kazakhstan.

Clinical Case: A 7-year girl was admitted to the pediatric endocrinology program with complaints of increased blood glucose, thirst, increased appetite, darkening of the skin in folds, lethargy, and an enlarged abdomen. At birth at 34-35 weeks of gestation, weight 2150 g, height 44 cm, neonatal diabetes mellitus, transient form (HbA1c 6.67%, insulin 1000 μIU/ml) was diagnosed at the age of 40 days of life. Genetic testing was not available. According to medical records, she did not need insulin therapy in a bolus-basal regimen. From the age of 2 months, manifestations of acanthosis nigricans began, and then hyperkeratosis of the skin in the neck, armpits and inguinal region. On physical examination at current admission: psychomotor retardation, extensive acanthosis nigricans in skin folds and hyperkeratosis, thickening of the nails, hypertelorism, large low-set ears, prognathism, macrodontia, facial pastosity, frog belly, umbilical hernia, hepatomegaly. Laboratory examination revealed hyperglycemia according to the glucometer 26 mmol/l, insulin 183.7 μIU/ml, HbA1c-12.0%, leptin <0.7 ng/ml, IGF-1 <15 ng/ml, glucosuria, ketonuria and subcompensated ketoacidosis. Total cholesterol, HDL, LDL, triglycerides within reference values. The patient was treated by dehydration and infusion insulin therapy started, then high-dose insulin therapy in a bolus-basal regimen, metformin was added to the treatment when the condition stabilized, and also compliance with the diet. During the treatment ketoacidosis was stopped, stable fasting, nighttime and daytime glycemia was achieved, however, slight postprandial increases in glycemia persist. At this stage, the syndrome exposed clinically, the result of a genetic and molecular study in the work. Genetic testing result will determine the further appointment of recombinant IGF-1 in the treatment, the effective use of which in this syndrome is described in the literature.

Conclusion: The case shows the severe course of the Rabson-Mendenhall syndrome from the neonatal age and further progression with the development of complications in the absence of timely adequate treatment. Therefore, the knowledge about non-immune genetic forms of diabetes mellitus in children should be expanded with the aim of diagnostics, treatment and prevention of complications, and improvement of the life quality and expectancy.

P2-62

Growth patterns according to glycemic control, CGM apply, and diabetic complications in type 1 diabetes mellitus patients

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Introduction: Chronic diseases such as type 1 diabetes mellitus (T1DM) may alter linear growth, but previous reports regarding growth in children with T1DM has been inconsistent. This study aims to investigate height and growth velocity of T1DM patients after diagnosis of diabetes and whether they are affected by various factors.

Methods: This retrospective study, included 151 patients (male, 45.0%; mean age at diagnosis, 7.8±3.6 years old) diagnosed with T1DM in Severance Children's hospital. Diabetic patients with thyroid disease, celiac disease, or any other chronic diseases were excluded. We compared mean of height standard deviation score (SDS) and growth velocity between groups divided based on HbA1c levels, continuous glucose monitoring system (CGM) application, and diabetic complications.

Results: The mean height SDS was higher in the well-controlled group (HbA1c < 7 %) than poorly controlled group (HbA1c ≥ 7 %). In addition, T1DM patients with CGM had a higher height SDS than patients without CGM. The growth velocity decreased for the first year after diagnosis in both groups, while growth velocity increased afterward in patients who applied CGM. There was no significant difference of height SDS and growth velocity between groups divided by presence of chronic complications. In linear regression model, differences between height SDS at diagnosis and 5 years after diagnosis was positively correlated with height at onset of diabetes ($p < 0.001$) and mid parental height ($p = 0.001$), and negatively with mean HbA1c levels ($p = 0.001$).

Conclusion: Based on the findings, good glycemic control and use of CGM positively affects linear growth of T1DM patients.

P2-63

The importance of genetic testing and the appropriate use of glibenclamide in neonatal diabetes

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Introduction: Neonatal diabetes is a rare condition that can present in the first months of life. Neonatal diabetes has more than 20 genetic origins that are currently known. About 40% of these patients carry mutations in KCNJ11 and ABCC8 genes, which impair the pancreatic beta-cell K-ATP channels and can be treated with oral sulfonylureas. The purpose of this case report is to present a patient diagnosed with neonatal diabetes and the subsequent management of the condition.

Objective: The objective of this case report is to describe the presentation, diagnosis, and management of a patient with neonatal diabetes. The report aims to highlight the importance of genetic testing for the appropriate use of medications such as Glibenclamide in the treatment of neonatal diabetes.

Case Report: 37 day-old male patient was admitted to the Muratsan University Hospital with weakness and hyperthermia. Upon examination, the patient's blood glucose level was found to be 51.0mmol/l, the patient was dehydrated, and insulin therapy was started. He was diagnosed with neonatal diabetes and despite the unavailability of genetic testing, a decision was made to change the treatment to Glibenclamide. C-peptide was 0.01ng/ml(N-0.92-3.73) before Glibenclamide treatment and 0.26ng/ml on 1mg/kg/day Glibenclamide together with the same doses of insulin. The diagnosis of Sulfonylurea unresponsive neonatal diabetes was made before the result of genetic testing. As soon as the opportunity arose genetic testing was performed, and a heterozygous KCNJ11 gene mutation of c.149G>C variant in exon 1 was found in the heterozygous state. When the child was 8 months old, he was hospitalized again with the aim of switching to Glibenclamide again, taking into account the results of the genetic analysis and glucose fluctuations from 2.2-32.2 mmol/l during a full feeding. This time there was a response to the treatment, with C-peptide-3.3 ng/ml. The child was discharged with glucose fluctuations from 5.4-8.9 mmol/l. We are in daily contact with the patient.

Conclusions: Neonatal diabetes is a rare form of diabetes. The proper identification and treatment of the disease require a thorough understanding of the underlying genetic causes and the appropriate use of medications like Glibenclamide. This case report highlights the importance of genetic testing in the diagnosis and management of neonatal diabetes. Even if genetic testing is unavailable, starting treatment with Glibenclamide may still be possible as long as regular communication with the patient to prevent the risk of hypoglycemia is maintained.

P2-64

Neonatal diabetes mellitus in a patient with a novel heterozygous mutation in GATA6

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Transient neonatal diabetes mellitus (TNDM) occurs in 50-60% of all cases of neonatal diabetes mellitus (NDM). The most common cause of TNDM (70%) is almost invariably associated with defect in chromosome 6 and mutations in the KCNJ11, ABCC8, INS, NHF1B etc. genes. TNDM is caused by mutations in the GATA6 gene in rare cases. This gene encodes a transcription factor that is important for the development of the hematopoietic, cardiac and gastrointestinal systems.

Clinical Case: Proband is a female born at 35 week of gestation with intrauterine growth retardation (weight 1580 g (SDS -2.29), length 40 cm (SDS -2.65)) via cesarean section. The proband was fedded using tube feeding in neonatal period. The proband was diagnosed with hyperglycemia 29.6 mmol/l in the neonatal period, insulin therapy was started. Insulin was stopped in 1 month of life. Normoglycemia was observed. Family history of diabetes was negative. The proband was relapse of diabetes in 3 years old after a respiratory infection. She had polyuria, polydipsia and weight loss. HbA1c 11.5%, glycemia 18.6 mmol/L. Insulin (Aspart, 0.4 U/kg/day) was started. Fasting C-peptide 0.69 ng/ml, stimulated C-peptide in 120 min - 2.32 ng/ml. Specific islet antibodies (GADA, IA2A, IAA, ZnT8A) were negative. Pancreatic hypoplasia was diagnosed due to ultrasound. Genetic test (NGS 27 genes) was performed, no mutations were detected. Proband had extrapancreatic features: moderate growth retardation (growth SDS -1.95), patent ductus arteriosus, mitral valve prolapse, gallbladder agenesis, umbilical hernia, autoimmune thyroiditis. At the age of 8 years (diabetes duration was 5 years) patient was treated fast acting insulin Aspart, 0.7 U/kg/day. HbA1c 5.2%, fasting C-peptide 0.71 ng/ml, stimulated C-peptide in 120 min – 0.9 ng/ml. Whole-exome sequencing revealed novel pathogenic heterozygous mutation c.1302+4 1302+7del in exon 3 of the GATA6 gene, leading to a deletion of 4 nucleotides.

Conclusion: TNDM is rarely caused by mutations in the GATA6 gene. The development of NDM due to mutations in the GATA6 gene is probably associated with pancreatic hypoplasia. Diabetes associated with mutations in the GATA6 gene is progressive. Patients with mutations in the GATA6 gene have extrapancreatic features (congenital heart defects, gallbladder agenesis, umbilical hernia).

P2-65

Systematic review on the effects of the COVID-19 pandemic on incidence of new-onset type 1 diabetes (TID), and glycemic control among children/ adolescents with pre-existing TID

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Introduction: There is some evidence to suggest that the SARS-CoV-2 virus affects endocrine organs and metabolic processes. However much of the available evidence involves adults. We conducted a systematic review to summarise recent evidence on the effects of COVID-19 on the incidence and disease control of type I diabetes mellitus (T1DM) among children and adolescents.

Method: We conducted a literature search up to 05/03/2023 on PubMed, Scopus, and Google Scholar to identify publications reporting incidence and disease control of type I diabetes mellitus (T1DM) among children and adolescents in association with the COVID-19 pandemic using pre-specified keywords, and additionally perusing additional references from relevant articles.

Results: Following the defined search strategy, 12 studies were found to be eligible for the systematic review. Six studies involving 1396 children/adolescents reported on the incidence of new onset T1DM/ DKA during the pandemic. Incidenc of TID increased. Two studies from Canada and Finland reported an increased incidence of new-onset T1DM from 0.13-6.25 before the pandemic to 0.38-20 during the pandemic, while 5 studies (from Canada, Finland, Kuwait, and the UK), reported and increased incidence of DKA among children with new-onset T1DM during the pandemic compared with the pre-pandemic era.

When considering disease control in children with pre-existing T1DM, six studies (three from Italy, one each from Canada, Spain, and Greece) involving 598 children/adolescents, all reported improved glycemic control during the pandemic (with improved blood glucose values including increased Time-In-Range, and reduced Time-Above-Range, Time-Below-Range, Coefficient-of-Variation and HbA1C during lockdown) compared with pre-pandemic values.

Conclusion: There appeared to be an increase in the incidence of T1DM among children/adolescents and the number presenting with DKA, during the COVID pandemic. Evidence on the effects of glycaemic control is somewhat conflicting but more studies reported an improvement of glycaemia control during the lockdown period. We postulate that the coronavirus could be an aetiological factor inducing rapid onset of T1DM, leading to increased incidence and presentation with DKA, while improvement in glycaemic control could be due to increased time available for self-care and parental supervision of diabetes control following reduced work/ school-activities due to lockdown.

P2-66

Physician and Family Awareness in the Diagnostic Process of Newly Diagnosed Type-1 Diabetes Mellitus

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Aim and Method: Diagnosis of type 1 diabetes (T1DM) may be delayed in some children, despite seeking medical care by the family. In this prospective/observational study, the time and process from consulting with a doctor to getting diagnosed with diabetes was investigated in patients hospitalized for newly diagnosed T1DM between 2021-2022.

Results: During the study period total of 114 newly diagnosed T1DM patients (49%F, age: 9.29±4.2 years) were admitted. 102 patients were diagnosed elsewhere and referred to our hospital for treatment. 53 patients applied initially to a pediatrician. T1DM diagnosis was missed in 9 (17%) at the first application. Eight of them were diagnosed at their second application. 49 patients applied initially to a family physician. T1DM diagnosis was missed in 12 (24%) at the first application.Eleven of them were diagnosed their second application. Of the patients whose diagnosis was missed at the first application, 24% were diagnosed with upper respiratory tract infection, 5% with gastroenteritis, and 71% did´nt receive a diagnosis. In all patients, the average number of doctor visits until the diagnosis of DM was 1.28. The time from patient seeking medical care to hospitalization was 2.09 ±3.6 (0-21) days. 4/44 (9%) and 10/37 (27%) of the patients diagnosed with T1DM (by a pediatrician and by a family physician respectively) had sought a second opinion.

While all 12 patients with a family history of T1DM were diagnosed at their first presentation to a doctor, this rate was 75% in those who did not. In 23% (26/114) of the patients, the family suspected the diagnosis of DM and reported it to their doctor, but despite this, 4 of them could be diagnosed at the second consultation. HbA1c of the patients who applied with suspicion of DM was lower than those who applied without suspecting the diagnosis of DM (11.45±2.03% and 12.85±2.56, respectively, (p:0.002). However, DKA (50.6% vs. 66.6%) and severe DKA (27% vs. 50%) were higher in those who could not be diagnosed at the first application (p:0.22). In those presenting with DKA, HbA1c levels were higher in patients whose mothers had less than high school education (13.03±2.4% vs. 11.4±2.3%, p:0.0010).

Summary of Results: The diagnosis of T1DM can be missed by 17% and 24% at the first examination by pediatrician and family physicians. However, the high rate of DKA at diagnosis of T1DM in our cohort suggests that families are delayed in seeking medical care. Families' awareness of DM contributes to early diagnosis.

P2-126

Relationship Between Time in Range (TIR), Time Below Range (TBR), Time Above Range (TAR), Glycemic Variability (GV), and HbA1c as predictor of glycemic control in children and adolescents with Type 1 Diabetes Mellitus

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Introduction: Glycated hemoglobin (HbA1c) is a rough indicator of glycemic control and not useful to evaluate aspects related to acute or daily glycemic changes in diabetic patients. With the emphasis on intensive management of type 1 diabetes (T1DM), data from studies support using Continuous Glucose Monitoring (CGM) to improve glycemic control and reduce glucose variability, which is related to an increase in macro and microvascular complications.

Aim of the Study: To find the relation, if any, between the CGM data of children with T1DM and glycemic control assessed by measuring HbA1c.

Patients and Method: We studied 20 patients (age 5-14 years) with T1DM using Flash monitoring CGM(FiCGM). The time in range (TIR) glucose (70-180mg/dl), time above range (TAR) glucose >180mg/dl, time below range (TBR) glucose <70mg/glucose variability (GV) and glucose management indicator (GMI) were recorded for 7 days) over 2 outpatient clinic visits at 6 months and 12 months post diagnosis. The estimated and measured HbA1C levels were recorded and compared with the CGM data.

Results: In our children with T1DM, the mean HbA1C after 6 and 12 months = 7 +/-1.24 % and 7.4 +/- 1.27% respectively. Growth parameters were normal (table 1). Highly significant negative correlations were detected between measured HbA1C and TIR ($r = -0.89$, $P < 0.001$), and measured HbA1c and GMI ($r = -0.898$, $P < 0.001$). A significant positive correlation was detected between HbA1C and TAR ($r = 0.895$, $P < 0.001$) and between the estimated and measured HbA1c. Glucose variability (GV) was correlated significantly with TBR ($r = 0.45$, $p = 0.003$)

Table1. HbA1C and growth data of children with T1DM

At Dx	6 mon	12 mon
HBA1C	HBA1C2	HBA1C3
10.82	6.98*	7.42*
1.94	1.24	1.27
BMISD1	BMISD2	BMISDS3
0.81	0.83	0.95
1.39	1.16	1.13
HtSD1	HtSD2	HtSD3
0.49	0.30	0.24
1.05	1.08	1.18

Conclusion: CGM is a good tool for day-to-day monitoring and accurately guiding management of diabetes in timely basis. Increasing the TIR and decreasing the TAR significantly improve long term glycemic control. However, tightening glycemic control (by increasing time below range (TBR) can increase glucose variability and compromise glycemic control. Diabetes control aims in A strategy for keeping glucose level in range while simultaneously avoiding hypoglycemia can optimize glycemic control.

P2-127

Celiac and Autoimmune thyroid disease in patients with anti-GAD positive type 1 diabetes mellitus

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Keywords: Anti-GAD antibodies, Anti-thyroid antibodies, celiac disease, HbA1c, type-1 diabetes mellitus.

Abstract: We analyze the association of anti-GAD positive type-1 diabetes mellitus (T1DM) with anti-thyroid antibodies and celiac disease. We analyzed children of both gender and aged between 1 to 18 years having known T1DM. Blood sample of each child was taken in sterilized container and sent to institutional laboratory for biochemical investigations. In a total of 115 patients, 67 (58.3%) were female and 48 (41.7%) male. The mean age was 8.87±3.43 (ranging between 1.5 to 17 years). The mean HbA1c was 11.86±7.31%. It was found that anti-GAD IgG was having signification association with celiac disease ($p<0.001$). Significant correlation of anti-GAD positive antibodies with Ttg-IgG antibodies (correlation coefficient=0.303, $p=0.001$), thyroid peroxidase antibodies (correlation coefficient=0.228, $p=0.001$). High proportions of children with anti-GAD positive T1DM patients were found to have thyroid disorders and celiac disease. Significant correlation was found between anti-GAD positive antibodies, celiac disease and anti-thyroglobulin antibodies.

P2-128

A Case of Latent Autoimmune Diabetes of Youth Initially Negative for Islet Autoantibodies

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Background: Islet autoantibodies such as Glutamic Acid Decarboxylase (GAD), Islet antigen-2 (IA-2), Zinc Transporter 8 (ZnT8), and Insulin autoantibody (IAA) are known to be detected at higher frequencies in pediatric patients clinically diagnosed with type 2 diabetes than in adults. Therefore, it is crucial to evaluate them for accurate diagnosis, prognosis, and treatment direction. However, guidelines for when to re-evaluate patients with negative islet autoantibody results have not been established yet.

Case Report: A 12-year-old boy was referred to our hospital with suspicion of metabolic syndrome related to severe obesity, hypertension, hyperglycemia, and elevated liver enzymes from a local clinic. His height was 163.1 cm, weight 81.9 kg, body mass index (BMI) 21.4 kg/m2 (BMI z-score 3.08), and blood pressure 125/89 mmHg. No glycosuria, proteinuria, or ketonuria was found in the urinalysis performed at our hospital. He showed increased AST/ALT levels at 98/154 u/L, HbA1c 7.8%, c-peptide 9.49 ng/mL (random glucose 146 mg/dL), acanthosis nigricans, HOMA2B 169.8%, and HOMA2IR 8.00, leading to a diagnosis of type 2 diabetes with insulin resistance as the main pathological mechanism. Initial treatment with metformin and basal insulin was started for induction.

At the time of the initial diagnosis, islet autoantibodies, including GAD antibody, islet cell antibody, and anti-insulin antibody, were all negative. During the 3-year follow-up, despite increasing the basal insulin dose to 1 IU/kg, his HbA1c remained poorly controlled at 8.4% and c-peptide decreased to 2.28 ng/mL (glucose 173 mg/dL). HOMA2B value decreased to 41.3%, and HOMA2IR was 2.06. The decision was made to switch to insulin multiple daily injections, and a retest of GAD antibody revealed a seroconversion to 2.4 U/ML (reference range <1.0), confirming a diagnosis of latent autoimmune diabetes in youth (LADY).

Conclusion: The prevalence of LADY in pediatric patients has not been accurately determined. When the clinical course differs from typical pediatric type 2 diabetes, evaluating for seroconversion to diagnose LADY may be necessary, even if initial islet autoantibody results are negative.

P2-129

The use of analogue insulins in children and adolescents with type 1 diabetes in Kashkadarya region

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Objective of the Study: Comparative assessment of the achievement of target levels of the therapy for type 1 diabetes mellitus using various types of insulin in an outpatient setting.

Materials and Methods: The study included 100 children and adolescents with type 1 diabetes aged 4–17 years old who received basic insulin Glargin and Insulatard, and short-acting Glilusin and Actrapid. Of these, 50 children and adolescents were switched to Glargine once in the morning before breakfast (basis), injections of simple ultra-short-acting insulin (Glilusin) two to three times a day immediately before meal.

Physical development, biochemical parameters (HbA1c, creatinine, cholesterol), daily dose and insulin requirement, frequency of acute and chronic complications were assessed in dynamics.

Research Results: In the group receiving Glargine + Glilusin, there was an increase in height by 3.9%, weight by 14.4%, and in

Clinical characteristics of the patients

Indicators	Glargine +Glilusin		Insulatard +Actrapid	
	before	**after**	**before**	**after**
Number of patients	50	50	50	50
Average age	10.0+1.0	11.2+1.0	11.8+0.8	13.1+0.9
Term of disease	4.3+1.0	6.0+1.0	6.0+0.6	8.1+0.58
Period of observation		12 months		12 months

the group receiving Insulatard + Actrapid, growth increased by 3.2%, and weight by 11.8%.

To achieve compensation in both groups, it was necessary to increase the doses of daily insulin, but within 12 months the need for insulin in the Glargine group was less and amounted to 1.0 U/kg, and in the Insulatard group it was 1.1 U/kg. The daily dose of Glargine was 5.7 units less than the dose of Insulatard. Comparative analysis of the use of various types of insulin showed that patients receiving insulin glargine achieved lower levels of HbA1c (7.4 ± 0.2%) compared with the children receiving conventional genetically engineered insulins (HbA1c 8.0 ±0.2%).

The proportion of patients with HbA1c levels below 7.5% transferred to Glargine therapy increased from 11.7% to 53%, and in the group receiving Insulatard from 5.8% to 29.4%.

Conclusions: 1) During the monitoring period, there was a greater extent improvement in height and weight indicators in the children and adolescents in the Glargin + Glilusin group.

2) Together with the background intensified insulin therapy with Insulatard, there was 1.5% decrease in HbA1c, and 1.6% with Glargine. Target levels of glycemia in the Glargine group were achieved with the background lower dose requirement.

3) The average daily dose increased by 20% with Glargine and by 14% with Insulatard.

P2-130

Insulin-dependent diabetes mellitus in a young child in the structure of monogenic immune dysregulation syndrome (LRBA deficiency)

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Objectives: Diabetes mellitus (DM) as part of autoimmune dysregulation syndromes holds a unique place among DM monogenic forms. Early diagnosis of the disease is critical for pathogenetic therapy to be prescribed.

We describe a clinical case of insulin-dependent DM in combination with severe autoimmune enteropathy in a young patient who had a novel compound heterozygous mutation in the LRBA gene.

Methods: The patient underwent clinical-laboratory and genetic examinations at the Russian Children's Clinical Hospital' Immunology Department in Moscow.

Results: A 2.5-year-old patient was admitted to the hospital in critical condition, complaining of frequent loose stools, vomiting and weight loss. His blood pH was 7.19, his VE was 18.5 mmol/l, and his glucose level was 11.9 mmol/l. The child's early development was normal, and hereditary endocrine diseases were not aggravated. As early as 10 months old, he began showing signs of insulin-dependent DM.

Beginning at 1 year and 11 months, the patient experienced several episodes of vomiting and frequent loose stools, which eventually led to the development of acute diabetic ketoacidosis (DKA) and inpatient admission to the intensive care unit.

Seronegative celiac disease, infectious enterocolitis, and Crohn's disease were all considered in the differential diagnosis.

Cytopenia was discovered during the examination. According to the immunological examination, the numbers of lymphocytes and serum immunoglobulin subpopulations were in the normal range. FOXP3 expression was at the lower limit of the normal range. Because the therapy had no effect, a male child with early signs of enteropathy and insulin-dependent diabetes was suspected of having the IPEX syndrome.

The entire exome was sequenced, and previously uncharacterized heterozygous mutations in the LRBA gene were found, i.e.: NM 006726.4: c.1028G>A (p.Cys343Tyr) and c.7561dupA (p.Thr2521Asnfs). His diagnosis was as follows: Primary immunodeficiency. Immune dysregulation syndrome: Diabetes mellitus. Autoimmune enteropathy. Autoimmune cytopenia. Targeted therapy with Abatacept at a dose of 10 mg/kg/day was prescribed to him, and the results showed that it had a positive effect.

Conclusion: This clinical case demonstrates the difficulties in diagnosing IPEX-like syndrome in young children due to the rarity of this pathology, the nonspecific clinical picture that occurs in these patients, and the need for a multidisciplinary approach to the management of such patients. Genetic validation of the diagnosis is required for differential diagnosis with IPEX syndrome and other IPEX-like syndromes, as well as for the selection of the most effective patient management tactics.

P2-131

Ketoacidosis in the newborn as a presentation of IPEX Syndrome

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Introduction: IPEX syndrome is a syndrome characterized by the following triad: immune dysregulation, polyendocrinopathy and X-linked enteropathy. It is produced by a variant in the FOXP3 gene. It is a rare disease with poor prognosis.

Clinical Case: We are reporting the case of a boy, 2nd child of non-consanguineous parents, normal pregnancy. Born at 39 weeks of gestational age, birth weight 2985 grams and length 49 centimeters, Apgar score 7-7. Discharged with her mother at 48 hours of life. At 7 days of life he was admittted with ketoacidosis and hypovolemic shock. At entry he had pH 7.01, bicarbonate 5.3mEq/L, BE -24, glycemia 700 mg/dl, ketonemia 4.7 mmol/L, ketonuria +++ and plasma creatinine 1.15 mg/dl. Hydration and continuous intravenous insulin infusion pump was started with insulin at 0.02 IU/kg/hr. He was treated with antibiotics until negative cultures were received. The study was completed with plasma B-OH butyrate 37 mg/dl, C peptide <0.02 ng/ml, HbA1c (glycosylated hemoglobin) 6.1%, thyroid function and basal cortisol appropriate for his age. He had mild hypotonia, so a study was carried out with brain ultrasound, electroencephalogram and brain magnetic resonance without pathological findings. He also underwent abdominal ultrasound showing presence of pancreas without pathological findings and echocardiography within normal ranges. Once ketoacidosis was resolved, basal-bolus subcutaneous insulin was started with diluted insulin and monitoring with capillary glycemia before and after feeding. These were compared with a continuous flash glucose monitor, showing good correlation, but difficult glycemic control. At 3 weeks of age, a microinfusion insulin pump was installed, achieving better glucemic control. During this period, a generalized self-limited rash appeared. At one month of life, he presented rectal bleeding, diarrhea and dehydration with hypoglycemia that needed change to amino acid-based formula.

The genetic study carried out found heterozygous pathogenic FOXP3 splicing variant in the mother and hemizygous for a likely pathogenic FOXP3 splicing variant in the patient and his sister.

Study for antibodies to β-cell proteins were positive (anti-insulin, anti-GAD and anti-beta cell) Rapamycin was started for enteropathy, improving the latter. Actually the patient is using insulin pump, rapamycin and amino acid-based formula.

Conclusion: Most of the patients with IPEX syndrome debut with entetopathy although diabetes is the first endocrinological manifestation. In our patient, the genetic study was essential for an accurate diagnosis, allowing differential diagnosis from other causes of neonatal diabetes and individualized treatment.

P2-159

Glucose monitoring systems in children and adolescents with type 1 diabetes and expectations from their use

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Introduction: Continuous Glucose Monitoring Systems (CGM), including real-time(rtCGM) or intermittently Ssanned CGM(isCGM, flash technology) are evolving technologies that can help both healthcare professionals and families to improve glycaemic control in children and adolescents with diabetes mellitus. The technology offers the possibility of monitoring glucose in real time or on demand through the interstitial fluid, contributing to the improvement of glycaemic control, reducing the incidence of hypo-/hyperglycaemia, and alleviating the anxiety and fear associated with both.

Aim: To record expectations by using CGM(rtCGM/isCGM) in a cohort of children and adolescents with type 1 diabetes (T1D).

Subjects and Methods: A questionnaire about the use of CGM(rtCGM or isCGM) was sent to 25patients with TID to record their expectations from its use.

Results: 25 questionnaires were completed by patients and their caregivers (56% girls). The mean age was 13 years, mean duration of diabetes 4.5years. 24 children/adolescents(92%) wore a CGM system, 10 iCGM (40%), 15 rtCGM (60%). 18 children/adolescents(60%) used an insulin pump, with a mean time of use of 2 years. 80% of patients preferred to place a CGM system to avoid finger pricks, felt safer in hyper-hypoglycaemia, reported improved quality of life. 96% reported an improvement in HBA1c levels, 75% said the sensor was more helpful in decision-making for calculating the correct mealtime insulin bolus, 60% for calculating basal insulin/basal bolus rate, 56% for making decisions about the insulin correction bolus. 60% of patients stated that using a sensor helped them make exercise insulin dose decisions. >52% of patients felt that wearing a CGM system made their favourite activities easier. 56% of respondents felt some discomfort when the sensor was noticed by others. Regarding the problems of the sensors, the majority stated that glucose measurements are often not downloaded, and there was mismatching with the capillary glucose measurements. When asked what features they felt were missing from the sensors used, most reported the high and low alarms, how to insert the sensor, and no need for calibrations.

Conclusions: An initial training is likely to ensure the maximum benefit of using a CGM system. Patients and caregivers should be committed to CGM education, practical aspects, evaluation and interpretation of results, day-to-day management based on CGM trends. The use of CGM has been shown to improve quality of life, reduce diabetes distress, and can help to improve the long-term complications of the disease.

P2-181

Demographic and clinical characteristics of children with type 1 diabetes mellitus at Notre Dames Des Secours University Medical Center Byblos Lebanon

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Keywords: Retrospective descriptive study, diabetes mellitus type 1, diabetic ketoacidosis, NDS-UMC, Byblos, Lebanon, single-center experience.

Background: Type 1 diabetes mellitus (T1DM) increases worldwide especially in the Mediterranean region. Epidemiological studies about T1DM are made in many countries, but Lebanon lacks such data.

Objective: This is a descriptive study of demographic and clinical characteristics of 78 patients presented to the Pediatric Endocrine Unit of Notre Dame Des Secours University Medical Center (NDS-UMC), Byblos, Lebanon between January 2002 and March 2020, with type 1 diabetes mellitus (T1DM) for the first time. Only 60 patients passed the exclusion criteria. The data was collected from medical files.

Results: In this study, the female/male ratio was (1:1.07), mean age at presentation was 7.48 years old for both genders combined, with 2 peaks of age category including 5 to 9 (40%) and 10 to 14 (33.3%). They presented mostly during winter (31.7%), fall (26.7%), spring (25%) then summer (16.6%) and from urban areas (66.7%). We found 11.7% of patients with family history of T1DM. The mean length of hospitalization stay was approximately 6 days. Two patients were admitted to the pediatric intensive care unit and the rest of the children were managed in the pediatric unit. Symptoms at presentation were 96.7% polyuria/ polydipsia, 56.7% weight loss, 33.3% fatigue/weakness, 31.7% abdominal pain, 23.3% nausea/vomiting, 15% Kussmaul respiration and 3.3% coma. Approximately 71.7% of children presented with diabetic ketoacidosis (DKA), severe DKA (62.8%), moderated (30.2%) and mild (7%). The mean pH at diagnosis was 7.25 ± 0.16 (6.82 – 7.48), mean plasma glucose was 517.33 ± 164.01 (162 – 948) and mean HbA1C was 10.56 ± 1.85 (9.2 – 19.7) and mean serum bicarbonate was 12.47 ± 7.92 (2 – 27.8). Regarding antibodies related to T1DM, anti-GAD antibody (61.1%), anti ICA antibody (50%), anti IA2 antibody (4 2.9%) and anti-IAA antibodies (6.25%) of children. Only 21.4% of patients were tested positive for anti-transglutaminase antibodies.

Conclusion: A very high proportion of children presented with DKA and almost all of them had polyuria/ polydipsia. The average number of hospitalization days was very high compared to other countries. Anti-IAA antibody had a very low percentage of positivity and a relatively important percentage of patients tested positive for anti-transglutaminase antibody.

P2-182

Evaluation of clinical outcomes in children and adolescents with type 1 diabetes switching from Insulin Glargin to Insulin Detemir

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Basal-bolus insulin therapy is currently, the most common treatment modality in children and adolescents with type 1 diabetes mellitus (T1DM) worldwide. Insulin glargine and detemir are two different molecules, produced with small modifications, of human insulin. In this prospective longitudinal study, we aimed to compare HbA1c, time in range in CGM, basal insulin doses and hypoglyccemia frequencies in children and adolescents with T1DM who underwent switching from insulin detemir to insulin glargine by usual practice.

Material Method: Eighteen patients aged 5-18 years who were using levemir and planned to switch to lantus were included in the study. Primary outcome measures were collected 3 months before conversion and compared with outcomes collected 3 months after conversion. Basal insulin dose, mean hemoglobin a1c values, time in range and frequency of hypoglycemia were investigated. Statistical analysis was performed using the SPSS software, version 22.Paired t tests were used for continuous variables, including insulin dose, A1C, and weight.

Results: A total of 18 patients (10M/8F) were included in the study. The mean age was 10,6 ± 1,85 years, and mean duration time of diabetes 33,6± 17,1 months. Insulin detemir were switched to insulin glargine due to the use of high doses, the inability to adapt to the two doses, and the fear of injection. The majority (15 patients [83.3%]) had a decrease in insulin dose on conversion and three were converted on a unit-for-unit basis. Three months after switching, significant change in mean insulin glargine dose was noted compared with baseline insulin detemir dose in patients (37.7 vs 31.1 units/day, $p<0.05$). When the hba1c levels of the patients were compared, it was not statistically significant, but a lower mean was obtained with lantus(8,5±1,5 vs 8,1± 1,02; p=0,074). However, time in range values were found to be significantly higher with lantus (65,7%± 11 vs 72.5%± 17;p=0.010) and the frequency of hypoglycemia was significantly reduced (2,1 vs 1,6;p=0.035).

Conclusion: In our study, children with T1DM using detemir or glargine as basal insulin had similar results in terms of Hba1c, but they remained time in range for a longer time with insulin glargine and the frequency of hypoglycemia and mean basal insulin dose decreased. Administration of lower and single dose basal insulin with glargin increased compliance and provided better glycemic control in our cases.

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P2-183

New onset diabetes – frequency of DKA and positive islet autoantibodies at Varna's diabetes center

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Background and Aims: Initial presentation of type 1 diabetes (T1D) is associated with different level of diabetic ketoacidosis (DKA). Four pancreatic islet cell autoantibodies (Abs) mostly associate with T1D - glutamic acid decarboxylase antibodies (anti-GAD65), tyrosine phosphatase antibodies (IA 2-Ab), insulin autoantibody (anti-IAA) and zinc transporter 8 antibody

Aim: To evaluate the prevalence of DKA, the frequency of positive islet autoantibodies and the laboratory differences between patients with and without DKA at T1D diabetes onset in youth at a Specialised diabetes center for a period of four years (March 2019 - March 2023).

Methods: A total of 160 newly-diagnosed patients were enrolled in the study. Demographic and laboratory data was collected. Participants were tested for anti-GAD65, anti-IA2 and anti-IAA by ELISA.

Results: The mean age of the participants was 9.0±4.3 years (57% boys). At the onset of T1D, 44.3% were with initial DKA while 16.9% were with severe DKA. In the group without DKA the prevalence of boys is significantly higher compared to those without DKA (64% vs 48%, p=0.002). The participants with DKA were younger (8.2±4.3 vs 9.6±4.3 years, p=0.04) with significantly higher levels of initial blood glucose levels (23.4±7 vs 18.3±9.1 years, p<0.001) and HbA1c (12.2±2.3 vs 11±2.4%, p<0.001). C-peptide levels were significantly higher in the patients without DKA: 0.84 vs 0.40 ng/ml, p<0.001. Weak significant correlations were found between the severity of DKA and age (r=-0.143, p<0.03), HbA1c (r=0.26, p=0.001) and C-peptide levels (r=-0.204, p=0.012). At diagnosis, 81.6% were with at least one positive diabetes related autoantibody. At the onset of T1D, 6.1% of patients were with 3 positive Abs, 41.5% had 2 Abs and 34% had 1 positive Ab. Of all positive, 84.1% had anti-GAD65, followed by 62.5% anti-IA2, and 19.1% anti-IAA positive, resp. (p<0.01). Of all participants, 81.6% had low level of C-peptide which correlates with age (r=0.356, p<0.0001)

Conclusions: Initial DKA in our study is associated with younger age, higher initial BGL and HbA1c levels as well as lower C-peptide levels. Incidence of DKA among youth and most frequent diabetes associated antibodies in new onset T1D are similar as reported worldwide, and with no relation with initial DKA.

P2-184

An Obese HNF1β Case Presenting with Diabetic Ketoacidosis

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Background: Hepatocyte nuclear factor 1β (HNF1β) is a critical transcription factor that regulates the development of the kidneys, pancreas, liver and genital tract. Patients with deletions and mutations in the HNF1 β gene present with renal and extrarenal manifestations. The most important extrarenal finding is diabetes, also known as MODY5. Although it is generally diagnosed with hyperglycemia, diabetic ketoacidosis is rarely seen.

Case: A fifteen-year-old male patient was admitted with diabetic ketoacidosis with polyuria, polydipsia, and weight loss for 1 month. History revealed that the patient was diagnosed with antenatal hydronephrosis and nonatal hyperglycemia on the postnatal 2nd day resolving in two days. There was no consanguinity in the family history of the patient who underwent right pyeloplasty at the age of 6 months. There were individuals diagnosed with DM at an advanced age on the paternal side of the patient. On physical examination, height was 174 cm (+0.33 sds), weight was 94.5 kg (+2.32 sds), and BMI: 31.2 (+2.32 sds), pubertal stage was Tanner 4. Laboratory

Results: pH: 7.13, HbA1c: 13.6%, c-peptide: 0.53 ng/mL, glucose: 592 mg/dl. Aanti-GAD,ICA,IAA antibodis were negative MODY5 was considered based on diabetes and the history of hydronephrosis, asymptomatic elevation of transaminases and hypomagnesemia. Ultrasound examination revealed multicystic kidney. Genetic analysis showed c.957_966del (p.Ser319Argfs*) heterozygous mutation in HNF1β gene confirming the diagnosis of MODY5. Pancreatic dorsal agenesis was also detected in the MRI of the patient. Additionally, MC4R gene, which was examined in the CES panel due to obesity revealed c.821A>G p.(Asn274Ser) missense mutasyon in Exon1. The patient was started on insulin tretment 1.5 U/kg/g which was discontinued during follow-up and the final HbA1c value was 5.9%.

Results: Since obesity is common nowadays (whether it is due to a genetic cause or not), it should be kept in mind that individuals with MODY may also be obese, and it should not be directly associated with Type 2 DM. In addition, although DKA is typically seen in Type 1 DM, MODY should be considered in the differential diagnosis in the presence of atypical findings such as a history of renal disease and antibody negativity.

P2-185

DEND syndrome (Developmental delay, Epilepsy and Neonatal Diabetes) in two Pakistani Families, A Case Report

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Introduction: DEND syndrome is severe form of neonatal diabetes mellitus characterized by triad of developmental delay, epilepsy and neonatal diabetes. It is caused by mutations in the K-ATP channel encoded by KCNJ11 or SUR1 sulphonyl urea receptor 1 encoded by ABCC8 gene. Its Incidence is <1/1000,000 and until now very few cases have been reported worldwide. There is intermediate DEND syndrome (iDEND), this is less severe condition in which there is neonatal diabetes and is accompanied by muscle weakness and developmental delayed but not epilepsy. Management includes oral sulphonylureas. We report two cases from two different Pakistani Families who have similar presentation and responded well to oral sulphonylureas.

Case Report: We have two patients admitted to our ward. First patient was five and a half months old male patient presented with fever cough and breathing difficulty. He was a globally delayed child with no neck holding achieved yet. He had generalized fits since two months of age. On examination he was microcephalic and marked hypotonia. Serum and urine ketones were positive. His BSRS was high, presented with DKA in ER. HbA1C was 8.5%. The patient was started on DKA protocol, anti-epileptics started. The patient got improved and discharged on long acting insulin (Insulin detemir). He again presented with severe DKA after 20 days of discharge. This time he was extremely sick with poor pulses and perfusion, His height, weight and OFC were less than third centile. Anti Insulin and Anti GAD antibodies were sent which came out to be negative. Genetics have been sent. He was started oral sulfonyl urea drugs. His BSRs improved and he was discharged afterwards. Second patient was three and months old female patient presented with focal fits, fever and breathing difficulty for the last 5 days. On examination she was microcephalic with weight and height less than third centile. She had not achieved neck holding yet. Her BSR was high and ABGs showed severe metabolic acidosis. HbA1c was 14.5%. Anti Insulin and anti-GAD antibodies were negative. Genetics have been sent. He was also started oral Sulphonyl urea drugs.

Discussion: Any patient presented with diabetes at an early age should be considered for Monogenic Diabetes Mellitus. Genetics should be sent as soon as possible. Oral sulphonyl urea should be started if there is triad of Developmentally delayed, Epilepsy and Neonatal Diabetes Mellitus

P2-210

Idiopathic Chronic Calcific Pancreatitis (ICCP) presenting with fibro calculus pancreatic diabetes (FCPD) - a rare case in a 9-year-old Sri Lankan boy

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Introduction: Chronic pancreatitis is defined as recurrent or persistent pancreatitis, which will result in irreversible morphological change in pancreatic structure leading to pancreatic exocrine and endocrine insufficiency. ICCP is a rare condition and only few cases in adults have been reported in Sri Lanka. Prevalence of ICCP is highly variable in Asian and western countries. We present a rare case of FCPD in a 9 a years old boy.

Case Presentation: 9 years old boy presented with polyuria, polydipsia and weight loss for one month duration. His fasting blood sugar and HbA1C were 213mg/dL and 11.28% respectively. Urine-ketones were negative and C peptide was 0.36ng/mL(0.7-1.9). Pancreatic autoantibodies were not done.

During follow up he developed burning type abdominal pain radiating to back which was worsening with meals. On examination weight was 30kg(25-50thCentile) and height was 99cm(25-50thCentile). He was in pre puberty. His FBC, blood-picture, calcium, liver functions, proteins and CRP were normal. USS followed by Contrast enhanced CT abdomen showed chronic calcific atrophic pancreatitis. He history of trauma, family history of pancreatitis, features of cystic fibrosis or autoimmunity. ESR,P-ANCA and C-ANCA were normal. Although he had endocrine deficiency there was no exocrine pancreatic deficiencies.

Discussion: There are several etiological factors for adult chronic pancreatitis. However, the causes remain trickier in children. ICCP is an infrequent entity with pancreatic stone formation with pancreatic endocrine and exocrine deficiency. Diabetes in chronic pancreatitis is classified as FCPD. Usual presentation is chronic abdominal pain followed by non ketotic hyperglycaemia in the 2nd/3rd decade of life. Unusually, our patient presented with diabetes and later diagnosed with ICCP.

Conclusion: Diabetes in childhood is commonly polygenic immune mediated Type1. However greater degree of suspicious is needed to identify rare occurrence of FCPD which is important in patient follow up and management. USS abdomen is an important investigation to be done in suspected patients.

P2-211

A rare association between congenital hyperinsulinism and congenital isolated ACTH deficiency

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Hyperinsulinemic hypoglycemia (HH) is common in newborns. If hypoglycemia occurs after the first 48 hours following birth, it may be a sign of an underlying condition.

We present the case of a baby girl born at 38 weeks of pregnancy, with good adaptation to extrauterine life and blood glucose of 60 mg/dl in the first days of birth. Approximately 2 days after discharge, she was addressed at the emergency unit because of food refusal for approximately 30 hours, with a blood sugar level of 17 mg/dl, presenting a hypoglycemic convulsive crisis.

Despite the administration of 10% glucose, hypoglycemia is maintained, requiring a switch to 12,5% glucose. C-peptide and insulin were dosed at a blood glucose value of 41 mg/dl, the results showing normal levels, 15,28 UI/ml for C-peptide and 2,2 ng/ml for insulin, abnormally associated with the hypoglycemic status. Low serum cortisol levels were registered with undetectable ACTH.

Thus, it is raised the suspicion of congenital hyperinsulinism and pituitary insufficiency on the corticotropic line, GH having a normal value with a TSH slightly increased. A Medtronic Guardian Connect 4 continuous glucose monitoring system was cutaneously attached, showing hypoglycemia in 15% of the time with more than 4% severe hypoglycemia. Treatment with diazoxide and hydrocortisone was initiated.

Abdominal MRI was performed, describing normal pancreatic and duodenal features without any identified tumor. Craniocerebral CT revealed ischemic areas at the occipital and posterior parietal levels, hypocapturing nodule of 3/3 mm in the anteroinferior segment of the pituitary gland. The INVITAE genetic test identified the presence of the ABCC8 gene – autosomal recessive, confirming the diagnosis of focal hyperinsulinism. Her father was also tested with a positive result for gene ABCC8 as a carrier.

At the maximum dose of diazoxide associated with hydrochlorothiazide, the patient maintains hypoglycemia. Thus, we decided to change the therapy with Sandostatin with a progressive increase of the dose up to 30 g 4 times a day. A reduced number of hypoglycemic episodes was registered.

In Romania, PET CT/MRI cannot be performed, as it is necessary to contact a center abroad in order to obtain a complete diagnosis which might suggest surgical intervention. Currently, the patient is undergoing treatment with Sandostatin 30 microg 4 times a day for hyperinsulinism, Hydrocortisone 3.5 mg a day in 3 doses for pituitary insufficiency on the corticotropic line and phenobarbital 30 mg a day for seizure prophylaxis.

P2-235

Frequency of autoimmune diseases in childhood type 1 diabetes

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Introduction: Type 1 diabetes is frequently associated with other autoimmune diseases which can sometimes be integrated into autoimmune polyendocrinopathy.

The objective of this study is to describe the frequency of autoimmune diseases in children with type 1 diabetes.

Patients and Methods: A retrospective and descriptive study, involving 102 patients (54 males, 48 females) with type 1 diabetes followed in our department. All our patients had undergone a systematic search for autoimmune diseases according to the ISPAD guidelines.

Hypothyroidism is screened for by measuring TSH and anti-thyroid peroxidase (anti-TPO) at the time of diabetes diagnosis and every two years thereafter in asymptomatic patients.

Celiac disease is screened for by measuring anti-transglutaminase antibodies and by performing a duodenal biopsy at the time of diagnosis of diabetes, then 2 and 5 years later.

Results and Discussion: The average age of our patients was 07 ± 2.9 years. Autoimmune diseases were found in 12 patients including 4 boys (33%) and 8 girls (67%). Hypothyroidism was the most common, found in 08 patients (8%). Celiac disease was found in 04 patients (4%).

Autoimmune diseases preceded type 1 diabetes in 03 patients, and occurred within the first year after diabetes diagnosis in 6 patients.

Conclusion:

The frequency of autoimmune diseases in type 1 diabetics encourages highlights the need for their screening. Early diagnosis will allow for early management of these disorders thus avoiding further complications.

P2-237

Genetic evidence for a causal relationship between severe hyperlipidemia and Type 1 Diabetes

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Background: In type 1 diabetes (T1D), the pancreatic βcells are selectively destroyed by the immune system resulting in absolute insulin deficiency. It has been long established that approximately half of the genetic risk for T1D is conferred by genetic loci associated with β-cell function, apoptosis, and regeneration.

Aim: We report the case of a 6- year-old boy with new onset type T1D, and identified genetic loci predisposing to T1D and hyperlipidemia. With informed consent from the parents, DNA was isolated from the patient’s peripheral blood leukocyte, and TWIST Standard Germline Exome assay were performed. Causative variants were confirmed by Sanger sequencing.

Case Presentation: The boy was admitted with severe diabetic ketoacidosis (DKA), and significant combined hyperlipidemia. He is the first child of the family, born after an otherwise full-term uneventful pregnancy. Family history was negative for cardiovascular disease and/or hyperlipidemia. The father was affected by Hashimoto thyroiditis. On examination his height and weight were above the normal range (122 cm; 97th percentile, and 19 kg; 75th percentile, respectively). There were noclinical findings associated with hyperlipidemia, e.g. hepatosplenomegaly, xanthelasma, and eruptive xanthoma.Initial laboratory findings were venous blood gas (pH 7.33, pCO2 25.1mmHg, pO2 59.5mmHg, HCO3- 13.6mM/L, SaO2 98.0%), glucose 156mg/dL, hemoglobin A1c 14.3%, C-peptide 0.112ng/mL, total cholesterol 764mg/dL, total triglycerides 5950mg/dL, low density lipoprotein cholesterol (LDL) could not be measured, high density lipoprotein cholesterol (HDL) 8 mg/dL,serum lipase 20U/L. Anti-glutamic acid decarboxylase (GAD), and anti-islet antibody-2 (IA-2) antibody were positive. Although DKA resolved within 24 hours, hyperlipidemia, and hypertriglyceridemia declined in a slower rate.

Patient’s genetic analysis revealed homozygosity for the APOL4c.332_333del:p.E111fs mutation (novel) and heterozygosity for the LIPA c.546G>A:p.Q182Q mutation, both genes responsible for dyslipidemia. Additionally, he is homozygous for KLF14 c.117T>A:p.A39A, c.172C>T:p.P58S, c.140C>A:p.P47Q,FDFT1 c.199_204del:p.67_68del, MAFA c.618_620del:p.206_207del, NEUROD1 c.133A>G:p.T45A, c.596T>C:p.F199S, and GLIS3 c.902C>A:p.P301Q, c.805T>C:p.S269P. and heterozygous for the C8B c.1282C>T:p.R428X, HBD c.82G>T:p.A28S and LIPA c.546G>A:p.Q182Q, all related with β-cells dysfunction and/ or apoptosis (with a MAF<0.01).

Conclusions: In many case reports, severe quantitative hyperilipidemia is observed during DKA associated with newly diagnosed T1D or attributed to poor diabetes control with severe insulin deficiency. Diabetic hyperlipemia can be caused not only by profound insulin deficiency but also due to genetic predisposition. We suggest that its pathogenesis can be exacerbated by a coexisting genetic predisposition to hyperlipidemia.

P2-238

CGK Gene nucleotide variant of uncertain clinical significance (Exon 4/10. c397G>A. p.Asp133Asn) in a pediatric patient with hyperglycemia, elevated HgA1c and negative anti-islet cell antibodies

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Maturity onset diabetes of the young (MODY) is a group of inherited disorders with a varying degree of severity, caused by variants in one of several genes (most common genes are: HNF1A, CGK, HNF4A,HNF1B), The majority of cases have impaired insulin secretion. Patients tend to present with hyperglycemia prior to age 25 years, but can present later in life. There is usually family history of diabetes. MODY accounts for 1-3% of all cases of diabetes.

The GCK gene has been associated with the following phenotypes: MODY type 2 (AD), permanent neonatal diabetes mellitus 1 (AR), familial hyper-insulinemic hypoglycemia 3 (AD), late onset noninsulin-dependent diabetes mellitus (AD).

We present the case of a thin pediatric patient with hyperglycemia, elevated HgA1c in the pre-diabetes range, with negative antibodies and family history of diabetes mellitus. She was found to have a CGK Gene nucleotide variant of uncertain clinical significance (Exon 4/10. c397G>A. p.Asp133Asn). C.394G>A has been reported in the literature in individuals affected with diabetes.

Although this variant can not be definitively associated with the patient’s phenotype, we postulate that most likely this is the cause for her hyperglycemia and elevated HgA1c, given her negative antibodies and family history of diabetes mellitus.

Broome DT, Pantalone KM, Kashyap SR, Philipson LH. Approach to the Patient with MODY-Monogenic Diabetes. J Clin Endocrinol Metab. 2021 Jan 1;106(1):237-250.

Tinto et al. Glucokinase gene mutations: structural and genotype-phenotype analyses in MODY children from South Italy. PLoS One. 2008 Apr 2;3(4):e1870.

Bansal V et al. Spectrum of mutations in monogenic diabetes genes identified from high-throughput DNA sequencing of 6888 individuals. BMC Med. 2017 Dec 6;15(1):213.

Tinto N et alGlucokinase gene mutations: structural and genotype-phenotype analyses in MODY children from South Italy. PLoS One. 2008 Apr 2;3(4):e1870.

P2-240

Fulminant Type 1 Diabetes Case With Positive Diabetes-Associated Antibodies

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Introduction: Fulminant type 1 diabetes (FT1D) occurs because of a sudden and almost total destruction of pancreatic β-cells, triggered by a viral infection. FT1DM may cause diabetic ketoacidosis (DKA) and even sudden death. Thus prompt diagnosis is vital.

Case Report: Antibiotic treatment was started for a 4-year-old female patient because of a fever and cough. On the second day of treatment, she was admitted with rapid breathing. Although she was given inhaler treatment, her clinical course worsened and admitted to the emergency. She was dehydrated and tachycardic and intercostal retractions were present, with hyperemic tonsils. She had a one-week history of polyuria and polydipsia. Laboratory test results are shown in Table 1. With the diagnosis of severe DKA, the patient was started on fluid and insulin therapy. After biochemical and clinical improvement was observed, subcutaneous insulin was started. FT1D was diagnosed, given the clinical course and laboratory results.

Conclusion: Early diagnosis of children with FT1D is vital to reduce the risk of sudden death and other complications. In children presenting to the hospital with flu-like symptoms, a detailed anamnesis should be taken and symptoms of hyperglycemia (polydipsia, polyuria) should be questioned. Detection of glucosuria and ketonuria on urinalysis will guide the diagnosis. Short-term symptoms, low c-peptide levels, and glycated hemoglobin below 8.7% should suggest the possibility of FT1D. Larger pediatric studies of FT1D are required to identify optimal diagnosis and management in the pediatric age group.

Table 1. Laboratory test results of the patient at presentation.

Capillary blood glucose	**445 mg/dL**
Blood ketone	5.6 mmol/L
BLOOD GAS	
pH	6.98
pCO2	9 mmHg
Lactate	15 mg/dL
Bicarbonate	5.5 mmol/L
Base Deficit	-29.8 mmol/L
HEMOGRAM	
White Cell Count	26.140
Hemoglobin	12.6 g/dL
Platelet Count	552.000
URINE EXAMINATION	
pH	6.0
density	1026
glucose	+++
ketone	+++
Protein	-
Nitrite	-
BIOCHEMISTRY	
Blood glucose	443 mg/dL
Urea	32.8 mg/dL
creatinine	0.58 mg/dL
aspartate aminotransferase	11.2 U/L
alanine aminotransferase	10.1 U/L
Sodium	129 mmol/L
corrected sodium	134.5 mmol/L
Potassium	4.67 mmol/L
Chlorine	102 mmol/L
Calcium	9.03 mg/dL
Phosphorus	4.03 mg/dL
Uric acid	10.6 mg/dL
Serum osmolarity	297 mOsm/kg (275-295)
Islet Cell Antibody	Positive
Anti GAD	306.95 IU/ml (positive)
Anti Insulin Antibody	19.2 U/ml (positive)
Hemoglobin A1C	7.1%
Fasting Blood Sugar	443 mg/dl
C-peptide	0.47 ng/ml
Insulin	55.4 mU/L

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Fat, metabolism and obesity

P2-31

Can Gender differently affect Growth and Metabolic Syndrome (MetS) Criteria in children with Classic Congenital Adrenal Hyperplasia (CAH)?

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We compared gender effect on growth and metabolic control with CAH. Morbidities associated with CAH, including risks of obesity, hypertension, dysglycemia, and dyslipidemia were investigated.

Methods: Data from 30 children with CAH were analyzed retrospectively. They received hydrocortisone (n = 11) or prednisolone (n= 19) and fludrocortisone (0.1: 0.15 mg OD) since early infancy. The mean hydrocortisone dose = 22.5 +/- 7 mg/m2. The growth data was recorded and the different metabolic criteria including fasting glucose, LDL, HDL, triglyceride, and cholesterol, were measured. Growth and metabolic data were compared between males and females.

Results: Comparison between the growth and metabolic data of males (n =11) and females (n – 19) with CAH (table) showed that the dose of steroid to achieve control did not differ among the two groups. Females had slightly higher BMI compared to males. 5 /11 males were overweight and 1/11 obese, while 5/19 females were overweight and 7/19 were obese. Blood pressure (especially diastolic BP) was higher in females versus males. One girl has both systolic and diastolic high BP. Height SDS did not differ between the 2 genders. 2/11 boys and 4/19 girls had HtSDS < -2. The components of the lipogram, fasting glucose, fasting insulin, and HOMA-IR did not differ among the two groups. High cholesterol was detected in 2/11 boys and 3/19 girls. High triglycerides were detected in 1/11 boys and 4/19 girls

Conclusion: Female children with classic CAH on CS treatment for > 5 years had a high rate of obesity and slightly higher BP compared to males. Some of them have high cholesterol and triglycerides. These patients shall be monitored closely for abnormal growth as well as for abnormal metabolic criteria.

Table 1. Anthropometric and biochemical data of children with CAH: males versus females

Males n =11	**Age yr**	**HC mg/m^2**	**SBP**	**DBP**	**HtSDS**	**BMI**
Mean	6.10	9.38	95.55	59.09	-0.37	17.64
SD	2.89	5.23	8.40	3.85	1.43	3.00
Females n=19						
Mean	7.01	7.07	99.32	64.37	-0.70	19.47
SD	2.62	4.51	8.60	5.19	1.55	5.22
p-value	0.3386	0.2128	0.286	0.0096*	0.557	0.28

Males n =11	**17OHP**	**Cholesterol**	**TG**	**HDL**	**LDL**	**F insulin**	**FBG**	**HOMA-IR**
Mean	2.64	157.27	69.64	54.64	86.64	5.39	71.27	0.96
SD	3.82	24.19	21.96	5.94	23.58	1.81	8.60	0.36
Females n=19								
Mean	3.01	157.42	74.58	54.74	86.26	7.10	75.37	1.26
SD	2.45	31.04	26.83	11.16	27.22	6.42	10.73	0.87
p-value	0.73	1.00	0.604	1.00	1.00	0.385	0.303	0.257

P2-32

The prevalence and risk factors of non-alcoholic fatty liver disease in obese and normal weight children in Latvia

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Background: Public health research shows that the prevalence of obesity is increasing rapidly not only among adults, but especially among adolescents and children. Obese children and adolescents are at risk of early chronic complications such as cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), type 2 diabetes mellitus, various types of tumors, orthopedic problems, serious psychological and neurological problems.

Aim: To investigate the prevalence and risk factors of NAFLD in obese and normal weight children.

Materials and Methods: 198 study children were divided into 3 groups according to weight and age: group I – children ≥ 10 years old with obesity, group II – children < 10 years old with obesity, control group – normal weight children. In the study, ALT and blood lipid levels were determined, abdominal ultrasonography was performed and the paediatric NAFLD fibrosis index (PNFI) was calculated. All study data were analyzed using RStudio V.1.4.1103. Differences were considered statistically significant if the significance level was $p < 0.05$.

Results: ALT level above 24 U/l was observed in almost half, 44.9 % of children in group I, 26.3 % of children in group II, but not found in control group. 34.2 % of children in group I had signs of NAFLD on ultrasound, 12.5% of children in group II and no signs in control group. Analysis of PNFI showed that predicted liver fibrosis was found in 72.9% of children in group I, 76.7% of children in group II and not found in control group. The median PNFI score in groups I and II was 9.7 (IQR 8.9; 9.9) and 9.7 (IQR 9.2; 9.9), respectively, but only 0.4 (IQR 0.2; 0.7) in the control group ($p < 0.001$). There were statistically significantly gender differences: boys had the highest median PNFI value in group I – 9.9 (IQR 9.3; 10.0) compared to girls – 9.5 (IQR 8.4; 9.9) ($p = 0.002$).

Conclusions: Our study shows that elevated ALT level and ultrasound changes are more common in obese children compared to normal weight children. The PNFI index was significantly higher in group I boys compared to girls.

P2-33

Obesity-related Hypothyroidism in Children

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Keywords: obesity, subclinical hypothyroidism, children

Introduction: There is a growing interest in the relationship between obesity and thyroid dysfunction, even more so nowadays when obesity has become a widespread global issue. Initially believed to be the cause of obesity, the risk of developing hypothyroidism may be increased in obese children due to adaptive mechanisms.

The study aims to evaluate the prevalence of hypothyroidism in obese children.

Materials and Methods: A retrospective observational study was conducted over a period of three years and included 183 children diagnosed with obesity who were admitted to the endocrinology department of the "Louis Ţurcanu" Children's Clinical and Emergency Hospital in Timişoara, Romania. Obesity was defined using age-specific Body Mass Index (BMI) reference guidelines from the 2000 Centers for Disease Control and Prevention Child Growth Charts. Subclinical hypothyroidism was defined as TSH values above 3.59 μU/mL, according to the normal reference ranges provided by the hospital's clinical laboratory, with normal T4 levels. The Excel 2019 Analysis Tool Pak was used for data analysis.

Results: Patients included in the study had a mean age of 11.6 years and a BMI mean of 30.86 kg/m^2; the male to female ratio was 1.2:1. The prevalence of subclinical hypothyroidism was 14.2% (26 patients), and four of these patients (15.4%) also had elevated anti-thyroid antibodies. The mean TSH level was 4.63 μU/mL among children with hypothyroidism and 2.04 μU/mL in children with normal thyroid function. Structural changes of the thyroid were detected by ultrasound in five patients (19.2%).

Conclusion: Evaluating thyroid function in obese children can help identify the presence of underlying subclinical hypothyroidism. As weight loss can lead to the normalization of TSH levels in some individuals with obesity-related hypothyroidism, future prospective studies are needed to monitor these patients. However, it is important to note that weight loss may not be effective in all cases of hypothyroidism, and that medication may still be necessary to manage the condition.

P2-34

Case Report: Massive Obesity secondary to a Homozygous MC4R mutation in a 3-year-old Boy

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We present a 3-year-old boy with massive obesity and hyperphagia. His appetite symptoms were evident from age 3 months, and his parents report he has an insatiable appetite, and seeks food constantly. At presentation to our clinic, his BMI was 37.21 Kg/m^2 [+ 6.87 SDS]. Sleep apnoea is suspected, for which he is undergoing evaluation. Parents are second cousins. Both parents are moderately obese, but his siblings are normal weight for age. The mother did not have a history of gestational diabetes mellitus. Paternal and maternal grandmother have type 2 diabetes mellitus.

In view of his early-onset obesity, monogenic obesity was suspected. His monogenic obesity panel revealed a previously unreported homozygous MC4R c.419T>C (p.Leu140Pro) variant of uncertain significance. It is known that he majority of disease-associated mutations in transmembrane protein-coding genes result in leucine to proline (as in our case) and glycine to arginine substitutions. Our patient's variant is not found in the Gnomad or GME population databases and given his phenotype, we consider this to be the cause of his hyperphagia and obesity. Segregation analysis for the patient's two siblings is planned.

Heterozygous loss-of-function mutations in MC4R are the most common genetic cause of monogenic obesity, occurring in approximately 2-5% of cases of severe, early-onset obesity, with an estimated population incidence of 1:500. In contrast, patients with homozygous MC4R mutations are extremely rare and their phenotype is characterised by intractable obesity with insatiable appetite, resistant to lifestyle modification or drug therapy. Even bariatric surgery is only transiently beneficial. However, we note the successful use of liraglutide in an adult with a homozygous MC4R mutation, and this may be worthy of consideration. [1]

Liraglutide, an analogue of the enteric hormone, Glucagon-Like Peptide-1 (GLP1 is known to inhibit appetite, directly through effects on anorexigenic proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) neurons. However, this would be nullified in the case of MC4R homozygotes. However, inhibition of hypothalamic orexigenic agouti-related peptide (AgRP)/neuropeptide Y (NPY) neurons could be the mechanism in the reported case. [1]

In summary, we present a 3-year-old boy with massive obesity secondary to a homozygous MC4R mutation and the challenging situation this presents.

Reference

[1] Iepsen EW, Have CT, Veedfald S, et al. GLP-1 Receptor Agonist Treatment in Morbid Obesity and Type 2 Diabetes Due to Pathogenic Homozygous Melanocortin-4 Receptor Mutation: A Case Report. Cell Rep Med. 2020 Apr 21;1(1):100006. doi: 10.1016/j.xcrm.2020.100006.

P2-67

The outcome of management for childhood obesity during COVID19 pandemic (2019-2021) in Qatar

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Introduction: Obesity is serious health concern that affect the children during pandemic due to school closing and shifting to online teaching with suspension of almost all physical activity. In addition, many overweight and obese children had irregular meal timing, frequent snacking, and increased screen time at home.

Objectives: To study the effect of COVID 19 on weight gain during the lock- down and shifting to online study.

Methods: In a randomly selected sample of 40 healthy obese prepubertal children (age = 8.4 +/- 2.4 years). Their weight for age SDS (WAZ), height SDS (HAZ) and BMIZ were conducted at regular interval for 2 years. They were followed in the dietitian's clinic and given the necessary nutrition advice either in the clinic or over phone every 3 months for this period.

Results: Forty obese children followed for two years during COVID 19 epidemic. According to the International Diabetes Federation (IDF) Metabolic syndrome criteria: 8/40 had fasting blood glucose > 5.6 mmol/L, 4/40 had high triglyceride level > 1.7 mmol/L, 11/40 had HDL <1.16 mmol/L and 7/40 had high blood pressure (> 120/80 mmHg). 5/40 had raised ALT, 7/40 had HbA1C = or > 5.8%, and 10/40 had hepatic fatty change detected by ultrasound.

Their mean weight gain/day increased significantly from 16.9 g/day at the first visit to 27.7 gm/day after 2 years of follow up. These rates were more than double than expected normal weight velocity (average 10gm/day). On the other hand, BMIZ mean had decreased due to faster increase in their HAZ compared to WAZ. BMI decreased in 20/40 obese children, remained same in 8/40 and increased in 12/40 during the 2 years of follow up.

	WAZ	HAZ	BMIZ
Mean 2019	2.62	1.2	2.49
SD	0.79	1.1	0.61
Mean 2020	2.51	1.02	2.36
SD	0.8	1.03	0.54
Mean 2021	2.52	1.14	2.29
SD	0.81	1.08	0.57

Conclusion: We conclude that the effect of pandemic accelerated weight gain/d in our obese children but did not increase BMIZ because of their rapid linear growth.

P2-68

Gut Hormones in Malnourished infants and children: Important Role in Adaptation

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The gastrointestinal (GI) tract is the body's largest endocrine organ producing hormones that have important sensing and signaling roles in the regulation of energy homeostasis and immune mechanisms.

Objectives and Methods: We performed electronic literature systematic review using PubMed, Google Scholar, and Web of Sciences with the aim of providing an update on the changes occurring in gut hormones (Ghrelin, GLP-1 and PYY, insulin, and Zonulin) in malnourished infants and children as well as lab animals. We reviewed 20 studies (2007-2022) fitting the search criteria.

Results: Ghrelin is a multifaceted gut hormone that regulates glucose hemostasis. One study reported hyper-ghrelinemia in undernourished children. The high Ghrelin stimulates GH secretion which promotes lipolysis and maintains blood glucose through stimulating hepatic gluconeogenesis.

GLP-1 is secreted in the small intestine in response to nutrients. It promotes glucose-dependent insulin secretion and decelerates gastric emptying. Intraluminal nutrients, particularly fats stimulate the secretion of PYY by enteroendocrine cells. Levels of GLP-1 and PYY were found to be considerably higher in undernourished infants compared to normal infants. The significant increase of these GI hormones during malnutrition help to delay gastric emptying and give a longer time for nutrient absorption.

Many undernourished children suffer from subclinical enteropathy (EED) characterized by mucosal inflammation and villus blunting mediated by T cell activation. Zonulin is a hormone secreted mainly from the liver and enterocytes. It is a master modulator of the intercellular tight junctions (TJ) and is a key player in the regulation of the mucosal immune response. Serum zonulin levels are correlated with stunted growth in EED patients. Vitamin D deficiency, a common association in undernourished children, could lead to a significant upregulation in mRNA expression of the intestinal zonulin that increases the serum level of zonulin.

In a meta-analysis review of 16 studies severely undernourished children had a high prevalence of hypoglycemia. Impaired insulin responses to oral glucose and to a meal occur in both kwashiorkor and marasmus, with low glucose clearance. A low insulin state decreases tissue and fat anabolism and permits the catabolic activity of other hormones to ensure energy supply for vital organs. Insulin is important in shaping the immune response during infection, therefore, low insulin status in severely undernourished children may adversely affect their immune response during an infection.

Conclusion: Changes in gut hormones play an important role in the adaptation process during malnutrition however these changes may adversely affect local and systemic immune mechanisms.

P2-69

A Young Woman with Morbid Early Onset Obesity, Progressive Hypothalamic-Pituitary Dysfunction, Bilateral Optic Nerve Atrophy, and a Combination of Variations in Four Genes Involved in Hypothalamic Satiety Signaling Pathways

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Background: Leptin receptor (LepR) deficiency is an autosomal-recessive rare condition causing early-onset severe obesity, hyperphagia, hypogonadotropic hypogonadism (HH), hypothyroidism, and/or growth hormone deficiency (GHD). Cohen syndrome is a variable autosomal recessive genetic disease caused by mutations in the VPS13B gene causing central obesity, characteristic facial features, hypotonia, non-progressive intellectual deficit, neutropenia, myopia retinal dystrophy and optic nerve atrophy,

Case Description: A 15-year-old female with morbid obesity, type 2 diabetes mellitus, obstructive sleep apnea and hypogonadotropic hypogonadism. She did not have facial features typical of a syndrome and no developmental delay. At age 16 y she was diagnosed with ACTH dependent cortisol deficiency and growth hormone deficiency. Her working diagnosis was ROHHAD syndrome with pituitary dysfunction, however sleep study showed no hypoventilation. The pituitary gland was of normal size, location and appearance on MRI, no neuroendocrine tumors were seen. She responded to metformin but continued with rapid weight gain, within 5 years her weight increased from 118 to 154 kg, BMI from 39.6 to 53 kg/m^2. She subsequently required insulin for glucose control. She received setmelanotide for 3 months with no improvement. At 19 years of age, she presented in critical condition with COVID pneumonia, adrenal crisis, severe dehydration, hypernatremia and was diagnosed with central diabetes insipidus, which responded to DDAVP. Repeat MRI of pituitary showed a diminished bright spot. There was a new finding of bilateral optic nerve atrophy with dis-conjugate gaze. Ophthalmology evaluation is pending to evaluate pigmentary retinopathy.

Results: A genetic obesity panel identified a heterozygous mutation in the LEPR gene: p.Leu210Pro (c629T>C) (VUS) not previously described and not predicted to be pathogenic. In addition, three other VUS were found: heterozygous, not previously reported likely pathogenic mutation in VPS13B (c3082+1G>T), a heterozygous mutation VUS in ADCY3 (c2356G>A); and heterozygous, intronic variation in KIDINS220 (c1622-10_1622-9del).

Conclusion: This case is compelling because she shas some features of leptin resistance such as rapid weight gain, obesity, and late onset hypothalamic dysfunction. However posterior pituitary hormone deficiency and optic nerve atrophy have not been reported in LEPR mutations. She has neutropenia, a characteristic of Cohen syndrome; optic atrophy has been reported as well. Her VPS13B (c3082+1G>T) not previously reported however is reported to be likely pathogenic for Cohen syndrome. Both heterozygous variations in ADCY3 and KIDINS220 gene previously linked to high BMI. Further mutational analysis will need to be done to elucidate the role in hypothalamic weight-regulating pathways.

P2-70

Association of osteoprotegerin and metabolic status in obese children

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Objective: determination of changes in metabolic status and osteoprotegerin (OPG) concentrations in obese children.

Methods: We examined 220 children in the University Hospital (Minsk) from 2022 to 2023 yrs. Their anthropometric parameters (height, weight, body mass index (BMI)) were determined. Blood levels of OPG, insulin were determined.

All children were divided into 2 groups: group 1 children with morbid obesity (MO) - 160 patients (90 boys(B)/70 girls(G)) (BMI more than 99th percentile for sex and age) (BMI 34.14±2.64 kg/m^2, age 13.37±2.22 years); group 2 - 70 patients (B/G=35/35) with alimentary obesity (AO) (BMI-95-99th percentile for sex and age) (BMI 27.16±2.36 kg/m^2, age 13.13±2.17 years). The control group (C) consisted of 60 patients (B/G=30/30) with normal body weight (BMI 19.66±2.34 kg/m^2, age 13.42±2.31 years).

Results: In boys and girls with obesity higher concentrations of insulin were detected relative to the control group (AO (G 17.35

(9.92–19.30) µU/ml; B 18.17 (8.41–22.00) µU/ml) and MO (G 23.16 (12.66–28.54) µU/ml; B 25.79 (12.76–29.40) µU/ml); C (G 8.35 (5.95–11.50) µU/ml; B 9.23 (7.90-11.21) µU/ml) (G U_{AO-C}=528.0; p<0.001; U_{MO-C}=776.0; p<0.001; B U_{AO-C}=453.5; p<0.001; U_{MO-C}=691.0; p<0.001)).

Insulin resistance index level (HOMA-IR) in patients with AO (G 3.26 (1.97–3.84); B 3.69 (1.55–4.37)) and MO (G 4.54 (2.37–6.12); B 4.21 (2.54–5.36)) was higher than in the control (G 1.60 (0.99–2.18); B 1.89 (1.53–2.30)) (G U_{AO-C}=219.0; p<0.001; U_{MO-C}=354.0; p<0.001; B U_{AO-C}=1150.5; p=0.001; U_{MO-C}=592.5; p<0.001).

In boys with obesity higher concentrations of OPG were detected relative to the control group (AO 250.89±22.17 ng/ml vs 189.91±11.32 ng/ml (p=0.04), MO 222.22±21.14 ng/ml vs 189.91±11.32 ng/ml (p=0.03)).

Conclusion: Changes in metabolic status were registered in obese patients: an increase in insulin, OPG levels compared with children with normal body weight.

P2-71

The first case report of a child with progeria syndrome in Oman

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Hutchison-Gilford progeria syndrome (HGPS) is a rare genetic disorder which is characterized by aging fast in affected individuals. The prevalence of HGPS is around of 1 in 20 million approximately. The exact etiology is not very well known, However it is believed to be an autosomal dominant disorder that occurs due to point mutations in lamin A (LMNA) gene. In this case report we share the challenges of being the first presented case in Oman.

A 6 years old Omani boy diagnosed with Hutchinson-Gilford progeria syndrome presented with aged looking skin. Early in Infancy, the child presented with failure to thrive, Upon examining the case it was found that there is distinctive dysmorphic features of small chin, peaked nose, prominent blood vessels and protruded ears, there was atrophic-sclerodermoid skin changes on lower back and abdomen. The patient was evaluated by multidisciplinary team for the various problems. ECG and Echo were done and all normal. A biopsy showed sclerodermoid skin changes. Hearing and eye assessment also done and were normal. However The genetic test showed mutation in the LMNAgene.

Pt was referred for dietician for failure of thrive and diet modifications because he is prone for early onset atherosclerosis. He was started on Lonafarnib as it is the current available treatment via clinical trial, and currently it is FDA approved.

Families with patients with progeria usually they have a lot of challenges. In our case the we help the parent to overcome the obstacles they have met. One example that parent were counselled about the possibility of contractures and the importance of doing exercises at home. Swimming is a good option, we advised for Swimming suit as the patient has no subcutaneous fat. Usually the average life span for patient with progeria is 14.6 years. Genetic testing by (PCR) with western blot protein analysis can confirm the diagnosis. Multidiscipline workup, including ECG, echocardiogram, carotid duplex scanning, hip X-rays and bone densitometry scans should be done annually. Dietary control and sometimes medical treatment in the form of low dose aspirin is recommended as prophylaxis to prevent atherosclerotic changes. Till now, no cure has been found for this catastrophic disorder however Lonafarnib is recently approved by FDA as the as the first treatment of progeria

In conclusion, Still There are multiple efforts and researches are ongoing to delay the process of ageing.

P2-112

Evaluation of Triglycerides to High Density Lipoprotein Cholesterol Ratio (TG/HDL-C) as a Predictor of Insulin Resistance among Obese Children and Adolescents, single center experience

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Keywords: Insulin resistance, triglycerides to high-density lipoprotein cholesterol-(HDL-C), HOMA-IR.

Background: Childhood Obesity is a chronic metabolic disease. The fundamental disorder related to obesity is Insulin Resistance (IR). The gold standard method to measure IR is by use the hyper insulinemic euglycemic clamp, rarely performed in children because of its invasiveness, complexity, time consumption and high costs. Practically, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) is generally used in adults and approved for children and adolescents. On the other hand, triglycerides (TG) to high-density lipoprotein cholesterol-(HDL-C) ratio is done as routine test, part of lipid profile. It is of lower cost compared to HOMA-IR especially in limited resource settings.

Objective: To evaluate TG/HDL-C ratio as an alternative tool used as an IR marker in overweight and obese children.

Patients and Methods: This was a cross-sectional study conducted on 75 children and adolescents with overweight and obesity attending Diabetes, Endocrine and Metabolism Pediatric unit (DEMPU), children Hospital. All subjects were subjected to full history, clinical examination and laboratory investigations including complete lipid profile, TG/HDL-C ratio, HOMA-IR, oral glucose tolerance test. Study group was classified into two subgroups according to the level of TG/HDL-C ratio, comparing their demographic and laboratory data.

Results: Thirty-one (42.3%) males, 44(58.7%) females with mean age 9.55±2.32 years. Sixty-eight percent (90.7%) of the study group were overweight with mean weight (61.33± 20.32 kg). Seventy-four (98.7%) had a high BMI with mean (24.54±3.57). Sixty-five (86.7%) had a high level of HOMA-IR. By comparing clinical and laboratory data of participants with normal and high TG/HDL ratio. It was shown that those with high TG/HDL ratio had higher weight, BMI, waist circumference with p values < 0. 001. The mean values of TC, LDL, TG, LDL/HDL ratio and HOMA-IR were higher among those with high TG/HDL ratio compared to those with normal ratio with statistically significant difference with p values (0.017, 0.014, < 0.001, 0.015, < 0.001 respectively). There was a significant positive correlation between TG/HDL ratio and HOMA-IR with p value < 0.001. By multivariate logistic regression analysis, acanthosis nigricans, and high TG/HDL ratio act as independent predictors of IR. TG/HDL ratio ≥2.5 had 75.4%sensitivity, 90% specificity.

Conclusion: TG/HDL ratio was an easy, non-invasive, and useful indicator of insulin resistance as there was a significant positive correlation between it and HOMA_IR.

P2-132

Body composition changes during interventions to treat obesity in children

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Introduction: Nutrition, bodily activity, and behavior-modifying practices are recognized interventions in managing obesity.

Our aim was to review available information on the short-term effects of intervention (3-4 months) on body composition of overweight and obese children and adolescents.

Methods: We reviewed the anthropometric data (Weight, height (HtSD), and BMI of 16 obese children aged 12 +/- 2.2 years. Body composition was done for those children using InBody 770 body composition analyzer. Detailed counseling about healthy food and my plate plan, and recommended daily exercise were given and followed up monthly. InBody 770 Body Composition was used to measure fat mass, muscle mass, and body water. The InBody analysis was done at the first visit to the pediatric dietetic clinic and repeated after 3-6 months. Data collected include total water, skeletal muscular mass (SMM), body fat mass (BFM), percentage of body fat (PBF), body fat mass (BFM), percent body fat (PBF), Fat/muscle ratio (F/M mass), waist-to-hip ratio (WHR), and fitness score.

Results: After 14.5 weeks of intervention, we noticed a significant increase in SMM by a mean of 1.2kg associated with an increase in height by 2cm, a mild decrease in PBF, and decreased F/M mass. Fitness scores increased significantly after the intervention. No change was detected in body weight BMI, BFM, or waist-to-hip ratio. The basal metabolic rate increased significantly from 1212 +/- 210 to 1266 +/- 222 Kcal/d.

Conclusion: In conclusion, we found a significant increase in SMM and a decrease in F/M mass with increased fitness scores after detailed counseling and close follow-up of children with obesity. Increasing lean muscle mass was associated with an increase in BMR even without a change in BMI or body weight. A regimen of reasonable dieting with increased exercise, can maintain or increase BMR and promote an increase in SMM in obese children.

	WT	HT	HTSD	BMI	SMM	BFM	PBF	F/M mass	WHR	Fitness Score
Before Interv	72.1	152	0.77	30.3	20.99	33.14	44.9	1.57	0.94	57.69
	21.1	13.3	0.73	5.49	5.72	12.76	6.86	0.39	0.10	8.01
After Inertv	72.1	154	0.80	30	22.28	32.91	43.6	1.47	0.94	59.86
	22.3	12.8	0.70	5.63	5.89	12.49	6.50	0.36	0.10	7.03
P value	0.5	0.00*	0.21	0.08	0.00*	0.37	0.04*	0.02*	0.50	0.00*

* = p< 0.05

P2-133

Integrated care for childhood obesity within the medical and municipal domain

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Childhood obesity is a chronic disease with detrimental effects on health and wellbeing. Treatment was traditionally focused on reducing caloric intake and increasing energy expenditure. However, considering the global increase in prevalence in obesity, especially in the paediatric age range, this approach is insufficient and transition to new initiatives is needed.

Obesity is a complex disease resulting from the interaction of multiple underlying factors, including personal characteristics (e.g. genetic, physiological and psychological) and environmental factors (e.g. socio-economic, cultural and physical environments) that can influence lifestyle behaviour and lead to the development or maintenance of childhood obesity. Adequate management of childhood obesity calls for taking into account biomedical factors, psychological factors and social factors at various levels.

In the approach towards overweight and obesity, focus should be on prevention aimed at a healthy living environment for children in general as well as on support and care for children that already developed overweight or obesity, which can be defined by a collaboration of different organizations and professionals from the healthcare domain and social domain in a network.

In the Netherlands, the transition in obesity care has started in 2009 and recently became the official national model of treatment to be implemented. The development of the national model was formed out of a collaboration with eight selected Dutch municipalities including input from local stakeholders (health insurers, healthcare organisations and partners from the social domain). The national model describes a structure for local integrated care that should facilitate support and care for children with obesity and their families. Learning communities were set up to exchange knowledge, experiences and tools between the participating municipalities. The accompanying materials are distributed into materials for policymakers to support local realization of the integrated care and materials for healthcare professionals. It is of importance to share our experiences with the international community so that they can make their own adjustments to achieve a national dynamic learning model. In this way, addressing obesity can sustainably improve the support and care and thus the health and quality of life of our patients.

P2-134

Short-term data of the newly opened pediatric obesity center in Ankara

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Childhood obesity has emerged as an important public health problem in the worldwide. It is important to follow these cases in multidisciplinary centers at an early age in order to prevent metabolic and psychosocial comorbidities that may develop. Bariatric surgery is a treatment method whose frequency is increasing in adolescent obesity. In the study, the 6-month results of the patients who applied to the obesity center were shared.

Materials-Methods: Cases between the ages of 9-18 and with a body mass index greater than 35 kg/m^2 who were referred to the obesity center from the pediatric endocrine polyclinics were included in the study. Cases who used drugs that could cause obesity, had endocrine disease, syndromic obese or monogenic obese were excluded from the study. The physical examination, metabolic data, radiological, cardiac and psychiatric evaluation results of the patients were analyzed.

Results: 62 patients referred to the pediatric obesity center between September 2022 and April 2023 were evaluated. 39 of the cases were girls (66.2%), 23 were boys (37.1%), mean age was 14.5, and mean body mass index was 38.6 kg/m^2. Impaired fasting glucose was detected in 2 cases and impaired glucose tolerance in 4 cases (6.45%). Antihypertensive treatment was started in 11 cases (17.7%) due to hypertension. Hepatosteatosis was present in 50 patients (80.6%). In 42% of these cases, stage 1, 36% stage 2, and 22% stage 3 hepatosteatosis. 9 patients (14.5%) had obstructive sleep apnea symptoms and polysomnography was planned. Child psychiatry detected psychiatric disorders in 17 patients. Bariatric surgery was performed in 2 patients. Bariatric surgery was planned for 2 patients. One of the patients who underwent bariatric surgery does not continue to follow up. The other case lost 32.5 kg at the end of the 6th month, and her body mass index decreased from 53.6 to 41.5.

Conclusion: Adolescent obesity is an important risk factor for cardiovascular diseases, orthopedic diseases and psychiatric disorders. Bariatric surgery can be applied in selected cases who do not benefit from lifestyle changes and medical treatments. Increasing awareness of bariatric surgery in adolescence will increase the access of morbidly obese cases to these centers in the early period.

P2-135

The influence of Vitamin D on the physical fitness of obese children

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Introduction: Obesity and vitamin D deficiency are global public health problems. There is evidence of a reciprocal link between vitamin D deficiency and obesity. Both conditions are risk factors for the development of chronic diseases, primarily insulin resistance and diabetes mellitus type 2, and contribute to a decrease in physical fitness (PF). The aim of this study was to determine the effectiveness of vitamin D supplementation on PF of obese children during puberty.

Participants and Methods: This one-year prospective study involved 47 obese children (BMI > 95th centile) of pubertal age, with vitamin D deficiency (25 (OH) D < 30 ng / dL), treated for 6 months with a multidisciplinary approach, and for the next 6 months vitamin D was also introduced. The physical fitness index (PFI) was assessed at the first visit and every 6 months using a modified Harvard step test.

Results: A correlation between obesity and vitamin D deficiency has been proven (correlation - 0.50; p<0.001); children who had a higher BMI value had a lower concentration of 25 (OH) D, and vice versa. Multidisciplinary treatment achieved a statistically significant increase (p<0.01) in the mean concentration of 25 (OH) D from 21.13 ng/mL to 22.98 ng/mL. At the end of multidisciplinary treatment with the addition of vitamin D in treatment, 80.85% of subjects (p<0.001) reached a concentration of 25 (OH) D above 30 ng/mL, and the average value was 32.60 ng/mL. Children who had higher BMI values had lower PFI values (correlation - 0.74; p<0.001). Children who had a higher concentration of 25 (OH) D also had a better PFI result (correlation - 0.40; p<0.01). Multidisciplinary treatment with vitamin D supplementation significantly increased PFI (p<0.001). Most of children improved their PFI (83%), and this in favor of girls (average increase 5.43; p <0.001). However, only one child is in the low average group (PFI 55 - 64), and all the others are below average.

Conclusions: Multidisciplinary treatment with vitamin D supplementation has significantly increased PFI. This study provides evidence of the association of vitamin D with PF in obese children during puberty.

P2-177

Correlations between the degrees of obesity and dyslipidemia in a pediatric population from Romania

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Keywords: pediatric obesity, metabolic syndrome, dyslipidemia, abdominal obesity, cardiovascular risk.

Introduction: The prevalence of pediatric obesity is rising globally as well as in Romania and so are the complications of obesity. Dyslipidemia is one of the most frequent complications and is associated with cardiovascular risk even in children or teenagers. Evaluating the degree of obesity and the correlations between dyslipidemia and metabolic syndrome is important for the primary prevention of cardiovascular diseases.

Material and Method: We conducted a retrospective observational case series and case-control study between 2019-2021, with observation sheets from the Kilostop Junior Nutrition Clinic. We included 241 children and teenagers from the southern regions of Romania, with ages 3-17 (median: 11.42), 114 males (47.3%), BMI median=27.67 and median of the degree of obesity=99 %.

Results and Conclusions: We performed a Fisher's correlation and found that an obesity degree over 110% positively correlates with an abdominal circumference over the 95th centile (p=001).

A negative Pierson correlation between the pathological ratio HDL cholesterol to triglycerides of 0.5 (p=0.008) and an obesity degree of over 110%.

A low HDL value negatively associates with a high obesity degree (r=-0.319, p=0.00).

Patients with dyslipidemia wave a higher risk of hyperuricemia (OR=3,7, 95%CI=1,44-9,45, p=0.0062)

Conclusions: The obesity degree and visceral obesity negatively influence HDL and HDL to triglycerides ratio and children with dyslipidemia have a higher risk of hyperuricemia. A standardized cardiovascular risk evaluation method is needed even for young children to prevent the onset of cardiovascular diseases at young ages.

P2-207

The association between physical activity and 25-OH vitamin D levels

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In children and adolescents, vitamin D deficiency negatively affects muscle physiology,exposing them to increased muscle damage and pain, stress fractures, and tendon structures. In addition, free radicals released when the body is exposed to oxidative stress after exercise can cause DNA damage. Vitamin D plays an important role in removing these radicals. The purpose of this study is to investigate the relationship between physical activity and 25- OH vitamin D in obese children. Specifically, we examine whether 25- OH vitamin D levels differ when children are regularly physically active.The study enrolled 115 obese children with a BMI &gt; of the 95th percentile. After a detailed history, anthropometric assessment, and physical examination in 115 cases presenting to our pediatric endocrinology clinic, 25- OH vitamin D levels were assessed. We defined regular physical activity as physical activity on three or more days (i.e., 60x3=180 minutes) per week. Based on the duration of physical activity, we divided our cases into two groups: (i) children who were physically active for less than 180 minutes per week and (ii) children who were regularly physically active. We also compared the 25- OH vitamin D levels of physically active and inactive obese children. The mean weight and BMI SDS were 72.31 kg and 2.98, respectively, and the percentage of physical activity ≥ 180 minutes and less than 180 minutes per week in those who were vitamin D deficient was 16.05% and 83.95%, respectively. Among children who did not have vitamin D deficiency, 38.24% and 61.76% were physically active ≥ 180 minutes and less than 180 minutes per week, respectively. We found that the average vitamin D levels of those who exercised regularly were higher than those who exercised less than regularly (p= 0.011). While the average 25- OH vitamin D level of the physically

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inactive patients was 14.71 ng/ml, the average 25- OH vitamin D level of the physically active patients was 18.04 ng/ml. Accordingly, the vitamin D levels of the physically active patients were higher than those of the inactive patients (p = 0.036). In this study, we demonstrate that regular physical activity or even physical inactivity prevents vitamin D insufficiency in obese children. In this regard, demonstrating this mechanism could be the goal of future studies.

P2-208

THe relationship between sunlight exposure and insulin resistance

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Childhood obesity (CO) is an important risk factor for the development of many chronic metabolic diseases in adulthood. Understanding the mechanisms that promote childhood obesity and eliminating these causes in childhood are critical for later life. One of the major complications of obesity is insulin resistance. The purpose of this study is to investigate the relationship between sunlight exposure and insulin resistance in childhood. Specifically, it examines how the duration of sunlight exposure in childhood is related to insulin resistance. The study involved 115 obese children with a BMI > of the 95th percentile. After a detailed history, anthropometric assessment, and physical examination, biochemical (fasting serum glucose, lipid profile) and hormonal parameters (fasting insulin) were queried in 115 children presenting to our pediatric endocrinology clinic. Clinical assessments included insulin resistance measured by HOMA-IR ([fasting blood glucose (mmol/L) x fasting serum insulin (mIU/L)]/22.5) and 25- OH vitamin D level. We also divided our cases into two groups according to how long they were exposed to summer sunlight: (i) 3 months and (ii) less than 3 months. The mean weight and BMI SDS were 72.31 kg and 2.98, respectively. The mean HOMA-IR index of those exposed to sunlight for more than 3 months was 4.16, and the mean HOMA-IR index of those exposed to sunlight for 2 months or less was 5.56. Accordingly, the HOMA-IR levels of patients exposed to sunlight for 3 months were lower than those exposed to sunlight for 2 months or less in the summer season (p = 0.005). The analysis shows that sunlight exposure reduces insulin resistance. In this study, we show that sunlight exposure significantly reduces insulin resistance and consequently prevents obesity. These results suggest that sunlight has a beneficial effect on glucose homeostasis by increasing vitamin D synthesis. Demonstration of this mechanism may be the goal of future studies in this area.

Fetal, neonatal endocrinology and metabolism (to include hypoglycaemia)

P2-22

Hyperinsulinaemic Hypoglycaemia in Term Neonates Without Known Risk Factors Leading to Neurological Damage: A Case Series of 5 Patients From Two Regional Centres in the UK

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Background: Little is known about the prevalence of neonatal hypoglycaemia in the absence of known risk factors, nor its associated neurodevelopmental outcomes. Neurological harm from hyperinsulinism induced hypoglycaemia (HH) may be due to the direct effect of hypoglycaemia as well as its sequelae, such as seizures or apnoeas, leading to secondary insults such as hypoxic brain injury. With our case series we highlight such risks and propose changes to support early diagnosis.

Methods: This study is a collaboration between two quaternary paediatric endocrinology centres in the UK. It comprises a literature review of congenital hyperinsulinism and guidelines on neonatal hypoglycaemia provided by national bodies. We present a case series reporting the clinical, biochemical, genetic, radiological, and neurodevelopmental findings of five neonates from two regional centres who, despite having no identifiable risk factors, presented with hyperinsulinaemic hypoglycaemia. Signed informed consent was obtained from the caregivers of patients involved in this case series.

Results: Each case followed the same presenting pattern of poor feeding, reduced tone and later, seizures. All five cases were treated with a combination of diazoxide and chlorothiazide. MRI findings were consistent across cases, showing restricted diffusion in the posterior cortical region and in particular, the occipital lobe. Further restriction was found in 4/5 patients in the precentral gyrus, temporal and frontal lobes. Genetic analysis via TGNS and Sanger sequencing showed no pathogenic variants of genes associated with hyperinsulinism. Development was assessed in 4/5 patients; two have severe global developmental delays, one has abnormal motor skills, and one demonstrates normal development. Two cases developed epilepsy. The unassessed case is at high risk of visual impairment, cerebral palsy, and epilepsy.

Conclusion: Guidelines on the identification of neonatal hypoglycaemia emphasise identification in neonates with risk factors. We recommend that healthcare providers remain vigilant to the signs and symptoms of hypoglycaemia in all neonates through having a low threshold for checking blood glucose and referring to specialist hospital teams if concerned. We propose strategies to increase awareness on the signs of hypoglycaemia (especially abnormal feeding). Costs of a lower clinical threshold for checking blood glucose may be offset by avoiding large medicolegal fees and long-term health costs incurred by a late diagnosis of HH. We recommend the re-evaluation of patients to identify genetic causes of hyperinsulinism and support research into the prevalence of this condition.

P2-72

Congenital hyperinsulinism; challenges in management and diagnosis. An experience from LMIC

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Abstract: Congenital hyperinsulinism is a rare genetic cause of symptomatic hypoglycemia carrying risk of significant morbidity and mortality if left undiagnosed and untreated. It is characterized by unregulated insulin secretion from pancreatic beta cells leading to hypoglycemia. It can be broadly classified into diffuse and focal types. Till date, at least nine different types of genes are identified among which ABCC8 and KCNJ11 are the most common genetic mutations. Genetic mutation can either be inherited as autosomal recessive or autosomal dominant forms. We present series of 3 challenging cases of congenital hyperinsulinism that presented to our pediatric endocrine department at NICH.

Case 1: 25 days old neonate with very sick early neonatal course requiring ventilatory support presented to us with respiratory distress and persistent hypoglycemia. Critical sampling at the time of hypoglycemia revealed endogenous hyperinsulinism. Genetic analysis revealed two pathogenic variants in ABCC8 gene associated with autosomal recessive and autosomal dominant forms of permanent neonatal diabetes and congenital hyperinsulinism. Baby was managed medically with intravenous fluids for maintaining GIR initially then was discharged on fantomalt milk cap dizoxide for managing hypoglycemic episodes after stabilization

Case 2: 2 months old female child presented with symptoms of persistent hypoglycemia. Her critical sampling at the time of hypoglycemia revealed evidence of endogenous non ketotic hypoglycemia. Whole genomic studies showed evidence of pathogenic variants of ABCC8 gene mutations associated with persistent diabetes mellitus and congenital hyperinsulism. She was also managed medically after initial stabilization at pediatric endocrine department of NICH with fantomalt milk capsule diazoxide and injection octeriotide

Case 3: 3 months old female child presented with symptomatic hypoglycemic episodes and respiratory distress. Her critical sampling also revealed endogenous non ketotic hypoglycemia. She was diagnosed using DOPA-PET scan showing findings consistent with diffuse congenital hyperinsulinism. This child was also managed medically with fantomalt milk and cap diazoxide. Later on injection octertide was given but still situation was not improved so ultimately patient underwent subtotal pancreatomy. Her genetic workup was negative.

Conclusion: Congenital hyperinsulinism is a medically challenging disorder which if timely diagnosed and treated can prevent neurological impairment and morbidity associated with persistent hypoglycemia. It is managed medically using nutritional supplements and diazoxide (potassium channel activator) with subtotal pancreatectomy as the last option.

P2-73

When the infant makes the diagnosis of Biermer's disease of his mother

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Introduction: The nutritional status of young breastfed infants is sometimes dependent on the nutritional status of their mothers. Investigation of poor infant weight gain should take into account possible nutritional diseases of the mothers including Biermer's disease.

Objective: through a clinical case, remind the importance of exploring the nutritional status of mothers of exclusively breastfed infants with poor weight growth.

Observation: We report the case of a 4-month-old infant followed for weight stagnation. The clinical examination showed: weight at -2 DS, pallor, disappearance of the smile-response, axial hypotonia and sharp osteotendinous reflexes. The blood count showed pancytopenia. A myelogram was performed and showed a rich marrow with cellular gigantism and asynchronous nucleocytoplasmic maturation affecting all lineages. The infant's plasma vitamin B12 level was collapsed with hyper-homocysteinemia confirming the diagnosis of vitamin B12 deficiency. Brain MRI was normal. The digestive fibroscopy showed a non-specific oedematocongestive duodenitis. The anti-FI antibody test was negative and the anti-stomach parietal cell antibody test was significantly elevated. The mother's blood count showed an isolated macrocytosis. Her vitamin B12 blood level was collapsed. The vitamin B12 deficiency of the infant, was related to exclusive breastfeeding in a non-vegetarian mother with unrecognised Biermer disease. Improvement in clinical symptoms (weight growth and psychomotor development) and haematological symptoms was rapidly observed under vitamin B12 treatment.

Conclusion:A delay in weight growth associated with a delay in psychomotor development in an infant, whether or not it is associated with a haematological anomaly, should necessarily prompt us to look for a vitamin B12 deficiency mainly of maternal origin.

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P2-74

A recessive heterozygous mutation in ABCC8 gene as the cause of severe congenital hyperinsulinism: a Case report

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Case Report: A preterm boy was born at 35 weeks gestational age by cesarean section due to fetal macrossomia and polyhydramnios, weight 4980g (4.3 SDS, Intergrowth 21st), length 53cm (3.1 SDS), 1-min-Apgar 2. He needed resuscitation after birth, and his glycemia was 20 mg/dL. At the Neonatal Intensive Care Unit (NICU), he presented with severe hypoglycemia (10mg/dL) and required intravenous glucose infusion rate (GIR) 10mg/kg/min that increased progressively up to 21mg/kg/min. At critical blood sample, glycemia was 7 mg/dL, insulin 57.2 uIU/mL, and cortisol 28.2 ug/dL; 30 min after glucagon (0.5 mg i.v.), glycemia was 22mg/dL and insulin, 9.17 uIU/mL.

At 13 days of age, somatropin (0.1 mg/kg/day) and prednisolone (15mg/m^2/day) were started, as counter regulatory hormones of insulin. At 21 days of age, diazoxide was initiated, with doses increased up to 20 mg/kg/day, with no improvement. It was replaced by continuous i.v. octreotide, dose gradually increased up to 35mcg/kg/day. At 2 months of age, octreotide was fractionated into three daily subcutaneous doses. Good control of hypoglycemic episodes was obtained at 2.6 months, with GIR reduction. Patient discharged at 5 months, with octreotide 34mcg/kg/day, somatropin 0.1 mg/kg/day and prednisolone 10 mg/m^2/day.

During follow-up over the first four years of life, patient presented with few severe symptomatic episodes of hypoglycemia. Currently, he is 4.3 years old, height 114.8cm (+2.0 SDS, WHO), weight 24 kg (+2.6 SDS). The neuropsychomotor development was delayed, particularly language development.

Whole-exome sequencing identified probable heterozygous pathogenic in the ABCC8 gene, position chr11:17424233 (p.Glu1208del).

Discussion: The ABCC8 gene codes the sulfonylurea receptor (SUR1), a subunit of the ATP-dependent potassium channels expressed in beta pancreatic cells. Gene inactivating mutations in this gene promote excessive insulin secretion. Diazoxide acts directly on the SUR1 receptor and is recommended as first-line treatment for congenital hyperinsulinism, but patients with ABCC8 gene mutation usually do not respond to the drug. Somatostatin analogues, such as octreotide, are recommended to control episodes of hypoglycemia. The aim of treatment in children consists in maintaining serum glycemia over 70 mg/dL. Neurogenic and neuroglycopenic symptoms generally occur when plasma glucose concentration is reduced to 50 to 70 mg/dL. Persistent hypoglycemia, particularly over the neonatal period, results in impaired neurodevelopment.

Conclusion: Congenital hyperinsulinism is a high morbidity condition with few therapeutic options. Early diagnosis and management are crucial to prevent irreversible neurological damage.

P2-75

Foetal exposures to endocrine-disrupting chemicals. INMA-ASTURIAS COHORT. SPAIN

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Background: Endocrine-disrupting chemicals (EDCs) are serious and urgent threats to public health, due to the potentially serious adverse effects of EDCs on endocrine processes during susceptible periods of human development.

Objective: To evaluate the levels endocrine disruptors at gestation.

Material and Methods: A pilot study. Data were obtained from 30 pregnant mothers recruited in Asturias between 2004-2007 and their children from of the Environment and Childhood [INfancia y Medio Ambiente] (INMA) Project, a population-based birth cohort study. Maternal endocrine disruptors urinary levels (phthalates, parabens, benzophenone and bisphenol A) were analyzed at 12 weeks of gestation.

Results: The urinary levels of the following endocrine disruptors are analyzed at 12 weeks of gestation: Mono(carboxy-isononyl), Mono(carboxy-isooctyl) phthalates, Mono-2-ethyl-5-carboxypentyl phthalate, Mono-2-ethyl-5-hydroxyhexyl phthalate, Mono-2-ethyl-5-oxohexyl phthalate, Mono-2-ethylhexyl phthalate, Mono-3-carboxypropyl phthalate, Mono-isobutyl phthalate, Mono-n-butyl phthalate, Monobenzyl phthalate, Monoethyl phthalate, 2 5-dichlorophenol, Ethyl Paraben, Methyl Paraben, Propyl Paraben, benzophenone-3 and bisphenol A, showing the results in table 1.

Conclusions: All the pregnant mothers were exposed to all the disruptors analyzed, with the potential risk to the health of their offspring.

Table 1. Levels of endocrine-disrupting chemicals at 12 weeks' gestation in INMA-Asturias Cohort.

	N	Mean	D. T.	P25	Median	P75	Range
Mono(carboxy-isononyl) phthalates	30	9.51	13.71	2.30	3.65	9.10	1.30-52.90
Mono(carboxy-isooctyl) phthalates	30	8.64	10.53	3.10	5.20	9.90	1.00- 45.50
Mono-2-ethyl-5-carboxypentyl phthalate	30	87.64	132.49	22.60	36.90	97.40	14.20- 609.00
Mono-2-ethyl-5-hydroxyhexyl phthalate	30	52.13	94.52	10.50	19.10	63.20	7.80- 419.00
Mono-2-ethyl-5-oxohexyl phthalate	30	46.67	83.15	10.90	18.55	51.90	4.30- 367.00
Mono-2-ethylhexyl phthalate	27	14.48	27.48	2.10	5.50	12.50	1.30- 129.00
Mono-3-carboxypropyl phthalate	30	6.04	14.54	1.10	1.80	3.40	0.50- 66.30
Mono-isobutyl phthalate	30	64.00	63.44	18.60	47.10	68.90	10.80- 273.00
Mono-n-butyl phthalate	30	219.22	947.12	20.50	34.10	62.80	9.70- 5230.00
Monobenzyl phthalate	30	26.21	41.70	8.10	14.50	26.90	2.40- 228.00
Monoethyl phthalate	30	506.07	685.18	120.00	291.50	449.00	30.90- 3270.00
2 5-dichlorophenol	30	40.98	70.95	9.50	15.15	27.00	1.50- 341.00
Ethyl Paraben	27	22.04	34.24	3.90	8.80	20.90	2.10- 151.00
Methyl Paraben	30	455.27	1244.24	34.50	114.40	304.00	1.50- 6780.00
Propyl Paraben	28	86.94	197.25	3.55	13.00	47.50	0.40- 947.00
benzophenone-3	27	21.85	41.05	2.30	5.40	26.60	0.40- 180.00
bisphenol A	30	6.80	11.51	2.10	3.30	5.90	0.50- 59.90

P2-113

The complexity of Hyperinsulinism in newborns

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Background: Hyperinsulinism represents a group of clinically, genetically and morphologically heterogeneous disorders characterised by β-cell dysfunction in glucose homeostasis leading to excessive insulin secretion with profound and recurrent hypoglycaemia. In most countries it occurs in approximately 1/25,000 to 1/50,000 births.

Mutations in at least 14 genes have been reported to cause congenital hyperinsulinism. In nearly half of the cases, cause remains uncertain.

Clinical Description: Two female siblings both born at term 3 years apart, both small for gestational age, antenatal history of assumed maternal gestational diabetes in both pregnancies, both presenting with decreased oral acceptance, lethargy, grunting, jitteriness and hypoglycaemia in the first 6 hours of age.

Two male siblings born 4 years apart, both born at term after uneventful antenatal period, both presenting in the first 4 hours of age with similar clinical picture compared to the newborn females. Predisposing factors for hypoglycaemia (infection, IUGR, perinatal asphyxia, maternal diabetes) were ruled out.

Management: All newborns had recurrent episodes of hypoglycaemia and required a glucose infusion rate up to 13.5 mg/kg/min to maintain blood glucose levels. All babies required glucagon infusion and diazoxide to achieve normoglycaemia. The hypoglycaemia was confirmed to be related with hyperinsulinism.

The female infants required Diazoxide for approximately 5 months, the male infants for 9 months.

At present, the four children are normoglycaemic and achieving their milestones. However, the two brothers presented with ketotic hypoglycaemia with intercurrent illnesses.

Genetic Studies: Both females were confirmed to have congenital hyperinsulinism with a heterozygous missense mutation at c.3539T>A on INS receptor.

The females' mother, grandfather, maternal brothers, and grandfather's brother had been diagnosed with Type 2 Diabetes Mellitus, despite their low BMI. They were all tested and proven to have the same mutation.

Both males had genetic studies, but no genetic mutation/variant was identified.

Conclusion: We report 4 cases of hyperinsulinism in neonates with similarities on presentation and clinical progress, although not sharing a genetic cause. There are possible genetic changes yet to be identified.

These cases highlight the importance of prompt diagnosis of persistent hypoglycaemia in neonates and prevention of complications such as neurodevelopmental deficits.

Further monitoring will inform us of the clinical course through to adult life. Lifestyle modifications could play a key role in long-term management, due to possible risk of patients developing diabetes mellitus, but these are no different from the healthy life style advice given to the general population.

GH and IGFs

P2-47

The Interaction between Growth Hormone (GH) -Insulin-like Growth factor 1 (IGF1) axis and Immune Systems in Infants and Children During undernutrition: Newly Discovered Pathological mechanisms

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Accumulating evidence indicates various interactions between the GH-IGF1 axis and the immune system in infants and children during undernutrition.

Objectives and Methods: We performed electronic literature systematic review using PubMed, Google Scholar, and Web of Sciences with the aim to provide an update on the link between the GH-IGF1 axis and the immune system in infants and children during malnutrition. We reviewed 22 studies (2007-2022) fitting the search criteria.

Results: GH resistance and low IGF-I production appear to be adaptive mechanisms to preserve calories during malnutrition. Protein deficiency results in a state of GH resistance as well as a state of end-organ resistance to IGF-I. Zinc, magnesium, and vitamin B6 deficiencies that occur in many children with malnutrition have been associated with GH resistance and reduced IGF-I levels (Unknown mechanisms). GH and IGF-1 have important immunoregulatory effects. GH and IGF-1 can protect the host from infection by promoting the maturation of myeloid cells, and phagocyte migration, producing superoxide anions and cytokines, and enhancing opsonic activity. Moreover, IGF-I plays an essential role in the growth, stimulation, proliferation, and function of T cells. IGF-I regulates various aspects of T-cell, B-cell, and monocyte function through its interactions with IGF-IR. IGF-I can prolong lymphocyte survival through the activation of T cell Akt. IGFs depress proinflammatory cytokine signaling by increasing IL-10 secretion via JNK and NF-κB pathways.

On the other hand, pro-inflammatory cytokines, which increase in severe forms of malnutrition especially those with infection, induce a dysregulation in GH–IGF axis and IGF system, both at central and peripheral levels. In the liver, TNF-α, a pro-inflammatory cytokine can cause GH resistance mainly through the down-regulation of liver GH receptor expression. Additionally, the predominance of proinflammatory cytokines decreases IGF sensitivity by enhancing IGFBP production and by decreasing signaling through the (insulin receptor signaling) IRS/ Akt pathway. The increase in local muscle cytokines produced during infections makes the muscle GH-resistant and reduces its own IGF-I production, leading to muscle wasting. Myokines secreted by the skeletal muscle in response to inflammation mediate wasting. A randomized controlled using the anti-inflammatory drug "mesalazine" treatment for 56 days in acutely undernourished children with enteric dysfunction increased IGF-1 levels and decreased the inflammatory markers with improving linear growth.

Conclusion: During malnutrition IGF1 deficiency and GH resistance can negatively affect the functions of the immune system (lymphocytes and cytokines) and predispose to infection and inflammation which further deteriorate growth and induce wasting.

P2-48

The Value of using IGF1/Growth Hormone Peak Ratio in Children with Idiopathic Short Stature

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Introduction: Stimulated GH peak values have been shown to correlate well with nocturnal GH peak values and with nocturnal mean GH values. In addition, the expression level of serum IGF-1 in ISS has been shown to be significantly lower than that in normal children despite their normal GH peak response to provocation.

Objectives: To investigate the value of using the IGF1/GH peak ratio in the anthropometric assessment of children with idiopathic short stature (ISS).

Methods: 20 short children with ISS (HtSDS < -2, with normal GH response to provocation) were randomly selected. Their IGF1 level and their peak GH response to provocation were analyzed in relation to their growth data for 1 year of follow-up. followed for 1 year.

Results: The growth and hormonal data of children with ISS are presented in Table 1:

Table 1.

	Age1	WT1	HT1	HTSD1	BMI1	BMISD1	MPHSD	IGF1-1	GH-P	IGF1/GHP Ratio
Mean	9.6	23.6	122.9	-2.1	15.2	-1.1	-1	197.7	18.1	10.4
SD	2.8	7.2	15.6	0.5	1.5	0.8	0.7	126.5	5.8	9.0
	Age2	WT2	HT2	HTSD2	BMI2	BMISD2	Wt gain g/day			
Mean	10.7	28.5	130.5	-1.8	16.3	-0.7	12.6			
SD	2.6	8.2	14.2	0.4	1.8	0.7	7.9			

Table 2. IGF1/GHP ratio correlation with the growth parameters

	Age 1	HtSDS1	BMI	BMI SDS	IGF-I	IGF1SDS	GH-P	IGF1/GHP	Age2	HtSDS2	wt gain g/d	Delta BMI
Age 1	1.00											
HtSDS1	0.37	1.00										
BMI	0.57	0.19	1.00									
BMI SDS	0.03	0.00	0.69	1.00								
IGF-I	0.57	0.57	0.51	0.17	1.00							
IGF1SDS	0.18	0.68	0.26	0.21	0.86	1.00						
GH-P	-0.19	-0.30	-0.27	-0.13	-0.23	-0.30	1.00					
IGF1/GHP	0.53	0.58	0.48	0.40	0.94	0.83	-0.33	1.00				
Age2	0.99	0.35	0.59	0.05	0.49	-0.10	-0.19	0.45	1.00			
HtSDS2	0.41	0.83	0.35	0.27	0.72	0.76	-0.30	0.63	0.39	1.00		
wt gain g/d	0.62	-0.23	0.67	0.25	-0.03	-0.37	-0.36	0.35	0.62	0.08	1.00	
Delta BMI	0.11	0.12	0.44	-0.22	0.35	0.04	-0.50	0.36	0.13	-0.04	0.51	1.00

IGF1/GHP ratio highly correlated with the growth parameters (HtSDS, BMI, BMISD) before and after a year of follow-up. In addition, IGF1/GHP ratio correlated significantly with weight gain/day and with delta- BMI at 1 year of follow-up.

Conclusion: The IGF1/GHP ratio correlates significantly with the weight and height growth parameters as well as the linear growth, and weight gain in children with ISS.

P2-107

Metabolic parameters in a series of patients with Prader-Willi syndrome treated with recombinant growth hormone

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Introduction: Prader-Willi syndrome (PWS) is a rare paternally inherited genetic disorder caused by alteration of chromosome 15q11-q13. Associated hypothalamic impairment leads to hyperphagia which therefore increases the risk for morbid obesity, dyslipidaemia, insulin resistance and arterial hypertension and in the end increases mortality. Patients with PWS benefit of recombinant growth hormone (rGH) treatment despite the GH reservoir to improve their impaired final height, but GH is known to improve cardiometabolic profile.

Aim: To describe the metabolic profile in rGH treated PWS patients in our centre.

Materials and Methods: Eight children (4 girls and 4 boys) with PWS treated with rGH at a median age of 6.7±3.2 years old were included. Follow-up period was 31±17 months. During the follow-up, 4 children needed levothyroxine, 2 stress hydrocortisone and 1 sex-hormone replacement.

Starting rGH dose was 0.53 mg/m^2/day. At diagnosis, height was -1.7±0.9 and BMI 20.3±4 SD (Z-score 1.5±0.6). IGF1 level was 0.1±0.8 SD. All patients were prepubertal, excepting one girl with adrenarche corresponding to Tanner 3 at 11.8 years. None of the patients had metabolic impairments - glycemia 77.3±7.5 mg/dL; HbA1c 5±0.4%; total cholesterol (TC) 171.7±29.4 mg/dL. Phosphocalcic parameters were normal - total serum calcium (Ca) 9.9±0.1 mg/dL; serum phosphate (P) 4.8±0.3 mg/dL; alkaline phosphatase (ALP) 0.6±0.2 x upper limit of normal (ULN).

At one year of follow-up patients had a median height increase of 0.5 SD and a BMI increase of 0.07 SD. Glycemia, TC and Ca levels were stable. P level increased to 5.2±0.3. ALP increased in 5/8 children with 0.4 points x ULN ($p<0.05$) and 3/8 patients had stable ALP values. IGF1 at 1.6 SD proved treatment compliance.

At the last follow-up, none of the patients completed the rGH treatment; 1/8 had to stop because of increased sleep apnea. Height gain during follow-up was 1 SD. BMI decreased to 1±1.8 SD, but not statistically significant. HbA1c increased to 5.3±0.4%, but none of the patients developed glucose intolerance. TC (168.6±28.7 mg/dL), Ca (9.9±0.4 mg/dL), P (4.9 ±0.2 mg/dL) and ALP (0.8±0.3 xULN) were not significantly changed during the rGH treatment.

Conclusion: No significant metabolic changes were observed in our series of patients, but bigger lots are needed to prove if rGH treatment in childhood could prevent adult-onset metabolic syndrome in these patients, along with lifechanging measures.

P2-108

Acromegaly in a 14-year-old girl with pituitary adenoma

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Introduction: Acromegaly is a rare disorder, developed by overproduction of growth hormone (GH) and insulin-growth factor 1 (IGF-1), in most cases based on a pituitary adenoma. The increased IGF-1 and GH levels lead to the growth of acres and organs as well as metabolic changes. When manifesting before epiphyseal closure, a giant growth develops.

Case Report: A Ukrainian girl presented at the age of 14 years with enlargement of acres (nose, hands and feet), headache, fatigue, and primary amenorrhea. A cranial MRI was performed, which revealed a pituitary adenoma. Transsphenoidal tumor resection followed, although the tumor could not be completely removed.

Postoperatively, the girl developed pituitary insufficiency and has since been treated with L-thyroxine, hydrocortisone, and estradiol. With additional central diabetes insipidus she receives a substitution with Minirin intranasal. The carpogram already showed closed epiphyseal joints, indicating the achievement of the individual final height. Until now, no signs of diabetes mellitus or other metabolic effects have been observed.

Re-operation is currently not indicated. Drug treatment with the somatostatin analogue Lanreotide to suppress the production of growth hormone is ongoing. The patient is under close clinical and radiological control at our endocrinology center.

Conclusion: In the case of acromegaly, there is often a considerable delay in the diagnosis of an average of 7 years due to the rare occurrence and gradual physical changes. After completion of the growth phase, the coarsening of facial features and the growth of hands and feet should prompt further diagnosis in order to reduce morbidity and mortality through early treatment.

P2-109

A real world experience of using Long acting Growth Hormone (Somatrogon) in Children with Growth Hormone Deficiency

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Introduction: Long-acting growth hormone (LaGH) therapy has emerged as a newer treatment option for children with growth hormone deficiency, offering a convenient way of administering growth hormone (GH) injections on a weekly basis. Trials have shown that LaGH formulations are effective in increasing height velocity, improving bone mineral density, and reducing body fat mass in children with Growth hormone deficiency (GHD). The once weekly injections also have a potential to improve adherence and compliance with treatment.

Objective: We aimed to evaluate the real-world experience of using Somatrogon (0.66mg/kg/week) injection in a group of children with growth hormone deficiency at a tertiary paediatric endocrine centre.

Methods: 13 patients (M:F, 9:4) with a mean age of 5.4 years were started on LaGH (Somatrogon) therapy. Out of this, 5 patients were GH naïve and started on LaGH therapy following patient choice. 8 patients were switched from daily GH to LaGH therapy. Baseline and follow up data including height measurements, growth velocity, and IGF-1 levels before and 3 months after starting treatment was available for 6 of these patients (3 switched from daily GH and 3 GH naïve).

Results: All patients demonstrated good height velocity (9.5cm/year) on LaGH therapy. The mean IGF1 levels improved compared to baseline in all the patients. The baseline mean IGF1 levels (prior to LaGH therapy) was 10.1nmol/L, (normal range; 12.6- 46.6nmol/L) and post LaGH therapy was 32.9nmol/L. All the patients preferred to continue to the once-weekly LaGH injections in the long term due to the reduced frequency of injections avoiding the stress of administering daily injections. No side effects were reported during this period.

Conclusion: Clinical trials have demonstrated the efficacy and safety of long-acting GH treatment in children with GHD. Our study, although limited in number and duration of treatment, provides early data to support the tolerance, safety, and efficacy of Somatrogon in a real-world setting. LaGH provides an additional choice for patients with GH deficiency and future research in larger long-term cohorts is necessary to determine the long-term efficacy and safety.

P2-115

Are there sex differences among patients to whom a growth hormone (GH) test with clonidina stimulus was required during the study of short stature?

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Introduction: GH stimulus test is usually performed in pacientes With short stature and/or growth delayed study if GH deficit is suspected. Several articles concluded that male are more frequently diagnosed and treated of GH deficiency than female

Objectives: To know gender's ratio and the possible anthropometric differences between patients that required a consult for short stature and to whom a stimulus test was performed with clonidine during 3 years.

Patients and Methods: We retrospectivelly reviewed all patients sent to a specialised ofrece between 2015 to 2017 due to short stature and/or growth delayed, in which a clonidine stimulus test was performed between. Patients with chronic diseases, syndromes, and patients diagnosed of oncologic diseases were excluded. Clonidine stimulus test was carried out in the morning. Pacientes came to the hospital fasting hospital during the day, fasting, and the clonidine dose was weight dependant.

After the administration of clonidine, GH levels were measured at minute 0, 60, 90, and 120 with a chemiluminescence Immunoassay with Inmulite 2000 (Siemens). For standard deviation conversion, we used local growth graphics. SPSS V25 was usted for statistical analysis

Results: 108 patients (39% girls) were included; mean age was 10.7 years. 65% were Prepubertal patients. Variables: Height-SDS, BMI-SDS and Target-Height (TH)-SDS.

Table 1. Clinical characteristics

	Age 1st consult (years)	Clonidine test age (years)	Height (SDS)	BMI (SDS)	TH- Height (SDS)
All	9.2±2.9	10.7±2.6	-2.4±0.61	--0.29±1.1	1.7±1.05
Boys	9.4±3.1	11.22±2.7	-2.3±0.53	-0.41±1.13	1.4±1.05
Girls	8.7±2.7	9.8±2.4	-2,6±0.68	-0.12±1.08	2.1±0.93

More than 75% of the patients had low weight. Only eight patients had obesity or overweight. Of them, seven had not response to the clonidine stimulus. All patients excepto two were below their mid parental height.

Even if there was a peak in the answer at every time, the 90% was present in the minutes 60 and 90 (52% in the minute 60 and 33% in the minute 90).

During follow-up, 30% were finally diagnosed and treated as GH deficit (30% of the girls and 29% of the boys).

No significant differences.

Conclusions:

1. In our series, male did not benefit from the diagnostic and treatment of GH deficiency.
2. In this samples, most of the patients that participated, presented low weight, a factor that may affect in the adequate growth rate.

P2-136

Human milk insulin-like growth factors and Cyclic glycine-proline (cGP) concentrations in relation to infantile and childhood growth

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Introduction: Insulin-like growth factor (IGF)-1, IGF binding proteins (IGFBPs) and regulatory metabolites, including cyclic Glycine-Proline (cGP), have a possible role in modifying infant growth trajectories through their effects on linear growth, and body composition. There is no consensus on how maternal BMI affects breast milk IGF1 level.

Aim: We reviewed the recent literature about human milk (IGF)-1, and cGP concentrations in relation to infantile growth and body composition.

Results: In 507 infants, higher milk IGF-1 was associated with higher weight at 13 months (p = 0.004) but lower weight at 3 and 5 years of age. Higher milk cGP concentration was associated with lower weight across the 5 years but with higher BMI at 5 years. In 675 unselected infants at ages 3 and 12 months, those who were formula milk-fed had higher IGF-I concentrations at 3 months, and they showed greater gains in weight, length, BMI, and adiposity between age 3 and 12 mo.

In a large cohort Korean study, (547,669 infants), breastfed (BF) children were shorter and lighter by 3.5 years and 4.5 years versus formula fed children. Exclusive BF children for 6 months (compared to < 1 month) eliminated the positive relation of high birth weight and rapid weight gain on the fat mass index at 3 years. In 103 mother -infant pairs, the breast milk consumed by the infants with high weight gain contained higher levels of IGF-1 than that consumed by those with low weight gain during 3 months of lactation. In 40 lactating women, pre-pregnancy BMI was associated with breast milk IGF-1 levels and post-feed breast milk IGF-1 levels of mothers with obesity were correlated with infant's weight for length z-score at 2 months.

In 45 mothers with Gestational diabetes mellitus (GDM) and their babies a positive correlation was detected between the breast milk IGF-1 levels and the weight, head and abdominal circumferences of their babies. Breast milk samples (n = 569) donated by mothers from five European countries showed that milk IGFI concentrations correlated with both protein and fat contents, suggesting a possible regulatory role of IGF in milk macronutrient synthesis. Milk-borne IGF-1 acts as a growth factor for gut maturation.

Conclusions: Human milk IGF-1 and cGP may have an important role in shaping infant growth trajectories during and after the first year of life. Breast milk of obese mothers has higher IGF1 than normal weight mothers.

P2-137

rhGH treatment in SGA patient with spondylo-epi-metaphyseal chondrodysplasia

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We report rhGH-treatment results in a 14-yrs-old SGA patient with spondylo-epi-metaphyseal chondrodysplasia. The patient carries a rare de novo eterozygous variant of COLA1 (c.1510G>A, P.Gly 504Ser) associated with a rare AD spondylo-epiphyseal dysplasia.

Born at term after olygohidramnios-complicated pregnancy, SGA for weight and lenght, the patient has showed a post-natal reducing growth with regular cognitive development. At the age of two height was -4 SDS, with parental-target of 160,6 cm (+/- 8cm). At his arrival in our department at the age of 6,2, height was 91 cm (SDS -5,27) and weight 17,3 kg (SDS -3,52). He showed short upper and lower limbs, short trunk/limbs ratio and hyperlordosis attitude. Two provocative tests confirmed GH deficiency and bone age showed 4 years delay. Short stature NGS genetic test was performed, exiting in a rare de novo eterozygous variant of COLA1 associated with multiple spondylo-epiphyseal dysplasia. Considering the severe short stature condition, in a SGA patient, recombinant grouth hormone (rhGH) treatment was started.

During follow-up, he received rhGH treatment with a mean dosage of 0,038 mg/kg/day with mean IGF1 SDS of +0,63. Auxological parameters at 14,5 years are height 133 cm (SDS -4,13) and IGF1 SDS +0,66, with a height gain of SDS +1,14 since the beginning of rhGH treatment.

Growth hormone deficiency in SGA patient has given the chance to pursue the rGH therapy, albeith with unsatisfactory results in consideration of the condrodyslasia diagnosis in our patient. Limb lengthening surgery has been proposed as a valid option to guarantee to these patients a better quality of life.

P2-138

Growth hormone deficiency and Glycogen storage disease type 0 in a girl with short stature and hypoglycemia: a Case report

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Introduction: Glycogen storage disease (GSD) type 0 and growth hormone (GH) deficiency cause ketotic hypoglycemia via diverse mechanisms and are not known to be associated

Case Report: 10 years old girl presented with recurrent fasting ketotic hypoglycemia, with short stature (HSD: - 4 SDS), with Tanner stage 1, golden sample revealed glucose 42 mg /dL, low insulin and low GH, cortisol and free thyroxine levels were normal. GH peak was 1.6 ng/ml after clonidine stimulation and 6.38 ng/ml after L- Dopa stimulation. The patient started growth hormone therapy. Antibodies for celiac disease were negative. The hypoglycemic attacks recurred. The ultrasound abdomen revealed mild hepatomegaly with increased echogenicity. Liver enzymes started to increase. The lipid profile was normal. A liver biopsy revealed steatosis. Although the genetic test WES detected a nonpathogenic mutation gene for glycogen storage disease type 0a. The patient was fed six times a day, with a low glycemic index and advised to avoid fasting. Liver enzymes were improved.

Conclusions: children with hypoglycemia need to be carefully evaluated because it could be a multifaceted problem. The right diagnosis may lead to fewer occurrences of hypoglycemia GSD type 0 should be taken into consideration in patients with fasting ketotic hypoglycemia.

P2-161

Maternal Factors affecting Human milk insulin-like growth factor (IGF) (HMIGF1) level

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Introduction: Accumulating evidence indicates various but significant effects of human milk IGF1 (HMIGF1) on infantile and childhood linear growth and weight gain. Studies on maternal factors affecting the level of HMIGF1 need to be clarified. .

Objectives and Methods: We performed electronic literature systematic review using PubMed, Google Scholar, and Web of Sciences with the aim to provide an update on maternal factors that may affect postnatal HMIGF1 level.

Results: We reviewed 12 studies (n = 745 women) fitting the search criteria.

In a cohort study (n =501) HM IGF-1 concentrations displayed a positive correlation with maternal weight gain during pregnancy, which was maintained when correcting for maternal pre-pregnancy weight.

In a prospective, longitudinal, observational cohort study, (n = 58) the levels of HM IGF-1 was higher in women with excess (> 32%) versus those with adequate (≤ 32%) total body fat. The IGF-1 / cyclic Glycine-Proline ratio (cGP) ratio displayed a positive correlation with gestational age ($\beta = 0.103, p = 0.033$). C-section was associated with lower HM IGF-1 vs those delivered vaginally. Moderate increases in HM IGF-1 concentrations occurred from early lactation to 4 months corrected age. IGF-1/ cGP ratio showed a sex-specific interaction with maternal basic education (p = 0.035). Higher IGF1 in maternal serum had a significant association with its HMIGF1. Post-feed HMIGF-1 levels of mothers with obesity were correlated with infant's weight for length z-score at 2 months (r -0·476; P = 0·034).

In a controlled study (60 patients with gestational diabetes (GDM), and 96 normal women, and their newborn babies), GDM did not significantly affect the concentrations of IGF-1, -2, IGFBP-3 in the peripheral blood and umbilical cord blood but decreased markedly maternal and fetal IGFBP-2 concentrations. Another study reported higher levels of HMIGF-1 in milk of diabetic mothers and the blood serum of their babies. (n=30) and found a significant correlation between their HMIGF-1 levels and all the anthropometric measurements of their infants. A significant association was reported between GDM and HMIGF1-1: cGP ratio (p = 0.035).

Conclusion: These data provide evidence that maternal factors (weight gain during pregnancy, obesity, gestational diabetes, preterm labor, and C-section) can affect the concentration of HMIGF1.

P2-162

Correlation between IGF-1 at diagnosis and adult height in children with short stature

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Background*:* Insulin-like Growth Factor-1 (IGF-1) is an amino acid peptide produced under the effect of Growth Hormone (GH), mostly secreted by the liver, which stimulates bone growth. IGF-1 levels have high specificity and low sensitivity for the diagnosis of Growth Hormone Deficiency (GHD). Higher IGF-1 levels are classically associated with a better response to growth hormone therapy. The aim of this study was to investigate the correlation between serum IGF-I levels at diagnosis and near adult height (AH), and the difference between AH and Target Height (ΔAH-TH), in children evaluated for short stature.

Patients and Method: This retrospective analysis included 96 patients (61 male, 68 prepubertal, age 10,62±2,82) evaluated in our centre for short stature.

68 patients had GHD (peak of GH <10 µg/L after two stimulation tests with arginine, clonidine or insulin tolerance test, or <20 µg/L after GHRH+Arginine test) and were treated with recombinant human GH (20-25 µg/kg/die). 27 patients had a diagnosis of Idiopathic Short Stature (ISS, normal stimulated GH peak, no evidence of other cause for their shortness).

AH was defined in a child whose height velocity (HV) fell ≤ 1 cm/year. Data are reported as mean ± standard deviation.

Results: At first evaluation height (H) SDS was -2,62±0,64, body mass index (BMI) SDS was -0,67± 1,21, IGF-1 SDS was -1,65±1,65, GH peak was 8,03±4,40 µg/L, and TH SDS was -1,53±0,78.

AH SDS was -1,69±0,95, ΔAH-TH SDS was -0,18±1,00, difference between H SDS and TH SDS (ΔH-TH) was -1,09±0,89, and difference between AH SDS and H SDS (ΔAH-H) was 0,91±0,82.

Pearson's correlation showed a positive correlation in the whole group between IGF-1 SDS and H SDS (r=0,247; p=0,015) and ΔH-TH (r=0,387; p=0,0001); negative correlation between basal IGF-1 SDS and age at diagnosis (r=-0,292; p=0,004), TH SDS (r=-0,238; p=0,019) and ΔAH-H (r=-0,250; p=0,014); no correlation was between IGF-1 and sex (p=0,533), BMI SDS (p=0,070), pubertal status (p=0,638), HV SDS (p=0,165), GH peak (p=0,248), AH SDS (p=0,595),and ΔAH-TH SDS (p=0,199). In addition, no correlation was found between IGF-I levels at diagnosis and AH or ΔAH-TH when children with GHD and ISS were analysed separately.

Conclusions: The results of this study indicate that IGF-1 concentrations are not predictors of the pattern of growth in short children.

P2-163

Taller in One Year: Early Intervention Emphasize of Growth Hormone Therapy in Children with Growth Hormone Deficiency

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Background: Growth hormone deficiency (GHD) is a disorder affecting children's linear growth and leading to short stature without initiation of treatment with growth hormone (GH). Administration of GH has been shown to be safe and effective to increase children's final height in GHD. It is important to start the treatment as early as the GHD is diagnosed. The objective of the current study is to evaluate the growth velocity and height standard deviation score (HtSDS) in pre- and post-pubertal children with (GHD), receiving growth hormone (GH) treatment during the first year of treatment.

Introduction: In the investigation, 23 patients with a confirmed diagnosis of GHD and treated with GH during one year were enrolled. They were divided into two groups: pre-pubertal (9 patients with a mean age of 11.4 years (age range 8-16)) and post-pubertal (14 patients with a mean age of 5.6 years (age range 3-7)). The male:female ratio in the two groups was 1:1.3 and 2:1, respectively. The height was measured at the beginning of the treatment and after one year of treatment to evaluate the effectiveness of GH therapy in promoting growth velocity in these children during the first year of intervention.

Results: Both pre- and post-pubertal groups showed a significant increase in height after one year of GH treatment obviously. The pre-pubertal group showed a significantly greater increase in height velocity compared to the post-pubertal age group mean of 8.86cm (3.5-20.4cm)/year versus the mean of 8.65cm (3.3-15cm)/year. The difference in HtSDS was also seen. In the pre-pubertal group before initiating GH therapy HtSDS mean was -2.66 (-4.6÷-1.63), and after treatment: -2.36 (-4.97÷-1.3). In the post-pubertal group respectively HtSDS mean increased from -2.76 (-5.68÷-0.15) to-2.58 (-5÷-0.37). Based on these results there is a statistically significant raise in HtSDS more in the pre-pubertal group (+0.3SD) than in the post-pubertal group (+0.18SD) (P<0.05). No statistical significance was observed in height velocity during the first year of GH treatment depending on sex (P>0.05).

Conclusions: The results of this study demonstrate that GH therapy is an effective treatment for children with GHD to promote growth, particularly if initiated before puberty. Early diagnosis and treatment of GHD in pre-pubertal children are essential to optimize the growth and development.

P2-201

Etiology and characteristics of children with short stature in endpcrinology department

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Objectives: childhood growth influences their social and psychological behavior, and abnormal growth may reflect underlying pathological etiologies.

We aim to study etiologies and carachteristics of short stature in children in endocrinology department.

Methods: 160 children ranging from 2 years to 21 years with short stature were retrospectively studied.

Results: In this study, a diagnosis of short stature was made in 160 patients.The proportion of boys to girls was 1.38.Average age at the presentation for all patients was 10.68. In 40% of the patients the study revealed pathological etiology, 53 children (33% of all patients) demonstrated to have growth hormone deficiency, 7(4.3%) patients have hypothyroidism, 5(3.1%)patients have syndromic disease, 2(1.25%)patients have bone disease. In 60% of the patients no pathological etiology was found the most common etiologies were constitutional delay of growth and puberty and familial short stature.

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Conclusion: Growth monitoring of children should start at an early age for boys and girls.referral to the pediatric endocrine clinic should be considered when growth problems are suspected for accurate diagnosis and etiology profiling.

P2-227

Study of different anthropometric factors on the patients with growth hormone deficiency before and after treatment

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Background: Growth hormone deficiency (GHD) is one of the main endocrine disorders causing short stature. It may be due to isolated growth hormone deficiency (IGHD) or associated with multiple pituitary hormone deficiency (MPHD). The aim of this study was evaluation of anthropometric factors before and after growth hormone (GH) therapy.

Patients and Method: This is a historical cohort study. The diagnosis of GHD in children was assessed by GH peak <10 ng/ml in two provocative tests. From 746 patients with short stature 563 children and adolescents had GHD, 423 cases (164 females and 259 males) who only received GH were enrolled into the study. GH peak < 5 ng/mL was considered as complete deficiency and the peak ≥ 5 ng/mL to < 10 ng /mL as partial deficiency.

Results: There were 354 patients (83.7%) in IGHD and 69 cases (16.3%) in MPHD group. Duration of treatment was [Mean ± standard deviation (SD)] 3.5 ± 2.4 yr in IGHD and 7 ± 4.6 yr in MPHD. The basal height SDS and peak of GH in provocative tests in MPHD were significantly lower than IGHD (P<0.001). Height standard deviation score (SDS) after treatment, in patients with IGHD was -1.5±1.1 and in patients with MPHD was -1.8±1.7 that in both groups was significantly higher than baseline (P<0.001). The change of height SDS by treatment in complete IGHD subgroup (1.2±0.9) was significantly higher than partial IGHD (0.95±0.7) (P=0.015) and in complete MPHD subgroup (2.2±1.7) was also significantly higher than partial MPHD (0.33±0.9) (P=0.005). The lower basal age was accompanied by higher height SDS gain in both IGHD and MPHD. Final height SDS significantly had positive correlation with the difference between basal height SDS and midparental height (target height) SDS in both groups. Increase of basal height SDS after treatment significantly had negative correlation with peak of GH in diagnostic provocative tests. First year growth velocity in IGHD had positive correlation with height gain after treatment, but had no correlation in MPHD patients. Change of height SDS had no correlation with birth weight in both groups.

P2-234

Growth Hormone insensitivity (Laron syndrome): Report of a case

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Introduction: Primary growth hormone (GH) insensitivity is an autosomal recessive pathology caused by molecular defects in the GH receptor gene. In Chile there are 3 reported patients.

Clinical Case: Female patient, newborn of 37 weeks, due to delivery, adequate for gestational age. Son of non-consanguineous parents.Hospitalized at 12 hours of life in the neonatology unit due to persistent tremors, jaundice and septic symptoms due to connatal pneumonia, HGT < 40 MG% is performed, repeated 3 times, it is assumed to be due to infection, it is cultured and started antibiotic therapy and glucose load at 6 mg/kg/minute which required an increase up to 8 mg/kg/min, with which he achieved preprandial glycemia between 60 and 90 mg/dL, for which it was decided to suspend glucose load at 48 hours. Clinically, the infectious picture evolves well, however, he presents hypoglycemia again, for which endocrinology evaluation is requested, who evaluates him on day 11 of life, highlighting the active newborn physical examination, preserved muscle tone, wide fontanelle, hypertelorism, nasal bridge flat, separate nipples, a study of hypoglycemia and measurement of glycemia prior to feeding is decided and a critical sample in case of presenting new hypoglycemia, which is taken at 12 days of life, in a critical sample the following stands out: glycemia of 31 mg/dL, insulin <.20 uU/mL, Cortisol 23.15 mmol/L, ammonium 57.1 ug/dL, ketonemia 0.59 mg/dL, GH61.3 ng/mL, C-peptide 0.2 ng/mL, Growth hormone resistance syndrome is suspected, igf-1 levels is measured resulting in <15 ng/mL (NR 18-172 ng/mL).

Faced with these results and phenotypic characteristics of the patient, a genetic evaluation was decided. Invitae hypoglycemia panel reporting GHR Gen / pathogenic variant c.181 C>T (p. Arg 61*) / Concluding two pathogenic variants identified in GHR Gen: Laron syndrome (autosomal recessive) and Hormone insensitivity syndrome partial growth (autosomal dominant).

Adequate contributions are achieved, with free-demand breastfeeding associated with initial formula reinforcement, to date there has been no new hypoglycemia event.

Discussion: Laron syndrome is a rare cause of hypoglycemia, in the case presented the genetic diagnosis has been achieved early, however children with severe IGF-I deficiency due to congenital or acquired defects in the action of GH have short stature that cannot be remedied with GH treatment. Studies with this treatment report an increase in growth velocity. Currently our patient is waiting to be able to obtain the treatment.

Growth and syndromes (to include Turner syndrome)

P2-5

Variations in body composition, IGF1 and Cyclic glycine-proline (cGP) concentrations in breastfed vs formula fed infants during infancy period

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Introduction: Breastfeeding is one of the most effective preventive measures of childhood obesity and many other chronic diseases. The effect of breastfeeding vs formula feeding in changing infant's body composition remains unclear.

Aim and Methods: The objective of this review is to update and summarize the recent literature (Pubmed, Google scholar, Scopus and Research gate in the past 10 years) on studies investigating the differences in body composition, in relation to IGF1 and cGP concentrations in breastfed vs formula fed infants.

Results: Breast fed infants (n = 117) had lower fat mass (FM) percentage versus exclusively formula-fed infants (n = 239). Exclusively formula-fed from birth doubles the risk of early rapid growth between birth and two months, which increased the odds of being overweight or obese at 24 months. Formula-fed infants gained more weight and BMI through 7 months of age, the weight gain was faster than linear growth (1 study).

A meta-analysis of 15 studies reported that in formula-fed infants, FFM was higher at 3-4 months, 8-9 months and 12 months and FM was lower at 3-4 months and 6 months compared to BF infants. Conversely, at 12 months, FM mass was higher in formula-fed infants than in BF infants. In 507 infants, higher IGF-1 during early infancy was associated with higher weight at 13 months but lower weight at 3 and 5 years of age. Cyclic glycine-proline (cGP) is a natural nutrient of breast milk and plays a role in regulating the function of insulin-like growth factor-1 (IGF-1). Higher (cGP) was associated with lower weight across the 5 years but with higher BMI at 5 years. In 675 unselected infants at ages 3 and 12 months, those who were formula milk-fed had higher IGF-I concentrations at 3 months, and they showed greater gains in weight, length, BMI, and adiposity between age 3 and 12 mo. In a large cohort Korean study, (547,669 infants), BF children were shorter and lighter by 3.5 years and 4.5 years versus formula fed children. Full BF for 6 months (compared to less than 1 month) eliminated the positive relation of high birth weight and rapid weight gain on the fat mass index at 3 years

Conclusion: Formula-fed infants have higher risk for early rapid growth and increased the odds of being overweight or obese at 24 months compared to Breast fed infants,

P2-6

Maternal, placental and fetal IGF-1 and IGFBP in Obese pregnancies and the effect on fetal/infantile growth

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Introduction: Placental hormones can control the transfer of maternal nutrients to the fetus and modulate fetal and neonatal growth. Data about the interaction between maternal, placental and fetal IGF1/IGFBP in relation to newborn size is not clear,

Aim: To review research paper published in Pubmed, Google scholar, Research gate, and Scopus in the past 20 years on the relation between maternal, placental and fetal/infantile/ IGF1/ IGFBP-1 in relation to birth size in pregnancies associated with maternal obesity.

28 research papers were selected and reviewed (n = 1902).

Results: In 47 women, serum IGF-I during pregnancy was positively correlated and IGFBP-1 was negatively correlated with maternal body weight and fat-free body weight respectively before and during pregnancy. In 289 women, who were pregnant with a single fetus, between 24- and 29-week gestational age (GA), maternal IGF-I levels were mainly determined by body weight, placental growth hormone (PGH), and insulin, while IGFBP-1 concentrations were negatively determined by body weight, insulin, and IGF-I.

In a pregnancy cohort (n = 307), maternal plasma IGF-1 concentrations increased by an average of 55.4% between 24–28 and 32–35 weeks of gestation. The maternal IGF-I correlated with birth weight and placental weight. Each SD increase in maternal IGF-I level at 24–28 weeks was associated with a 75-g increase in birth weight, a 20-g increase in placental weight, and 1.91-fold higher odds of macrosomia. Maternal and fetal IGF-I levels were significantly higher in GDM vs nondiabetic pregnancies. In 23 Swedish non-diabetic pregnant women, birth weights (range, 3025-4235 g) were positively correlated to maternal BMI and the activity of placental insulin/IGF-I and mTOR signaling was positively correlated to birth weight. One study reported that the Circulating IGF-I, basal membrane GLUT1 expression and glucose transporter activity was correlated with birth weight, in non- diabetic women

In 27 obese pregnant women, birthweight was positively correlated with maternal body mass index, umbilical vein glucose and insulin. Umbilical vein glucose levels were positively correlated with placental weight and maternal BMI. Women entering pregnancy obese had higher circulating concentrations of IGF-1 and insulin, and more pronounced insulin resistance, compared with pregnant women with normal BMI. A positive correlation of IGF-1 levels with FBG was detected in obese women.

Conclusion: In obese mothers or who had gain excessive weight during pregnancy, the occurrence of higher maternal IGF1 can increase the size of the placenta, stimulating mTOR signaling, contributing to fetal overgrowth.

P2-7

Survey of the Prevalence of Balance Issues in Turner Syndrome

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Background: Turner Syndrome (TS) is commonly complicated by otological problems, of which middle ear infections, conductive and sensorineural hearing losses are most frequent. Middle ear infection and hearing loss, isolated or in combination, have putative roles in balance disturbance and may be related to the increased fracture risk exhibited in TS in adulthood. Our aim was to both establish the prevalence of balance problems in TS during childhood and explore factors which may be implicated in aetiology.

Methods: Girls, aged 6-18 years, with a confirmed diagnosis of TS, were invited to complete an online questionnaire, using an online platform created by the Turner Syndrome Support Society UK. Consent and assent were obtained in all those who agreed to participate. The Movement Assessment Battery for Children-2 Checklist, modified to include additional questions addressing hearing, ear infection, visual problems, dizziness, previous fracture, motion sickness or support needs, was completed by girls and parent/guardian together.

Results: 9 girls responded (mean age 10.3 years, range 6.25 - 16). 7/9 girls were assessed as having movement difficulty on basis of their responses. 6/9 (67%) had hearing problems, 4/9 (44%) ear infections, 3/9 (33%) had visual problems and 2/9 (22%) had additional support needs, respectively. None of the respondents offered a history of dizziness, motion sickness or previous fracture. The 4 girls reporting ear infection also reported hearing problems. 4/9 (44%) girls considered themselves to have movement difficulty.

Discussion: Movement difficulty in girls with TS is common and has implications on activities of daily living and attaining developmental milestones. We were unable to draw any conclusion on those factors which may be related to balance disturbance in TS and this requires further research.

P2-8

Growing Tall and Staying Slim During a Pandemic: The Power of rGH

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Keywords: COVID 19, height trajectory, rGH

Background: Various factors can interfere with height and body mass index (BMI) trajectories and therefore, auxological parameters reflect children's health status. The COVID-19 pandemic has had an important impact on all the social determinants of health.

Aim: The aim of the current study was to assess the effect of recombinant growth hormone (rGH) treatment on height and BMI trajectories in children before and during the first three years of the COVID 19 pandemic.

Methods: This was a retrospective data analysis of children evaluated between 2019-2022 in a tertiary Pediatric Endocrine Clinic from Romania. Demographic (age, sex, environment), anthropometric (height and BMI SDS) diagnosis and treatment (rGH) data was recorded and yearly changes in height and BMI were computed. Only subjects with at least one visit during each year analyzed were included. Data was analyzed using SPSS v25.0 with a level of significance $\alpha=0.05$.

Results: Seventy-three children were included in the analysis, 48 under treatment with rGH and 25 without, all followed prospectively during the analyzed period. The treated group had a higher median age (13 vs.10 years, $p=0.048$) and male preponderance ($p=0.025$). Both groups had a positive BMI SDS trend during the first 2 years, and negative in the third, with no significant difference from start to finish (0.03 SDS in the non-treated vs. 0.2 SDS in the treated group, $p=0.189$). During the first year height had a positive trend in both groups, but the last two years the trajectories diverged, with the rGH treated children maintaining a positive trend, while the comparison group had a negative trend, leading to a significant difference in the end (0.09 SDS in the non-treated vs. 0.53 SDS in the treated group, $p=0.003$). In logistic regression, age and GH treatment were the significant contributing factors, with sex, environment, diagnosis and pubertal status having no statistically significant influence.

Discussions: All major social determinants of health were impacted by the COVID 19 pandemic and led to changes in auxological parameters trajectories. In our cohort, BMI trajectory recovered during the third year. Height trajectory had a negative trend during the second and third year of pandemic, but rGH treatment seemed to protect against it. Data from larger cohorts (rGH treatment registries) might bring useful new information.

Conclusions: The COVID 19 pandemic doesn't seem to have had an influence on growth trajectories in this cohort of rGH treated children.

P2-9

A novel COL11A1 gene mutation in a patient with short stature mimicking Noonan syndrome

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Background: Fibrochondrogenesis 1 (FBCG1) is known as an autosomal recessive syndrome, which is related to short-limbed skeletal dysplasia. The disease is clinically characterized by a flat midface with a small nose and anteverted nares, significant shortening of all limb segments but relatively normal hands and feet, and a small bell-shaped thorax with a protuberant abdomen. Mutations in the gene encoding the α1 chain of type XI collagen

(COL11A1) are seen to be the main cause of this disease. We present a case of a male patients with FBCG1, presenting facial dysmorphism, abnormal skeletal development, and severe short stature.

Case Presentation: He had a characteristic appearance resembling Noonan syndrome such as hypertelorism, ptosis in the right eye, webbed neck, and micrognathia, and showed a triangular facial shape and displayed severe short stature (height SDS < -3). Radiographically, the ribs were broad, metaphyseal cupping at the ends, and the lumbar vertebral bodies looked platyspondyly. Whole exome sequencing revealed compound heterozygous variants, c.3478C>G (p.Pro1160Ala) and c.2771C>T (p.Pro924Leu), in the COL11A1 gene, the former of which is a novel variant.

Conclusions: We have reported a novel mutation in COL11A1, which represents the first Korean report of FBCG1 mimicking Noonan syndrome. This finding may provide insights into the phenotypic spectrum of FBCG1.

P2-10

Overgrowth in a 12-years-old boy with distal chromosome 16 duplication syndrome

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Background: Distal chromosome 16 duplication syndrome, also known as 16q partial trisomy, is a very rare genetic disorder. Smaller chromosomal copy number variants (CNVs) within the 16q region create partial trisomies, which occur less frequently than full trisomy 16q. Trisomy 16q is generally associated with a multisystemic phenotype including intrauterine growth restriction (IUGR), brain and cardiac defects, intellectual disability and an increased risk of both prenatal and postnatal lethality.

Case Presentation: Here we present the clinical case of a 12-years-old Caucasian boy who referred to Pediatric Endocrinology Outpatient Clinic because of early-onset severe obesity associated with high stature, intellectual disability and facial dysmorphisms. The familial history was negative and his twin brother was healthy. On physical examination he presented cleft palate (surgically corrected at the age of 6 years) and minor dysmorphic facial traits including sparse eyebrows, epicanthus, hypertelorism, midface hypoplasia and thin lips. Height (+1.39 SDS) was above the mean for age and target height, associated with accelerated height growth rate; weight was significantly above the mean for age and BMI SDS was +3.2. Moreover, bone age was found to be about 13 years, in accordance with the chronological age, but testicular volume was still prepubertal in size according to Tanner stage. Biochemical and hormonal evaluation documented high values of LDL-cholesterol and fasting hyperinsulinemia. Audiological tests, echography of the abdomen and heart, brain MRI ruled out major abnormalities or functional disorders. Karyotype and molecular analysis for Kabuki syndrome resulted normal. The genetic analysis has been extended to chromosomal microarray analysis (CMA), that revealed a de novo heterozygous duplication of 16q22.3q24.1 of 10.5 Mb and a heterozygous deletion of 5q14.3, paternally inherited. During follow-up, at the age of 14, the boy seemed to present spontaneous onset of puberty (bone age 14.6 years), persistently severe obesity, slowing of height growth rate with stature still above target height.

Conclusions: Our patient presents a rare genetic abnormality involving chromosome 16 associated with an auxological picture characterized by overgrowth in height and weight, significantly different from the very few cases (18 cases) reported in the scientific literature characterized by stunted growth in height and weight in patients with 16q partial trisomy. This case highlights the great heterogeneity in clinical manifestations and provides new evidence for better defining the phenotypic picture for smaller 16q CNVs.

P2-11

GH-IGF-1 axis in *PTPN11* and non-*PTPN11* Noonan syndrome: Effects on growth and response to GH treatment

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Introduction: The mechanisms underlying short stature in Noonan Syndrome (NS) are poorly understood and may include inadequate GH secretion or action, decreased IGF-1 production, growth plate dysfunction, or other factors. In this retrospective study, we aimed to evaluate the function of the GH-IGF-1 axis in NS.

Method: We took all patients with genetically proven Noonan syndrome among 1001 children and adolescents currently treated with GH in our center. We evaluated their birth length, standardized height, GH secretion and IGF-1 before GH therapy, IGF-1 within 3-6 months thereafter, and the first-year growth response to GH. Data are presented as median and IQR.

Results: We identified 42 patients with NS (25 males) in total, their current age is 10.5 years (median; IQR 7.5-12.8). Of them, 29 had a *PTPN11* pathogenic variant, and 13 other gene variants (*SOS1*, *RAF1*, *KRAS*, *SHOC2*, or *HRAS*). GH secretion was tested in 32 patients.

At birth, newborns with NS had a shorter median birth length of -1.19 SD for gestational age (IQR -0.59 to -1.77; p<0.0001) which correlated with both maternal height (r=0.39; p=0.01) and mid-parental height (r=0.32; p=0.04), and also predicted growth retardation later in childhood (r=0.31; p=0.05).

After birth, children with NS failed to catch-up and further deteriorated in height-SDS to -3.17 (IQR -2.71 to -3.87) by age 4.9 years (IQR 3.3 to 7.2). IGF-1 before GH therapy was low (-1.63 SD; IQR -1.21 to -2.20; p<0.0001). The life-minimum height was not predicted by GH secretory status but rather by IGF-1 ($r=0.32$; $p=0.04$), suggesting that growth failure is due to limited GH sensitivity, and not GH deficiency.

Following the first year of GH therapy (0.033 mg/kg/day), height-SDS increased by 0.65 (IQR 0.46 to 0.79; $p<0.0001$) to height-SDS -2.73 (IQR -2.23 to 3.26). IGF-1 following 3-6 months' therapy increased to -0.91 SD (IQR +0.23 to -1.51). Those with a more profound initial IGF-1 deficiency had a better growth response ($r=0.35$; $p=0.04$), regardless of GH secretory status. We observed no apparent differences between individuals with *PTPN11* or other gene variants.

Conclusion: Our findings suggest that growth retardation in NS is due to both prenatal and postnatal factors and is not due to insufficient GH secretion but rather to limited GH sensitivity. Short-term GH treatment response is predicted by a more severe initial IGF-1 deficiency, indicating a mechanism of overcoming GH insensitivity. Individual gene variants have no apparent specific impact on growth pattern or response to therapy.

P2-12

A novel heterozygous pathogenic variant in the *HMGA2* gene causing Silver-Russell Syndrome, a case-report

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Background: Genetic workup is negative in up to 40% of children presenting with clinical signs of Silver-Russell syndrome (SRS). *HMGA2* variants causing SRS are rare, accounting for less than 1% of all reported cases.

Case description: A 1y,8m-old boy was referred to our endocrinology institute due to severe failure to thrive (HAZ=-4.6 SDS, WAZ=-4.8 SDS) and feeding difficulties requiring nutritional support via PEG. He was born at 36 weeks of gestation weighing 1770 g, to non-consanguineous parents of Jewish Iranian (M-148 cm) and Yemenite (F-158 cm) origin. Physical features suggestive of SRS included relative macrocephaly and typical facies. Workup for etiologies of short stature, including a GH stimulation test, was normal.

Genetic workup: The patient underwent prenatal genetic testing because of a maternal abnormality in the corpus callosum, which was later ruled out in our patient by MRI. Amniocentesis was performed during the 2nd trimester. Chromosomal Microarray Analysis and trio exome sequencing were interpreted as normal.

Postnatal revision of the raw data according to the updated phenotype revealed a novel heterozygous pathogenic variant in the *HMGA2* gene, inherited from the father: c.27dup (p.Gln10fs, NM_003483.6, hg19). This frameshift variant is classified as pathogenic as this is a null variant in a gene where loss of function is a known mechanism of disease; it has not been reported in the healthy population databases; and the patient's phenotype is highly specific and consistent with this genetic etiology.

Discussion: Pathogenic variants in the *HMGA2* gene, de-novo or transmitted by either parent, are a very rare cause of SRS, also referred to as SRS type 5. The phenotype of these patients is similar to that of patients carrying 11p15.5 epigenetic defects, however, as this is a germline mutation, body asymmetry is not present. Using the LOVD and ClinVar databases, only 4 other frameshift likely pathogenic/pathogenic variants have been reported to date.

Conclusion: In patients with IUGR and postnatal growth failure, rare etiologies of Russell-Silver Syndrome, such as variants in the *HMGA2* gene, must be considered, especially as the recurrence risk is 50% in inherited cases.

P2-13

Transition of patients treated with growth hormone – case series

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Introduction: Rare endocrine diseases are lifelong chronic conditions requiring constant medical follow up of the affected individuals. More common among them are patients with hypopituitarism, Turner syndrome (TS), and Prader-Willi syndrome (PWS). The age between adolescence and adulthood, despite being difficult to define by age category alone is an important time for the personal development. This time may be made more difficult if accompanied by a chronic rare endocrine condition.

Objectives: The objective of this case series presentation is to describe a single Expert center of rare diseases experience concerning the transition of care for a contingency of rare endocrine disease patients.

Material and Methods: Medical data of all patients transferred from pediatric to adult endocrine department was analyzed for a period of 5 years (2018-2022). Disease specific characteristics of the patients were analyzed.

Results: During the 5-year period 43 patients with rare endocrine diseases have reached the age of 18. Of them, 27 (62.8%) patients were transferred to the adult department and 6 from the transferred were subsequently lost to follow-up thus decreasing the rate of successful transfer to 48.8%. From those 27 patients, 18 had one of the three conditions requiring growth hormone (rhGH) treatment, the rest were with other rare genetic syndromes. Ten of the transferred patients had hypopituitarism (2 with acquired and 8 with congenital pituitary hormonal deficiency). Among the patients with hypopituitarism the average age at the transfer was 19.8±3.7 (18-30) years. Five of the patients had panhypopituitarism, other 3 being with partial deficiencies. Two patient with isolated GH deficiency have been transferred successfully. The patients with PWS and TS were all transferred at the age of 18 and in both groups three out of four were treated with rhGH.

Conclusion: Our preliminary data shows that transition at our Expert center has started primarily with patients who had not completely finished their growth and development by 18 years of age. Close follow-up of patients with rare endocrine diseases is important at the time of transition. Time of the transfer to the adult department was subject to expert evaluation and is individual on case basis. This further highlights the necessity of predefined measures to determine the best transition approach as well as its outcomes.

P2-14

Unmet needs and challenges experienced by patients with growth disorders and their caregivers: A patient expert view

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Background: The diagnosis, treatment, and management of growth disorders can have a substantial burden on patients and caregivers. Research was conducted with patient experts to understand challenges experienced by patients with growth disorders and their caregivers, and identify opportunities to improve care.

Methods: A mixed-methods approach was used to obtain insights from patient experts between October 2022-January 2023, via multiple methods of engagement: a pre-meeting survey to obtain qualitative and quantitative feedback across key themes; a 3.5-hour virtual global roundtable, chaired by ICOSEP, including patient advocates from eight countries (France, Italy, Brazil, UK, Netherlands, Canada, US, and Argentina), alongside a pediatric endocrinologist from Turkey; and a patient advocate interview from Japan.

Results: Patient experts identified three challenge areas negatively impacting growth disorder care: delays to diagnosis, low adherence to treatment, and a lack of shared decision-making (SDM) with healthcare professionals (HCPs).

Most [80% (n=8)] of patient experts were only moderately satisfied with diagnostic processes in their country. Patient experts highlighted that delays to diagnosis are largely attributed to a lack of awareness and limited understanding of the medical consequences associated with growth disorders beyond height, among the public and HCPs. Long wait times for specialist consultations, costly diagnosis processes, and inequities in care access, can also contribute to delays. Patient experts stated that education of parents, schools, and HCPs is needed to improve growth disorder diagnosis.

Most [90% (n=9)] of patient experts reported low or moderate satisfaction with treatment support in their country. The burden of daily injections, emotional and practical challenges associated with treatment, and lack of robust treatment support, particularly for adolescent patients, may contribute to adherence challenges. Patient experts highlighted a need for standardized information on treatment administration, alongside support programs and materials that encourage adherence throughout the patient journey.

SDM in growth disorders may improve treatment adherence. However, 60% (n=6) of patient experts were unsure of its use in practice. Systemic barriers and varying familiarity with SDM contribute to the lack of widespread adoption. Patient experts stated that HCP and patient education, combined with patient empowerment, are required to facilitate uptake of SDM.

Conclusion: Patients with growth disorders and their caregivers face many challenges on the path to diagnosis and throughout treatment, impacted by low treatment adherence and a lack of widespread SDM. There is an urgent need for solutions to overcome these challenges and improve the care experience for those affected by growth disorders.

P2-15

Autosomal dominant inherited VUS 3 in the fibrillin 2 gene in a patient with tall stature

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Background: The reasons for tall stature, defined as a height above the 97. percentile or above 2SD from the mean, are heterogeneous. Besides non-pathogenic forms like familial tall stature or constitutional advance of growth there are pathogenic forms like obesity, growth hormone excess, hyperthyreoidism, precocious puberty or some genetic disorders and syndromes that need to be concerned.

Case Report: We report on a 14 years and 6 months old boy who presented at the outpatient clinic with a tall stature of 192,7cm (above the 99. percentile), a narrow trunk and myopia. In his past medical history it was referred to motor development retardation in early childhood with impaired joint mobility of knees and elbows. Familial tall stature, growth hormone excess and constitutional advance of growth had been excluded by physical examination, family history and laboratory tests. The Marfan-like appearance led to genetic testing in consideration of a syndrome associated to tall stature.

In our patient we detected a heterozygous pointmutation c.7201A>C in the fibrillin 2 gene (FBN2), which is classified as a variant of unknown significance class 3 (VUS 3). In silico analysis are ranking this VUS 3 differently. FBN2 is encoding for fibrillin-2, a matrix protein involved in the construction of elastic fibres. Mutations in this gene cause congenital contractural arachnodactyly (CCA; Beals-Hecht syndrome), whose prevalence is unknown. Typical symptoms of CCA are long limbs, narrow body, joint contractures, tall stature, crumpled ears and aortic dilatation. To determine the VUS 3 either as a de novo-mutation or as an autosomal-dominant inherited mutation, the patient's parents were tested subsequently. In the patient's mother the same VUS was verified and an adjacent screening of the mother regarding typical symptoms of CCA showed an aortic dilatation, whereas the mother had no tall stature and no myopia.

Results: We found a VUS 3 in the FBN2 gene in our patient and his mother revealing an autosomal dominant inheritance. Both of the affected family members showed clinical signs according to congenital contractural arachnodactyly, so that the correlation between the VUS3 and the described symptoms in our individuals seems to be likely.

P2-16

Clinical heterogeneity of Kabuki Syndrome in a cohort of pediatric Romanian patients

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Introduction: Kabuki Syndrome (KS) is a rare genetic disorder characterised by dysmorphic facies, poor developmental growth, hypotonia, skeletal abnormalities, intellectual disability, as well as systemic malformations. The pathogenic or likely pathogenic variants of the KMT2D or KDM6A genes are responsible for about 70% of the cases, while the rest are diagnosed based on clinical features consistent with KS. This paper reviews the clinical features, genetic testing and management of KS in a Romanian Pediatric Endocrinology clinic.

Methods: Retrospective observational study.

Results: We examined data from 6 patients evaluated for KS in the Pediatric Endocrinology clinic, analyzing dysmorphia, growth development, malformations, intellectual abilities and genetic diagnosis. All were females, with ages between 2-18 years (average 9.9 years), with 5/6 having mild to severe intellectual disabilities. 3/6 already had a confirmed de novo KMT2D mutation, we tested the other 3 - 2 of them had Turner mosaicism with KS (2/6), while the other one didn't present any known pathogenic mutation (1/6).

1/6 patients had a family history of Hashimoto's thyroiditis and multiple sclerosis, with 3/6 cases having personal history of autoimmune thyroiditis and 1/6 suffering from psoriasis, atopic dermatitis and autoimmune thrombocytopenia.

All (6/6) had elongated palpebral fissures, 3/6 had arched eyebrows with thinning of the external third, 3/6 had microcephaly, 2/6 had hypertelorism, with 6/6 having ear abnormalities. Scoliosis was present in 2/6 cases, brachydactyly in 2/6 patients, fetal pads were present in 1/6 patients and vertebral anomalies in 1/6 of cases. No cases presented hypotonia or hearing loss. Harmonious short stature was found in 4/6 of cases, with a mean of -2.5 SD, with all of the 4 patients either receiving treatment presently or having been treated in the past with rhGH. Multiple cardiac malformations were found in 2/6 patients and 2/6 presented with renal malformations, while 1/6 patients presented with arterial hypertension of unknown etiology.

Discussion: Genetic testing was positive for a de novo mutation in half of the patients, a smaller number of cases had Turner mosaicism with KS, with a minority having no pathogenic mutation. Some form of facial dysmorphia was present in all the cases, short stature was present in almost all the cases, skeletal abnormalities were present in a small number of cases, while malformations were found in a smaller number of patients.

Conclusions: KS is a rare genetic disorder with an identifiable mutation in most cases, which requires active surveillance for systemic complications.

P2-17

Efficacy and safety of recombinant growth hormone therapy in a girl with a Loeys-Dietz syndrome

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The Loeys-Dietz syndrome (LDS) is a genetic heterogeneous, autosomal dominant aortic aneurysm syndrome with widespread systemic involvement. As defined by Loeys et al. (2006), the disorder is characterized by the triad of arterial tortuosity and aneurysms, hypertelorism, and bifid uvula or cleft palate.

We present a 16.5-year-old girl with LDS2 caused by a mutation c.1582C>T (p.R5228C) in the *TGFBR2* gene and treated with recombinant growth hormone (rGH) due to coexisting growth hormone deficiency (GHD).

The case analysis (observational study) presents the efficacy of rGH therapy and the safety aspects of this treatment, including aortal imaging follow-up (echocardiography; ECHO). To our knowledge, this is the first investigation of the effects of a long-term rGH treatment on aortic dimensions in LDS.

LDS was recognized in the presented patient in the 2nd year of life due to typical dysmorphic features. Since 3rd year of life, growth deceleration was observed. Based on parental height, the target height was 154 cm. At age 6, the partial GHD was recognized (max GH after clonidine and glucagon was respectively 7.2 and 3.6 ng/ml; IGF-1 - 35 ng/ml; IGFBP-3 - 2851 ng/ml). At the age of 6.5, rGH was initiated (htSDS -2.4) and continued up to 14 years and 3 months (htSDS -1.4). The present height at the age of 16.5 is 155 cm. The dose of rGH was adjusted during treatment according to the clinical response and laboratory data and was between 0.025-0.028 mg/kg/day. The IGF-1 and IGFBP-3 levels were kept within the normal range.

Since the age of 16 months, the widening of the aortic root was observed on ECHO. With time the aortic root diameter increased. At 16, due to a markedly dilated aortic root (Z-score +5.95), the girl underwent a plastic operation of the aorta with a satisfactory outcome. The patient's current status is stable, but management in a patient with LDS requires multidisciplinary cooperation due to many coexisting comorbidities.

P2-18

Central precocious puberty in KBG syndrome due to a rare ANKRD11 variant

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Introduction: Establishing a clear diagnosis in patients with short stature can be challenging. Careful examination and investigation of patients with short stature may identify additional features that help to make a diagnosis or direct genetic testing. We describe a patient with severe short stature with additional features on examination suggestive of KBG syndrome. A subsequent skeletal survey revealed radiological features suggestive of the diagnosis. In addition, the patient developed central precocious puberty (CPP) which has only been rarely reported in cohort studies of patients with KBG syndrome. KBG syndrome is most frequently caused by mutations in ANKRD11. The most significant clinical features include developmental delay, skeletal abnormalities and abnormal facies. We present a patient with a rare mutation in ANKRD11 with typical skeletal abnormalities and CPP.

Case Presentation: A 5-year-old girl was referred for short stature with a background of autism, severe learning disability, sleep disturbance, bilateral hearing loss, constipation and abnormal hand movements. Birth weight was 3.2kg. Height was 96.9cm (-2.2 SDS), weight 14.8kg (+0.2 SDS), BMI 15.8. Maternal height was 150.4cm (-1.6 SDS) and paternal height 160.2cm (-2.2 SDS). Additional features included bilateral clinodactyly, foetal finger pads, broad toes, low hair line, mid facial hypoplasia, short neck, simple ears and macrodontia. Full blood count, urea and electrolytes, thyroid function tests and coeliac screen were all normal. IGF1 was elevated 195microg/L (34-172), although subsequently normalised by age 6 (227microg/L [31-343]). Skeletal survey revealed wormian bones, bilateral cervical ribs, and macrodontia. Bone age was delayed by 2.5 yrs. Genetic testing revealed a previously described de novo heterozygous ANKRND11 variant c.1903_1907del; p.(Lys635Glyfs*26). She then developed into puberty before age 8 years. LHRH test at 8.7 years showed a LH peak 6.3 IU/L, FSH peak 9.3 IU/L, in line with CPP. She commenced on GnRH-analogues.

Conclusion and learning points: ANKRND11 modulates chromatin, thereby affecting growth by increasing P21, a cell cycle inhibitor. The role of ANKRD11 in pubertal development is currently unknown. This case highlights clinical examination and radiological features that direct clinicians towards a diagnosis of KBG syndrome, including macrodontia and costovertebral abnormalities. CPP has been described rarely in patients with KBG syndrome but can be added to features that may help to direct to a diagnosis of KBG syndrome. Other syndromes with short stature and early puberty include Temple syndrome and Williams Syndrome.

P2-19

Gonadotropin and Estradiol levels in Turner Syndrome: does an old dog teach new tricks?

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Background: Hypergonadotropic hypogonadism (HH) is an hallmark of Turner Syndrome (TS) and hormone replacement therapy (HRT) is often required for pubertal induction; this retrospective study highlights the pituitary-gonadal axis during infancy (<5 years), childhood (5–10.9 years) and adolescence (> 11 years) in a cohort of TS patients enrolled between February 1999 to March 2023. Our aim is to underline the diagnostic role of Gonadotropins as a marker of early ovarian failure and to evaluate Gonadotropin's trends by comparing it with a control group.

Methods: We collect measurements of LH (n=587), FSH (n=592) and 17BetaEstradiol (17βE) (n=546) prior to HRT in a cohort of 83 patients with TS [Group A: 45,X0 (n=32); Group B mosaicism (n=19); Group C X-ring chromosome (n=8); Group D miscellaneous karyotypes (n=24)] comparing them with 220 age matched controls. The results are expressed in median (1st – 3rd quartile) and Mann-Whitney U test was performed to compare the values between the groups.

Results: Regarding puberty, 43 patients (51.8%) needed HRT for pubertal induction, 19 (22%) were prepubertal, 10 (12%) had spontaneous puberty (1 Group A, 8 Group B, 1 Group D), 6 (7.2%) needed HRT due to failure to pubertal progression and 5 (6%) for oligomenorrhea after spontaneous menarche.

At the first evaluation [median age 7.4 years (2.9 – 11.4)], FSH and LH were higher in TS than in control group in childood (p <0.001 for each) and adolescence (p=0.003 and p<0.001), while 17βE was lower in adolescence in TS (p=0.008). Considering the whole follow-up, both FSH and LH were significantly higher in the 3 age categories (p=0.004 and p=0.001 in infancy and both p<0.001 for childhood and adolescence) in all of the patients' group except for B. 17βE was lower in adolescence in TS than in control groups (p=0.026).

Conclusions: Measuring LH, FSH and 17βE is an helpful tool to detect early ovarian failure and to diagnose TS; the levels of LH and FSH were significantly higher in the three age categories with a diphasic pattern. We confirm a less-severe Gonadotropins' trend in mosaicism with no differences between controls: in this category, 42% of the patients experienced spontaneous puberty without the necessity of HRT. Classic TS patients have higher peak of LH and FSH than other patients groups and this is related to their ovarian function, lower than other groups.

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P2-20

Temple Syndrome in monozygotic twins with GH and GnRHa treatment in one twin

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Temple syndrome is due to loss of methylation in the imprinted locus 14q32 and is characterised by low birth weight, hypotonia, short stature, early puberty. Adult height is approx -2.0SD. Other features are small hands and feet, premature birth, feeding difficulties, delayed milestones, mild learning difficulty, variable obesity.

We report monozygotic twins diagnosed with Temple syndrome aged 13 yr. Twin 1 received GH for SGA and short stature from age 9.5yrs when his height was -2.7SD, as well as GnRHa for early puberty. Response to GH was good, but pubertal staging at 9.7yrs was P2G2A1 testes 6-8mls, after which puberty progressed quickly. Bone age was mildly advanced at 12.0yrs at a chronological age of 10.8 yrs. GnRHa were started aged 11.2yrs when height was -0.86SD, testes volume was 12/12ml, LH and FSH were 4.1 and 3.2U/L and testosterone 7.6nmol/L.

He was born at 31+2 weeks with mild SGA (1120 g, <10th centile), head circumference 27cm, and undescended testes. He had a difficult start, requiring ECMO, severe hypotonia, laryngomalacia and needed NG feeding. He had camptodacyly, mild learning difficulties and scoliosis requiring rodding. He started Levothyroxine for mild hypothyroidism aged 2 months. Glucagon testing showed a GH peak of 7.6ng/ml, when IGF1 was well in the normal range. IGF1 continued to be in the lower third of the normal range with a low normal IGFBP3. Last auxology at 12.8yrs showed: height 144.8cm (-1.13SD), height velocity 3.1cm/yr, BMI 22.3kg/m2 (+1.60 SD), G3P3A2 testes 8/8-10ml and advanced bone age of 14.0 yrs.

His twin brother was born without SGA, and had no GH treatment. He had bilateral camptodactyly, mild scoliosis and absence of lateral incisors. His pubertal onset was before the age of 10, but he had reduced follow up due to COVID, and was well developed into puberty (P3G3A2 testes 8/10-12 ml) with a good growth spurt (9.7cm/yr) at 11.2 yrs. Bone age was 12.66 yrs at CA 10.8yrs. At 12.8 yrs, his height is 145.8cm (-1.0 SD), heigh velocity 1.9cm/yr, BMI 22.1(+1.5SD), G3P3A2, testes 12-15ml. However, bone age is well advanced at 16.3yrs.

They were entered as a trio in the 100K genome study which revealed no abnormalities. !4q methylation testing was then performed which revealed Temple Syndrome.

In conclusion, Temple syndrome needs to be considered in patients with short stature and additional features. A combination of GH and GnRHa my improve final height.

P2-21

Schaaf-Yang syndrome: Report of two cases

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Schaaf-Yang syndrome (SYS) is a genetic disorder caused by truncating pathogenic variants in the paternal allele of the maternally imprinted, paternally expressed gene MAGEL2, located in the Prader-Willi critical region 15q11-15q13. SYS is a neurodevelopmental disorder that has clinical overlap with Prader-Willi Syndrome in the initial stages of life, being the intellectual disability, developmental delay, autism spectrum disorder, neonatal hypotonia, infantile feeding problems, and distal joint contractures the most consistently shared features of patients with SYS. Endocrine changes include high levels of ghrelin, low IGF1 and growth hormone deficiency.

Here we present 2 siblings, with clinical characteristics of SYS, one of them with a heterozygous MAGEL2 variant.

Case 1: A 6-year-old boy was born within normal weight and height Z score range. Since birth he had facial dysmorphisms, macroglosia, short stature, small hands and short feet, feeding difficulties with requirement of a nasogastric tube; hypotonia, intellectual disability, hypogonadism, temperature instability, obesity and chronic constipation. He then presented behavioral abnormalities. Laboratory results showed a low IGF1 level. A whole-exome sequencing was done in which a heterozygous MAGEL2 variant was detected: c2873G>Ap. (Trp958*) (NM 019066.4).

Case 2: A 4-year-old girl was born within normal weight and height Z-score range. She had the same facial dysmorphisms as her brother, macroglosia,short stature, small hands and short feet, hypotonia and intellectual disability. Laboratory results showed a low IGF1 level.

Conclusion: Our results indicate that testing for MAGEL2 variants should be considered in Prader Willi-like phenotype, as it exists a significant but incomplete overlap between these two syndromes, in order to achieve an early diagnosis of SYS, for genetic counseling, and for early intervention to manage its complex manifestations.

P2-81

Small for age gestational: puberty status, metabolism and growth of an epipeg-premeb clinical cohort at 7-9 years after onset

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Objective: Observe in children born SGA the relationship that the different variables have in the evolution towards metabolic syndrome, adrenarche and/or early/advanced pubarche or short stature and treatment with GH.

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Material and Methods: A retrospective observational study analyzing in SGA children at birth (n=103) and who are currently between 7-9 years of age, variables such as: sex; "Catch Up" at 2 years old and the type; GH treatment; presence of adrenarche and/or early/advanced pubarche ; presence of metabolic syndrome through BMI and other measures such as BP and blood levels of LDL/HDL, insulin, and HbA1. These last values could not be analyzed in all patients, only in those who had performed a measurement or analysis for some other reason (n=1, n=9, n=1, n=1 respectively). Statistical study SPSS 11.0. Study X squared, paired samples. Significance $p<0.05$.

Results: Of the 103 cases collected, 61 are boys and 42 girls. 89 of them (86.4%) performed the catch up before the age of 2, of which 28 (27.2%) were classified as fast catch up. 14 did not catch up (13.6%). At the current age, only one patient has received GH treatment, none has presented signs of adrenarche and/or precocious/advanced puberty and 7 of them (6.8%) have evolved to obesity.

Associating the different variables, a statistically significant relationship has been seen between a catch up before 2 years of age and obesity ($p<0.05$). No significant results have been seen between gender and the other variables ($p>0.05$). It has not been possible to draw conclusions about adrenarche and/or early/advanced pubarche since no case has been registered. Nor could it be seen the relationship between the absence of Catch up before 2 years and the need for GH ($p>0.05$).

Conclusions: Our findings determine that the correct coding of SGA children at birth, a close follow-up of growth and preventing a rapid catch up could prevent the subsequent development of obesity and, therefore, future Sd. metabolic. Probably this result would be even more significant if there were measurements of the rest of the parameters that complete the Sd. metabolic.

In this work we have studied children who are currently between 7-9 years old. It would be interesting to conclude the follow-up of this same group and re-analyze them at the end of puberty, in order to obtain more significant results about the relationship between SGA children and puberty itself.

P2-82

Adipocyte Hormones (Leptin- Adiponectin) Changes and Their Possible Effects on Metabolism, and Immunity During Malnutrition; New Mechanisms of Action

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Background: Adipose tissue plays a central role in regulating whole-body energy and glucose homeostasis through secreting hormones that regulate multiple functions at both organ and systemic levels

Objectives:

Objectives and Methods: We performed electronic literature systematic review using PubMed, Google Scholar, and Web of Sciences with the aim to provide an update on the link between adipocyte hormones and the immune system in infants and children during malnutrition. We reviewed 24 studies (2007-2022) fitting the search criteria.

Results: Low leptin levels have been documented in all studies of children with malnutrition (mild, moderate, and severe). During fasting, leptin levels fall rapidly before and out of proportion to any changes in fat mass. The fall in serum leptin concentration leads to neurohumoral and behavioral changes. Evidence suggests that starvation hypo-leptinemia increases the activity of the hypothalamic-pituitary-adrenal axis, promoting lipolysis, increasing hepatic acetyl-CoA concentrations, and maintaining euglycemia. This function sustains the supply of energy substrates to the brain, heart, and other vital organs. In addition, leptin induces lymphopoiesis and seems to deliver survival signals to T cells. Leptin promotes IFN-γ secretion by memory T cells, inhibits Th2 responses, and induces activation markers (CD69, CD25, and CD71). Leptin enhances the activity of neutrophils by the release of oxygen free radicals and stimulates the migration of the immune through increasing intercellular adhesion molecule-1 (ICAM-1). Leptin activates the monocytes and dendrite cells (DCs) that lead to the production of pro-inflammatory cytokines such as TNF-α, and IL-6 along with IL-12. Leptin also promotes DCs survival by triggering the activation of nuclear factor-kappa B (NF-kappa B). Leptin deficiency in both mice and humans is characterized by a decrease in total lymphocytes, CD4+ helper T cell number, increased thymocyte apoptosis, and a shift from the Th1 toward Th2 phenotype. These changes increase susceptibility to intracellular infections and correlate with several bacterial, viral, and parasitic infections. In undernourished children, leptin level was the most reliable predictor of mortality. Adiponectin is reported to be low during malnutrition. Adiponectin improves insulin sensitivity and enhances lipid and glucose metabolism. It increases fatty acid oxidation in the liver and muscle. The anti-inflammatory properties of Adiponectin are due to its suppression of M1 macrophage activation and supporting M2 macrophage proliferation. It decreases inflammation, apoptosis, and oxidative injury in muscles, heart, and brain.

Conclusions: Low leptin and adiponectin can lead to impaired insulin secretion,decreased insulin sensitivity, encourage inflammation and increase oxidative tissue injury.

P2-83

Therapeutic compliance in 100 children treated with growth hormone

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Context: The outcome of a treatment depends largely on the observance and compliance of the patient. Studies analyzing therapeutic compliance in chronic endocrine diseases are rare and especially controversial in childhood. Studies have reported poor adherence in 6-50% of cases.

Patients and Methods: We studied treatment compliance in 100 children treated with subcutaneous growth hormone for growth hormone deficiency, intrauterine growth retardation

(IUGR), Turner syndrome and idiopathic short stature, followed for at least one year in pediatric endocrinology consultation at the Central Hospital of Army in Algiers. This compliance was assessed by a quiz. The number of missed injections, change of injection site, injection technique, presence or absence of pain and storage conditions were investigated.

Results: Questionnaires were completed in 100 children (52 boys and 48 girls). The average age was 10.98 ± 3.98 years at the evaluation, and 7.26 ± 3.71 years at diagnosis. The mean duration of treatment was 3.26 ± 2.04 years.

The treatment was stored in the refrigerator in 97% of cases. The mother in 46% of cases performed the injection. It was done in 46% of cases in the arms, and the injection site was changed in 95% of cases. Twenty-eight of the children declared that the injection was painful, and this pain was evaluated at 4/10 on average. The number of missed injections was 0.12 times per week, 0.56 times per month and 6.83 times per year. Thirteen % of children admitted that they made a mistake in the dose of treatment, especially when switching from the old pen to the new one. Children maintain the injection for 10 seconds in 89% of cases.

Conclusion: This study demonstrated a good therapeutic compliance of children and their parents, probably in relation to the benefit of the treatment which improved height. Growth hormone treatment is generally well accepted and not very demanding.

P2-84

Two cases of Wiedemann-Steiner syndrome including novel gene mutation

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Wiedemann-Steiner syndrome (WSS) is a rare genetic disease characterized by growth retardation, developmental delay, intellectual disability, facial gestalt, and with or without congenital anomalies. The disease is diagnosed based on suggestive findings and mutation of *KMT2A* gene.

I am presenting 2 cases of WSS including novel mutation of *KMT2*A gene.

Case1: A 10 years old girl visited the clinic due to short stature. She was 127.2cm (2 percentile, SDS -1.89), 31 kg and bone age was same for the chronologic age. (midparental height 166cm) Growth hormone stimulation test confirmed that she had no growth hormone deficiency. Her puberty already began based on breast budding Tanner stage II. She was started growth hormone due to idiopathic short stature. However, she has intellectual disability (IQ 59), history of feeding difficulty until she was 8 years old. She has widely spaced eyes, downslanted palpebral fissures, thick eyebrows, wide nasal bridge, micrognathia and hairy elbow which her parents does not have. Genetic test results c.5701T>C;p.Trp1901Arg of novel heterozygote mutation of *KMT2A* gene. Her parents does not have the same mutation. Echocardiography and brain MRI showed no combined anomaly. She is now treated with HGH which seems to have low effect.

Case2: A 7 years old boy visited the clinic due to recent rapid growth. He was 121.3cm (44 percentile, SDS -0.58), 22.6kg and bone age was 8.9 years old. The volume of testicles is over 4cc each, no pubic hair. He was diagnosed as central precocious puberty after the gonadotropin-releasing hormone stimulation test result showed 10.07 mIU/mL of peak LH level. He showed developmental delay, widely spaced eyes, downslanted palpebral fissures, thick eyebrows, wide nasal bridge and hairy elbow which his parents does not have. He was treated with methylphenidate due to ADHD. GnRH agonist was started for CPP. The brain MRI was normal. Genetic test results p.Arg1081Ter of known pathogenic mutation of *KMT2A* gene. He also developed right inguinal hernia which is high prevalence of WSS.

WSS is usually known as related with short stature. However, I experience also male central precocious puberty patient. When a short stature patient has feature of developmental delay and facial characteristics, we should rule of not only Coffin-Siris syndrome, Noonan syndrome, Cornelia de Lange syndrome, Rubibstein-Taybi syndrome, Kabuki syndrome but also WSS.

P2-85

Challenges in treating delayed puberty in a girl with Marfan syndrome

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Introduction: Marfan syndrome is an autosomal dominant disorder due to a mutation of the FBN1 gene of chromosome 15 that produces fibrillin, a connective tissue protein. Tall stature can be of a major concern especially in a girl patient. Here we discuss a case of a 13-year-old girl with MFS with tall stature and multiple associated comorbidities that pose challenges in her management for the whole family.

Case Report: A 13-year-old girl, a known case of MFS from a family of MFS with her mother and younger 8 years old sister also been affected. She also had multiple associated cardiac comorbidities: mitral Valve prolapse, aortic root dilatation with premature ventricular contraction, myopia, scoliosis, and severe pectus excavatum, referred to endocrine for a delayed puberty and tall stature. On a previous assessment, the patient was treated by a relatively high 0.625 mg conjugated estrogen daily dose for 7 months that did not slow down her growth velocity, neither, resulted in breast development. A high dose of 1.25 mg once daily was then tried that resulted in a withdrawal bleeding alongside alternate doses of 10 mg PO progesterone, On examination her height was 178 cm (> 97th centile). She had severe chest deformity and prepubertal Tanner staging of breast development. Bone age assessment had shown appropriate skeletal maturation. Her mother, as well as younger sister, both had normal progress of puberty and breasts development. Mother attained menarche at 13 years of age.

Discussion: Patients with MFS present with tall stature, cardiovascular, ocular and other systemic findings. Delayed puberty is not a common encounter in MFs. After an initial assessment of our patient, the possibilities were true versus peripheral delayed puberty. GNRH Stimulation test confirmed central puberty. It is possible that the patient has estrogen resistance giving a history of failure of response to high doses of estrogen in terms of breast development and vaginal bleeding as well as continuing to grow. We also thought of amastia, a rare anatomical abnormality with absent breasts.

Conclusion: A major concern of stopping further height gain can be challenged by a superadded problem of possible estrogen resistance. In the same time, using high doses of estrogen may risk clinical outcome in MFS with cardiac complications awaiting surgery.

P2-142

Wolf-Hirschhorn syndrome: severe short stature and growth hormone deficiency

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Introduction: Wolf-Hirschhorn syndrome (WHS) is a rare congenital disorder occurring in approximately 1/50.000 births, with a 2:1 femaleto-male predominance. It results from the hemizygous deletion encompassing the 4p16.3 region. The typical craniofacial phenotype is described as a « Greek warrior helmet appearance ».

Case Report: A 5-year-old boy is brought to the pediatric endocrinology consultation for short stature. He was born at term to a non-consanguineous couple with intrauterine growth retardation. Follow-up for epilepsy and put on background treatment for 2 years. The clinical examination objectified a particular craniofacial phenotype, namely: a wide nasal bridge, microcephaly, a high forehead and prominent glabella, hypertelorism, a nose with straight and parallel edges, a thin upper lip and drooping corners, a small chin and micrognathia. Examination of the genitals found hypospadias with cryptorchidism. In addition, there is mental retardation, poor language and severe retardation of height and weight. Bone age corresponded to a delay of 3 years. The rest of the somatic examination is unremarkable apart from a hemangioma. IGF1 level was low with a GH peak at < 7ng/ml on stimulation tests. Cerebral MRI was without abnormalities.

Discussion: For our patient, the genetic study was made objectifying: 46,XY ish dell (4) (p16.3p16.3) (WHSCR-) thus confirming the diagnosis. Genetic counseling is desirable. Paraclinical exploration in search of other malformations or associated anomalies returned to normal. Given the severe short stature with a confirmed GH deficiency, treatment was started.

Conclusion: WHS diagnosis is based on physical examination and confirmed by molecular genetics or cytogenetic analysis. Most cases are sporadic, but an unbalanced translocation can be inherited from a parent with a balanced rearrangement. Treatment is symptomatic and requires a multidisciplinary approach.

P2-143

Improving detection of rare overgrowth syndromes referred to the endocrinology ward for analysis of acromegaly

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Background: In our center for adults with rare genetic syndromes, we see adolescents and young adults with overgrowth syndromes, among others. In our 'general endocrinology' outpatient clinic, we also see patients with overgrowth, but in these cases the overgrowth is due to excess of growth hormone (GH). Our clinical impression is that the differentiation between the two is often challenging. Therefore, we believe it is important to emphasize the differences between the two, in order to improve recognition of overgrowth syndromes (OS) among general practitioners, internists and pediatricians. Whereas patients with acromegaly benefit from endocrine treatment, OS patients need multidisciplinary care due to the associated organ and hormone problems and neuropsychological phenotype. Therefore, it's crucial to refer patients with OS for multidisciplinary care once acromegaly is ruled out. Unfortunately, this is often not done. We provide a systematic approach to guarantee appropriate care for this vulnerable and complex patient group. Even though this approach is focused on adults, increasing awareness of overgrowth syndromes amongst pediatricians is of even greater importance since appropriate diagnosis and care earlier in life prevents health problems in adults.

Methods: We present a case series of adult patients visiting our outpatient clinic for 'acromegaly', from presentation to diagnosis. We describe the diagnostic challenges and illustrate the added value of multidisciplinary treatment, initiated once patients were diagnosed with overgrowth syndromes. Additionally, we conducted a systematic review of the literature on overgrowth syndromes.

Results: The patients presented with acromegaloid characteristics without growth hormone/IGF-1 axis abnormalities. Endocrine and genetic work-up ruled out acromegaly and revealed mutations in CHD8. Neuropsychological assessment revealed a mild intellectual disability in one of the patients, which had remained unnoticed for years due to relatively strong verbal performance. To initiate ID support, the patient was referred to the physician for intellectual disabilities.

Based on our own expertise in combination with the existing literature, we made an algorithm to improve diagnostics and management of adults with overgrowth syndromes. Multidisciplinary care is often necessary due to the physical and neuropsychological problems associated with some overgrowth syndromes.

Conclusions: When a patient presents with acromegalic features in the presence of normal IGF-1, the diagnosis of overgrowth syndromes should be considered as underlying condition. As overgrowth syndromes may be associated with neurodevelopmental delay, we recommend to screen for mild ID and refer patient for multidisciplinary management to prevent the complications of undiagnosed ID.

P2-144

Beyond the surface: A Tale of Uncovering the True Diagnosis

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Introduction: In a large series, approximately 65% of boys with delayed puberty have constitutional delay in growth and puberty (CDGP). We report an adolescent male who presented with delayed puberty and managed as presumed CDGP. Unexpected pubertal progression while receiving treatment made us question the diagnosis of CDGP.

Case-report: A 15-year-old African adolescent male presented with delayed growth and puberty. He reported development of minimal pubic hair, no deepening of voice and no growth spurt. There was no associated history of headache, visual disturbances, anosmia or synkinesis. He had left proximal radioulnar synostosis and was Haemoglobin-C carrier. He attended mainstream school without additional help. His father also had delayed onset of puberty. On examination, his height and weight were between 9th-25th centile (midparental height 50th centile). Clinical examination showed no dysmorphic features or gynecomastia, prepubertal testes (2ml) with genitalia stage 1 and pubic hair stage 2. Investigations showed normal renal, liver and bone profile, and negative coeliac screen. Endocrine investigations showed normal thyroid function, insulin-like growth factor-1, and serum prolactin. Basal serum gonadotropins (LH <0.8IU/L, FSH 2.6IU/L) were pre-pubertal with low serum testosterone (0.3nmol/l). Bone age was delayed (12.6 years TWII). Probable diagnosis of CDGP was considered and treatment started with monthly testosterone injections. COVID-19 restrictions prevented regular pubertal assessment. No significant increase in testes volumes by 16.67 years (4ml testes after 18months of testosterone injections) resulted in MRI pituitary and olfactory bulbs, which was normal. Continued absence of increase in testes volume by 17.42years led to further investigations after interruption of testosterone injections (LHRH stimulation test and molecular genetic testing for hypogonadotrophic hypogonadism). An exaggerated LH/FSH response on LHRH stimulation test (LH 5.1 – 72 - 66U/L; FSH 8.9 - 17.9 - 22U/L) and early afternoon serum testosterone (7.4nmol/L) off testosterone injections in the presence of small testes made us consider the diagnosis of Klinefelter syndrome (KS). Subsequent comparative genomic hybridisation (CGH) array identified two copies of X chromosome and one copy of Y-chromosome in approximately 35% of cells, confirming mosaic KS.

Conclusion: Klinefelter syndrome is a profoundly underdiagnosed condition. Approximately 25% of adult males with KS are ever diagnosed. Mosaic KS is even rarer contributing to 15 - 20% of KS patients and requires a high index of suspicion. Regular assessment of testicular volumes until mid-late pubertal testicular volumes are achieved is vital in the management of adolescent boys with presumed CDGP.

P2-194

Impact of Undernutrition and Short Stature on The Quality of Life (QOL) in Children and adolescents with Beta thalassemia Major (BTM)

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Introduction: Quality of life (QoL), comprises physical, psychological, environmental, and social aspects, is an index designed to measure the burden of chronic diseases and evaluate the treatment outcome. Thalassemia major (BTM) is a chronic disease in children that harms children QoL by interrupting physical function, emotional function, social function, and school function. Objectives

Aim: This study aims to identify the link between nutritional status and QoL among children and adolescents with thalassemia major.

Methods: We reviewed the articles used three databases including Pubmed, Google scholar and Science Direct, and NCBI with Keywords: "quality of life" AND "children" AND "thalassemia major" AND "malnutrition" AND "BMI". The articles of the past 20 years were included.

Results: Out of 25 articles addressing QoL only 4 articles addressed the nutritional status in relation to QoL and were reviewed according to the inclusion criteria.

All the studies showed that the prevalence of Malnutrition and/or low BMI is considerably high in patients with BTM. In the 4 studies, (n = 676 children and adolescents) the score of QoL among patients with BTM was lower than that for healthy control children. In an Indian study, on 328 children with BTM, multiple linear regression analysis revealed that malnutrition negatively impacted total QoL (unstandardized beta [standard error], -4.4 [1.7]; P=0.009) as well as the physical and emotional domains of QOL adjusted for age, sex, place of residence, parents' educational level, and socioeconomic status. In two controlled Egyptian studies on 127 and 64 thalassemic children respectively, thalassemic children with significantly lower BMI, BMISDS and Height SDS had significantly decreased total (Physical, emotional social and school QoL) compared to healthy controls. Household income and high serum ferritin were statistically significant predictors for poor emotional and social QoL respectively. A study from Sri Lanka showed that thalassemic patients with undernutrition (n= 157) had lower total, psychological and school QoL scores compared to thalassemic patients with normal nutrition (n = 85). In these studies, factors that possibly contributed to decreased QoL and nutritional status in children with BTM included low household income, parents' education and efficiency of transfusion and iron chelation.

Conclusion: regular anthropometric and nutritional assessment and appropriate nutritional interventions should be incorporated into the therapeutic plans for thalassemic patients to improve their growth status and QoL.

P2-195

Morbid obesity revealing a rare genetic disease

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Introduction: Prader-Willi syndrome (PWS) is a rare genetic disease characterized by hypothalamic-pituitary dysfunction associated with major hypotonia during the neonatal period. In childhood, the main problems are the appearance of hyperphagia with the risk of morbid obesity, learning difficulties and behavioral disorders. It concerns one case in 25.000 births.

Observation: A 15-year-old boy from a non-consanguineous marriage. Referred to our specialist consultation for management of severe obesity. Parents report the notion of hyperphagia with lack of satiety. The clinical examination revealed: almond-shaped eyes, thin upper lip and drooping corners of the mouth with abdominal obesity as well as impuberism. In addition, we note a metabolic syndrome retained according to the criteria of the IDF 2007. The rest of the biological and hormonal assessment was without abnormality. Abdominal ultrasound was normal. The genetic study was able to confirm the diagnosis.

Discussion: There is now a consensus among experts on the fact that the diagnostic suspicion of PWS is clinical (criteria of Holm et al. from 1993, reviewed in 2001) and its confirmation is genetic. It is due to an abnormality of chromosome 15 (15q11-q13). These genetic abnormalities are often accidental and sporadic and familial recurrence is very rare.

Conclusion: PWS requires comprehensive and multidisciplinary care. The use of growth hormone transformed the quality of life of these children. The metabolic syndrome in our patient is a real vascular risk factor and its management must involve healthy eating habits as well as physical activity.

P2-196

A case of ACAN mutation: from onset to final stature

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Short stature is a frequent disorder in the pediatric population caused by multiple possible reasons. One of them it can be the mutation of the ACAN gene, with an autosomal dominant transmission, which also correlates with accelerated bone maturation and early osteoarthritis up to bone dysplasia.

A 10.8-year-old patient came to our observation for poor statural growth (125.8 cm, -2.6 SDS) with a parental target of 150.4 cm +/- 8 cm (-2 SDS), on Triptorelin braking therapy, since she was ten years old, for central precocious puberty (CPP) diagnosed by another center. She was born full-term from regular pregnancy with eutocic delivery (birth weight 3.3 kg, length 46 cm, head circumference 36 cm; AGA); psychomotor development was normal and statural growth was always on the lower centiles for sex and age. Our patient had positive family history for short stature (maternal lineage and younger sister). At the first visit the objective examination showed B1 PH 2 of pubertal stages (Tanner Scale), vitiligo, plantar flatness, mild frontal bumps, alonate eyes, flat nasal filter, stubby fingers and toes, thickened articulation between I and II metacarpals and macrocephaly. In subsequent follow-up bone pain occurred (especially at knee level) and it was subsequently diagnosed as osteoarthritis.

Several investigations were performed, among which serial first-level blood checks with assessment of IGF-1 (in normal range), Arginine stimulation test for GH (negative), hand x-ray (bone age and chronological age matched); MRI of the hypothalamic-pituitary axis (normal); karyotype analysis (46 XX), SHOX gene analysis (no alterations), genetic analysis for Noonan syndrome (negative) and Ehlers-Danlos syndromes (negative; but it was positive in her dad and in her sister), NGS panel for short stature was positive for variant in exon 12 of ACAN gene (pathogenic feature).

Biosynthetic growth hormone therapy was administered, after Regional Commission approval, from when she was eleven to when she was sixteen, obtaining a constant good growth velocity. She continued therapy until reaching her final stature of 146.6 cm (1°; SDS -2.5 with a statural gain of -0.23 SDS from the start of GH treatment and 0.35 SDS from the interruption of braking therapy) with complete bone maturation, confirmed by hand x-ray. Bilateral osteoarthritis dissecans was treated with surgery and it is currently in orthopedic follow-up.

P2-222

Height control using estradiol valerate considering chronological and bone age in patient with Marfan Syndrome

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Introduction: Estrogen treatment can be used for pediatric patients with Marfan syndrome who wish to control the rate of excessive height growth. However, the appropriate timing of treatment initiation is controversial and studies were limited. In this study, the authors aimed to find out when the initiation of estradiol therapy is most appropriate for controlling height growth rate in patients with Marfan syndrome.

Methods: This study was a retrospective study targeting patients who started estradiol treatment for height control between 2000 and 2020 and completed the treatment within this period. Before the start of treatment, the expected final height was first calculated through the growth curve and bone age suitable for the patient with Marfan syndrome. After treatment with estradiol valerate, the height at the end of treatment was compared with the height predicted before the start of treatment. The difference between actual height and predicted height was analyzed according to the time fo treatment initiation.

Results: There was a significant difference between predicted height according to chronological age and bone age before treatment and actual height after treatment, based on the age of 10.5 years at the start of treatment. When treatment was started before the age of 10.5 years, the actual height was 10.6 cm (interquartile range [IQR] 10.2, 13.5) smaller than predicted by the growth curve and 10.1 cm (IQR 7.31, 11.42) smaller than predicted by bone age. On the other hand, when treatment was started after 10.5 years of age, the difference between the final height and the height predicted through the growth curve was 0.6 cm (IQR -3.65, 5.85), and the difference between the height predicted through bone age was 3.83 (IQR 0.84, 6.4).

Conclusion: When a pediatric female patient with Marfan's syndrome wants to adjust her height, treatment with estradiol should be performed before reaching the age of 10.5 to expect a great effect.

P2-223

The Impact of Different Karyotypes on the Response to Growth Hormone Therapy in Girls with Turner Syndrome

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Background: Short stature is the most common clinical feature in patients with Turner syndrome (TS). The relation of different karyotyping to growth hormone (GH) level in provocation tests or to the response to GH therapy is debatable.

Aim: to study the impact of different karyotypes on the GH level in provocation tests and on the response to GH therapy among a cohort of Egyptian girls with TS.

Patients and Method: This is a cohort non concurrent study conducted on 60 girls with confirmed TS by peripheral blood karyotyping. The included girls either were receiving or had finished GH therapy. The following data were extracted from the patients' medical files; the age at onset and duration of GH therapy, annual changes in the height standard deviation scores (SDSs), GH dose, and the results of GH provocation tests by either by insulin or clonidine. Mid parental height (MPH) and predicted adult height (PAH) have been estimated. All cases have been examined for the phenotypic characteristics of TS. Investigations included thyroid function, pelvic US, abdominal US, ECHO have been done.

Results: The mean age of included girls with TS was 13.24±2.99 years. They started GH therapy at mean age of 10.81±3.03 years with a median duration of GH therapy of 4.5 (1-7) years. The frequency of karyotypes were 50% (45, X), 26.7% (46, X, del (Xp-), 16.7% (46,X,i[Xq10]) and 6.7% other karyotypes. GH deficiency was detected in 73.3% (44 out of 60) of girls with TS with different karyotypes. The highest response to GH therapy were detected in the 1st year of therapy with mean height increment 7.0±2.03 cm/year and decline thereafter with no significant difference in relation with different karyotypes (P=0.277).

Conclusions: GH deficiency was the most frequent result of provocation tests among different TS karyotypes. There was no significant difference in height increments in relation to different karyotypes in girls with TS under GH replacement therapy.

P2-230

Silver-Russell Syndrome: knowing how to think about it

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Introduction: Silver-Russell Syndrome (SRS) is a rare genetic disease with an estimated prevalence of 1/100,000. It is characterized by the association of severe intrauterine growth retardation, postnatal failure to thrive, particular facial dysmorphism and asymmetry of the limbs. SRS is a pathology of parental imprinting. It is dependent on several imprinted genes, acting through different molecular mechanisms.

Case Report: A 30-month-old female child is brought to the pediatric endocrinology consultation for short stature. She was born at term to a non-consanguineous couple with intrauterine growth retardation and feeding difficulties from birth, requiring prolonged nasogastric feeding. The current clinical examination has objectified a delay in psychomotor development with severe growth retardation: weight at -4.6 Zs, height at -3 Zs, BMI at -4 Zs and relative macrocephaly +1.6 Zs. A prominent forehead, a slightly triangular face, muscle tone less than expected for his age and no obvious asymmetry of body or limbs noted. The rest of the somatic examination is unremarkable. Bone age corresponds to a delay of 1 year.

Discussion: SRS is a clinical diagnosis, based on the presence of at least 4 signs out of 6 of the Netchine-Harbison score (NH-CSS). Molecular testing can confirm the clinical diagnosis and molecular stratification can help guide management. Apart from the persistence of short stature and weak build, the long-term prognosis is good. The genetic counseling is possible.

Conclusion: SRS is a multi-system disorder and requires a specialised multi-disciplinary team for optimal management. Nutritional management is a key aspect from diagnosis throughout childhood. Growth hormone therapy is indicated for SRS, usually starting at 2–4 years old to improve height during childhood and final height prognosis.

P2-231

Growth hormone treatment of short SGA children – experience of tertiary clinic in Bulgaria

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Introduction: Fenton (2013) defined small for gestational age children (SGA) as born with birth length and/or weight < 10th percentile for the corresponding gestational age, and clinicians use it ever since. According to the literature, 1 of 10 children born SGA does not catch-up in growth. Wit (2021) suggested to address them as short SGA children. Recombinant human growth hormone (rhGH) treatment in those children have been approved by the FDA in 2001 and two years later by EMA. Unfortunately, in some countries this treatment is still not reimbursed by the health care system, and growth outcomes data is needed.

Aim: The aim of the current study is to analyze age at start, duration, and the efficacy of rhGH treatment in short SGA children.

Patients and Methods: After receiving approval by the Ethical Committee of the Medical University of Varna, written consent from the patients was collected. All patients who were patients of the center at 31.12.2021 and were rhGH treated, were included. Data about baseline, 1st and 2nd year growth indices were retrospectively extracted from the clinical records and analysed. All parameters of interest were assessed, using SPSS by Windows, version 25.

Results: A total of 43 short SGA children were included in the current study, 26 (60.5%) of them rhGH treated with starting dose of 0.029±1.94 mg/kg/d. The average age at the commencement of rhGH in the treated group was 6.57±3.67 years. The ratio between boys and girls was 15:11. The most common clinical diagnosis was the Silver-Russell Syndrome (SRS) presenting with 15 patients (57.7%), followed by short SGA (5 patients, 19.2%), cleidocranial dysplasia (2 patients, 7.7%). Some of the other patients were with DiGeorge syndrome, Noonan syndrome, Löwe syndrome, and others. On the average, the treatment duration was 3.61±2.58 years. The average growth velocity for the first year was 9.49 ± 2.63 cm and for the 2nd year of treatment was 6.8±2.01 cm. Respectively height improved with 0.57±0.46 SDS for the first year and with 1.63±1.01 SDS for the 2nd year. The weight in our cohort increased with 0.94±1.21 SDS for the first year of the treatment and with 0.36±0.45 SDS for the 2nd year.

Conclusion: The presented patients started treatment relatively late and with lower rhGH doses than the recommended for the SGA indication. These are potential targets for the improvement of future treatment outcomes.

Multisystem endocrine disorders

P2-1

Prevalence of Malnutrition and Underweight in Children and Adolescents with Beta-Thalassemia Major (BTM)

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Introduction: Blood transfusion and iron chelation are conventional treatments for β-thalassemia (BTM). Malnutrition affects the growth, efficacy of treatments, and quality of life in children suffering from BTM.

Objective: To evaluate the prevalence of malnutrition (BMI < 3rd centile for age and sex) or BMISDS < -2 in 10 Mediterranean and Middle east countries and the USA in the past 20 years.

Methods: We performed an electronic search in PubMed, Google Scholar, and Web of Sciences to evaluate the prevalence of malnutrition in children and adults with BTM

Results: Twenty studies were included from 14 Mediterranean and Middle East countries after 2000.

The total number of patients was 5554, (2036 children and 3518 adults) reported from 10 countries (Greece, Turkey, Pakistan, India, Thailand, Bangladesh, Egypt. Iran, Iraq, and the USA).

In children with BTM, malnutrition prevalence varied significantly from 7.8% in the USA to 74% in Iran. In adults with BTM, the prevalence of malnutrition varied from 5.2 % in the USA to 74.5% in Thailand. The pooled prevalence of malnutrition in children was 42.1% and for adults was 35%. The overall pooled prevalence In adults and children with BTM is 40.1%. The prevalence of malnutrition was significantly higher in children versus adults with BTM and in lower-income countries versus middle and higher-income countries.

Discussion: The results of this study show that malnutrition, especially underweight is prevalent in thalassemic children, adolescents, and adults. The nutritional status of thalassemic varies greatly in different countries and appears to be related to their nutrient intake of macro and micronutrients. Therefore, nutritional interventions and nutrition education can play important roles in achieving normal growth and quality of life in thalassemic children and adolescents. Evidence showed that stunted growth is related to underlying malnutrition or irregular frequency of blood transfusions or compliance to chelation therapy

Conclusion: It appears that regular nutritional assessment, improving the dietary intake, and correction of macro and micronutrient deficiencies can markedly improve nutritional status and linear growth in patients with BTM.

P2-2

Genetic test is useful in diagnosing nephrogenic diabetes insipidus

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Background: Congenital nephrogenic diabetes insipidus is a rare disease that is sometimes diagnosed after failure to thrive or febrile illness during infancy. Long-term habitual polydipsia to compensate for polyuria is sometimes difficult to distinguish from habitual polydipsia and polyuria or compulsive drinking.

Case: The case is a 10-year-old girl. Her father was diagnosed as having congenital nephrogenic diabetes insipidus (CNDI) at the age of 12 (details unknown). At her birth, the parents were told from the obstetrician that CNDI was X-linked inheritance and female would not show any symptoms, thus both parents did not pay attention on CNDI although the child has been showing polydipsia, polyuria, and fever. Her mother, however suspected dehydration and urged her drinking water; her fever subsided. Her water intake increased to 3-4L /day from around the age of 1 to 2 years old, and had 2 to 3 times urination during night. She was referred to us for further workup when she was 10 years old. During hospitalization, her ad lib total fluid intake and urine output was about 4 L/day. Her abdominal ultrasonography revealed right hydronephrosis (SFU grade 2). Her urine specific gravity was 1.001 and a urine osmolarity 75 mOsm/L. Plasma AVP level was 3.8 pg/ml. Water deprivation test was performed and plasma osmolality reached to plateau at 282 mOsm/L with partial concentration of urine (urine osmolality of 429 mOsm/L at the 7th hour) of along with a weight loss of -1.4 kg (4.8%). In the subsequent Pitressin loading test, the increase in urine osmolality was only up to 453 mOsm/L. In order to exclude abitual polydipsia from partial NDI, genetic test was performed and pathogenic heterozygous variant in AQP2 gene (721del) was found, which confirmed the diagnosis of NDI.

Discussion/Conclusion: We report the familial case with NDI. The clinical manifestation was moderate in proband and the diagnosis was delayed. Partial urine concentration was observed in water deprivation test, which could be observed in habitual polyuria and polydipsia. Given these ambiguous clinical findings, genetic testing was essential to confirm the diagnosis of NDI.

P2-86

Consequences of Hypogonadism and Potential Benefits of Sex Steroid therapy (HRT) in Children and Adolescents with Beta Thalassemia Major (BTM)

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Introduction: A recent review from 14 Mediterranean and Middle East countries (n =4477, mean age = 16.5 years) showed that the pooled prevalence of delayed puberty / hypogonadism in patients with BTM was 45.6%.

Objectives: We reviewed the literature (Pubmed, Google scholar, Scopus, Research gate) (1995: 2022) on the consequences of hypogonadism and benefits of Sex Steroid therapy (HRT) in children and adolescents with BTM. 26 papers were included and analyzed.

Results: (table)

Conclusion: Proper and wise use of sex steroid therapy in patients with BTM significantly improved many consequences of hypogonadism.

Consequences of Hypogonadism in BTM	Potential Benefits of Sex Steroid therapy
Osteopenia and osteoporosis. The prevalence of osteoporosis and low bone mineral density (BMD) in BTM patients varies. The highest rate is 40-72% depending on age, studied parameter. Hypogonadal (untreated) BTM patients had the lowest BMD and the highest BMD were observed in patients on continuous HRT.	HRT can maintain BMD in BTM patients, with significant improvement of BMD Z score in thalassemic females who received HRT for around 5 years. The BMD values increased during the first 2-3 years of HRT treatment by (7.7% at lumbar spine and of 8.9% at femoral neck).
Short stature (disproportionate) 74 studies showed a pooled prevalence of short stature = 48.9%. Etiology: Disturbed GH-IGF1 axis, loss of pubertal growth spurt, and nutritional.	Low dose sex steroid therapy priming (6-12 months) induced pubertal maturation and increased growth spurt and final adult height in 80% of BTM adolescents.
Delayed/absent puberty, primary amenorrhea (PA) (47%) and secondary (SA) (23%) were reported in BTM.	50% of BTM females with PA respond to 2-3 years of sex steroid treatment with a mature uterus and endometrial thickness. 45.2% had partial response and 4.8% failed to respond.
Decreased muscle mass (MM) and strength Decreased libido Decreased Quality of life (QOL) BTM adolescents had poor perception of their general health and scored significantly lower in all the subscales compared with the controls. The high prevalence of short stature and pubertal delay was associated with lowest scores for physical and psychological domains	HRT can increase MM and strength Increase libido and erectile function Improve QOL: A metanalysis confirmed the broad and sustained benefits of TRT across major QOL dimensions, including sexual, somatic, and psychological health, which were sustained over 36 months in the HRT treatment cohort

P2-87

Undernutrition, abnormal body composition, and impaired linear growth in children and adolescents with Beta-Thalassemia Major: possible contributing factors

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Introduction: Blood transfusion and iron chelation are conventional treatments for β-thalassemia (BTM). Malnutrition negatively affects their growth, efficacy of treatments, and quality of life.

Objective: To evaluate the nutritional status and linear growth in 10 countries in the past 20 years.

Methods: We performed an electronic search in PubMed, Google Scholar, and Web of Sciences to evaluate the prevalence of malnutrition in children and adults with BTM

Results: Ten studies were included from 10 Mediterranean and Middle East countries after 2000. The total number of patients was 2036 children reported from 10 countries (Greece, Turkey, Pakistan, India, Thailand, Bangladesh, Egypt. Iran, and Iraq). Undernutrition (Low WAZ, low BMIZ, low WLZ) occurred in a considerable number of children and adolescents (42.2%). The prevalence varies greatly among different countries (from 20% to 71%). This great variability can be explained by the income/nutritional status of each country. The developing (lower middle income) countries (India, Pakistan, Iran, Egypt) had the higher prevalence versus the high -middle and high income (Turkey, Greece). In addition, abnormal body composition including reduced muscle mass, lean body mass, and Bone mineral density (osteopenia) occurred in BTM patients even those with normal BMI. Thalassemic children and adolescents had low levels of circulating nutrients which signifies either nutrient excretion or loss, or higher micronutrient requirements. The energy intake appears to be low (65 to 75% of the RDA) in a good number of these patients. They have a high prevalence of vitamin D, alpha-tocopherol, retinol, zinc, selenium, and copper deficiencies versus controls. Being Underweight is associated with short stature in a good number of thalassemic children and adolescents. Underweight and short stature can be explained by many contributing pathologies. These include poor transfusion regimen (tissue hypoxia), poor chelation with iron toxicity, high prevalence of endocrinopathies (disturbed GH-IGF1 axis, low insulin secretion and/or insulin resistance, delayed or absent puberty, reduced physical activity, lack of maternal education, and psychosocial stress.

Conclusions: In thalassemic children and adolescents nutritional stunting and change in body composition can partially result from reduced nutrient intake. Proper blood transfusion and effective chelation therapy, in addition to nutritional surveillance and support, are important to maintaining normal linear growth and weight gain.

	Low BMI	Short stature
Greece	34.30%	ND
USA	5.20%	ND
Turkey	31%	24%
Iraq	ND	36.20%
Pakistan	42%	65%
India	48%	33.10%
Bangladesh	62.40%	ND
Thailand	71%	ND
Egypt	20%	33%
Iran	60.40%	52%

P2-88

A glimpse of the presentation of Pseudohypoparathyroidism in children.A Case series from a tertiary care Pediatric Endocrine center in Sri Lanka

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Background: Pseudohypoparathyroidism (PHP) is a condition primarily caused by impaired hormonal signaling through the stimulatory G protein (G2 alpha) for the activation of adenyl cyclase, which is coupled to G protein receptors(1). This occurs due to the molecular defects in the receptors related to the alpha subunit. (1–3). The condition results in resistance to Parathyroid hormone (PTH) and other hormones. Less than 60 cases have been reported worldwide up to December 2016(1) as the condition is rare. Pseudohypoparathyroidism is a spectrum characterized by abnormal physical characteristics, neurocognitive impairment, and multiple endocrine abnormalities. Young children may remain asymptomatic, and disease may manifest in mid or late childhood along with the growth(1). Several subtypes of pseudohypoparathyroidism are being described in the literature. We describe 8 patients diagnosed with PHP and followed up in the endocrinology clinic at Lady Ridgeway Hospital for Children Sri Lanka.

Case Presentation: Patient 1 presented with hypertension and short stature. Patients 2-5 presented with hypocalcemia. Inpatient 2 hypocalcemia was incidentally detected on routine investigations. Patient 3 presented with carpopedal spasms and patients 4 and 5 presented with hypocalcemia seizures. Patients 6-8 were evaluated for short stature. At presentation 3 of them were diagnosed with hypothyroidism during the neonatal period or early infancy. The age of diagnosis ranges from 7 months to 10 years. All the patients were diagnosed on the basis of the clinical criteria as genetic testing is not available in the country.

Patient	Corrected Ca(mmol/l)	P(mmol/l)	ALP(IU/l)	PTH (pmol/l) (1.6-7.9)	Vitamin D nmo/l (50-120)	Other
1	2.5	1.54	254	138	77	AHO, brachydactyly, advanced bone age, hypertension
2	1.68	1.8	287	122	55	
3	1.6	1.77	321	135.6	43	
4	1.31	2.1	258	170	65	Developmental delay, advanced bone age, AHO, brachydactyly
5	1.6	1.9	276	154	84	TSH resistance, GH deficiency, AHO, brachydactyly.
6	1.7	1.97	322	165	53	TSH resistance. AHO
7	1.84	2.3	265	174	62	TSH resistance, GH deficiency, AHO, brachydactyly, advanced bone age
8	2.45	2.1	248	68	48	AHO, Brachydactyly, advanced bone age

Conclusion: Pseudohypoparathyroidism is an important diagnosis that needs high clinical suspicion as the clinical symptoms evolve with time and have a wide spectrum in presentation. The diagnosis can be made clinically. Genetic testing is important in subclassification and counseling. These patients should be referred to a Paediatric endocrinologist for further evaluation and management.

P2-89

Autoimmune polyendocrine syndrome type 1 (APECED): Case report

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Introduction: Autoimmune polyendocrinopathy type 1, or APECED syndrome (Autoimmune Polyendocrinopathy Candidiasis EctodermalDystrophy), is a genetic disease with a juvenile onset, associating chronic mucocutaneous candidiasis, hypoparathyroidism and adrenal insufficiency of autoimmune origin.

It is a rare disease, more common in certain populations due to inbreeding or a founder effect such as in Finland where its prevalence has been estimated at 1/25,000.

Case Report: We report the case of a 9-year-old child from a consanguineous marriage referred at the age of 2 for treatment of severe dehydration which required treatment in an intensive care unit, the clinical examination objectified a thrush and onychodystrophy and a bilateral cataract, the assessment revealed a salt loss syndrome and hypocalcemia, the exploration was completed by a hormonal assessment which returned in favor of adrenal insufficiency and hypoparathyroidism. In front of this association the diagnosis of APECED syndrome was retained,treated with glucocorticoids; Alfacalcidol; calicium syrups and fluconazol ,during the evolution of his disease the patient presented at the age of 8 years a diabetic ketosis put under insulin and a bilateral keratitis.

Comment: APECED syndrome is a rare disease, of autosomal recessive transmission, linked to a mutation of the AIRE gene, located in 21q22.3. This gene codes for the AIRE 1 protein, a transcription factor, which plays a role in central thymic self-tolerance and in the periphery in the regulation of T lymphocyte activation by dendritic cells. The diagnosis of APECED syndrome was not confirmed in the case described by the mutation of the AIRE gene but in the face of clinical signs suggestive of the syndrome, in particular chronic mucocutaneous candidiasis and polyendocrinopathy associated with keratitis.

Conclusion: APECED syndrome is a rare and difficult to diagnose condition due to its very polymorphic nature. Its clinical expression must be known to allow early detection and treatment of its various components, some of which are likely to be life-threatening.

P2-90

Autosomal dominant hypocalcemia: A diagnostic and therapeutic challenge

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Introduction and Aims: Autosomal dominant hypocalcemia or type V Bartter syndrome is characterized by hypocalcemia, low parathyroid hormone (PTH), and calciuria, which marks its prognosis due to the risk of nephrocalcinosis. It is caused by activating mutations in the calcium-sensing receptor (CASR) gene (3q21.1), which is expressed in the parathyroid and renal tubules, causing salt and potassium loss, due to the inhibition of the ROMK and NKCC2 channels. We show an early-onset refractory hypocalcemia case with polyuria and hypokalemia, in order to disseminate its knowledge.

Clinical Case: We show a 22-day-old neonate with generalized tetany, irritability and seizures due to severe hypocalcemia: 6.4 mg/dl, hyperphosphatemia: 10.7 mg/dl, hypomagnesemia: 1.2 mg/dl, undetectable PTH, normal levels of calcidiol: 27 ng/ml and elevated levels of calcitriol: 86 pg/ml. He also showed metabolic acidosis and hypokalemia. In order to stop seizures, he required bolus and continuous intravenous infusion of calcium gluconate associated to phenobarbital. During his evolution because of persistent hypertonia instead of intravenous calcium, he required low phosphorus diet and supplementation with magnesium, oral calcitriol, acetazolamide, hyperhydration and furosemide. With all of this, he got stabilization of calcium and phosphorus levels, and he could advance to oral treatment with calcium, magnesium, and calcitriol. But he also needed to associate calcidiol because of a new seizure. In addition, he had a tendency to hypokalemia and moderate hypercalciuria, so we added hydrochlorothiazide, spironolactone and high fluid intake to treatment. The brain resonance, renal ultrasound, echocardiography, lumbar puncture, and eyes fundus were normal. The electroencephalogram showed continuous cerebral bioelectrical activity with a mixture of diffuse theta-delta rhythms.

In genetic study it was detected two heterozygous variants of uncertain significance in the CASR gene, compatible with autosomal dominant hypocalcemia with hypercalciuria or type V Bartter:

-CASR NM_000388.3Chr3:g.122257242C>A c.347C>A; p.Ala116Asp(De Novo Mutation)

-CASR NM_000388.3Chr3:g.122284925A>C c.2971A>C; p.Asn991His (Inherited from father)

After diagnosis, he required one more admission for calcium decompensation in context of pharyngotonsillitis and vomits, in which he needed intravenous calcium. After that, he has remained stable.

Conclusion: Bartter V syndrome is a rare disease, but it should be suspected in cases of hypokalemia associated with hypocalcemia.

Gain-of-function CASR mutations inhibit PTH secretion.

It is important to ensure adequate levels of calcium, magnesium and phosphorus, but avoiding hypercalciuria. Oral calcitriol can regulate these levels, but it could increase the risk of nephrocalcinosis.

P2-152

Clinical Characteristics of patients seropositive for any one or more of 4 serological tests of celiac disease in a Singaporean paediatric endocrinology clinic

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Celiac Disease is being increasingly recognised among Asians, but the spectrum of presentation may differ from that of Caucasian populations. The clinical phenotypes of celiac disease and diseases of gluten intolerance have not been well studied in Singaporean patients. We describe the clinical, biochemical and genetic phenotype of each seropositive individuals from a single private sector paediatric endocrinology clinic in Singapore over the period 2008 to 2020. These 67 patients with Singaporean citizenship or permanent residency presented to the clinic before 21 years of age and had a serological level above the test manufacturer's upper limit of normal for at least one of 4 serological tests for celiac disease (tissue transglutaminase IgA, tissue transglutaminase IgG, deamidated gliadin IgA and deamidated gliadin IgG) and their HLA DQb1 patterns were characterized by sequence-based typing. There were 34 male: 33 female, M: F ratio 1.03 : 1, age range 3.13-20.21 mean 10.94 yr Ethnic composition: 53 (79.1 %) Chinese 2 (3.0 %) Malay 6 (9.0%) Indian 6 (9.0%) 3 (4.5%) Eurasian, 2 (3.0%) Caucasian). Of these patients 61 (91%) presented for problems of growth and pubertal development, 6 (9%) had Type 1 diabetes mellitus, 6 (9%) presented for thyroid pathology. Of these 21(31.3 %) had gastrointestinal symptoms, 4(6%) had skin rashes, 2 (3%) had a history of oral ulcers, 5 (7.5%) were on treatment for ADDHD, 13 (19.4%) had asthma or nasal allergy symptoms. Known gestational age in 44 patients was mean 38.6 wks (range 34-41.5 weeks gestation), Mean birth weight in 43 patients with BW data was 2.809 kg (range 1.785-3.315 kg) and 14 out of 29 patients with known mode of delivery were delivered by caesarean section. Of these patients, 37 (55.2%) were positive for a single test 20 (29.9%) were positive for 2 tests, 10 (14.9%) were positive for 3 tests and none were positive for all 4 tests. TTg IgA was positive in 23 (34.3%), TTg IgG was positive in 26 (38.8%) DGP IgA was positive in 14 (20.9%) and DGP IgG was positive in 4 (6.0%) patients. Of these 67 patients, 40 (59.7 %) were positive for HLA DQ 2 and or DQ8, while another 21 (31%) were positive for either DQ7 or DQ9. HLA DQ 2 and or DQ8 alleles were present in 22/37 (59.5 %) of those with single positive ,13 /20 (65%)of those with double positive and 5 /10 (50%)of those with 3 tests positive.

P2-153

Assessment of some endocrinal disorders in children finished cancer treatment: a single center study

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Endocrine complications are common among children who have finished their cancer treatment. Approximately half of those children will experience at least one hormonal disorder. The risk of endocrine deficiency is related to the child's gender and age, tumor location and therapies used (surgery, chemotherapy or radiation therapy).

Aim of the Study: To address the main endocrine abnormalities following cancer therapies that occurs later in children for early recognition of long-term endocrinal disturbances.

Patients and Method: This cross sectional study conducted on seventy children who completed their cancer treatment successfully. All data related to age, type of cancer (leukemia, lymphoma or solid tumor), date of diagnosis, lines of treatment (chemotherapy, radiotherapy, and surgery), duration of cancer treatment, and duration since finishing treatment (follow up duration) has been collected. Physical examination included anthropometric measurements (Z-score for weight, height, and BMI) and Tanner staging for all children. Laboratory detection of endocrine abnormalities included TSH, free T4, HbA1c, and if affected, oral glucose tolerance test was done. FSH, LH, testosterone or estrogen for cases of delayed puberty has been done. GH provocation test for cases of growth failure (Z-score <-2) has been done.

Results: This study was done on 70 children (males constitutes 54.3%) who finished their cancer treatment with mean age (11.18±3.88 y). Their median duration for treatment was 1.37y ranging from (0.5y-12y) and follow up duration ranging from (0.5y-10y). Pubertal assessment by Tanner staging showed that 52.9% of studied children were in the prepubertal period. About 32.9% of studied group were treated from leukemia, 22.9% were treated from HL, 10% from NHL, Brain tumors were 7.1% and other tumors (such as rhabdomyosarcoma, Wilms tumor) were 27.1%. Out of our studied group, 21.4% showed endocrinal problems. Hypothyroidism constitute 5.7%, prediabetes was 5.7%. Growth retardation constituted 8.6% with 4.3% of them was due to growth hormone deficiency and 1.4% was found to have combined hypothyroidism and prediabetes. There is statistically significant correlation between Exposure to neck radiation and developing hypothyroidism. Sixty% of cases having diabetes predisposition were treated from HL and 40% were treated from leukemia (associated with chronic steroid use) with no significant data among NHL, brain and other tumor.

Conclusion: Long-term follow-up is crucial since endocrine side effects from cancer treatments may persist for years after they are finished.

P2-154

Hypoglycemia in a 9-month-old infant due to hyperinsulinism by ABCC8 variant

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Introduction: Hypoglycemia due to Congenital hyperinsulinism is a phenotypically heterogeneous disease. Depending on the cause it is most frequently seen in the neonatal period but it can present later in life, with risk of neurological complications in the event of late diagnoses.

Clinical Case: Patient with a normal perinatal history, born at 40 weeks, weight 3600 grams and 50.5 centimeters of length. Because café au lait spots neurofibromatosis was ruled out. At 7 months of age anticonvulsants were started for a convulsive syndrome. At 9 months of age she went to the emergency room with a new seizure episode. Blood studies showed glycemia 27mg/dl, insulinemia 3UI/ml, negative ketones, and thyroid, cortisol and growth hormones in normal range. Amonia and lactic acid were in normal levels. Abdominal ultrasound, echocardiography, electroencephalogram and cerebral computed tomography showed no pathological findings. Treatment with Diazoxide at 7.5 mg/kg/day was started, and progressively increased to achieve normoglycemia.

Genetic study of parents and patient´s NGS for hyperinsulinism was heterozygous for a paternally inherited pathogenic ABCC8 frameshift variant, consistent with focal hyperinsulinism. PET-CT Galio68 DOTATATE study was requested. To date patient hasn't repeat neither hypoglycemia nor convulsions under diaxozide treatment.

Conclusion: Hypoglycemia due to congenital hyperinsulinism usually has an early presentation. Our patient first manifestations were after 6 month of age. Despite having a later presentation, a high suspicion and sequential study guided us to the diagnostic etiology and personalized treatment.

P2-228

Evaluation Of Bone Health And Endocrine Functions İn Children With Mucopolysaccharidosis

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Introduction: Mucopolysaccharidoses (MPS) are lysosomal storage diseases. The frequency of endocrinological problems such as osteoporosis and hypothyroidism among children with MPS is not known and there are limited studies.In this study, the clinical findings, bone health and other endocrine functions of patients with MPS diagnosis and access to current treatments were retrospectively evaluated.

Materials and Methods: This is a single-center prospective study.44 patients with a diagnosis of MPS were included.All patiens were performed following parameters: body mass index (BMI),BMI-SDS, hormonal analysis ,the clinical findings. The relationship between 25-hydroxyvitamin D3(25(OH)D3) level and dual energy X-ray absorptiometry (DEXA) results, height growth rates were evaluated in patients. 25(OH)D3 levels were defined as normal for> 20 ng/ml, insufficiency for 12–20 ng/ ml, and deficiency for<12 ng/ml.Bone mineral density(BMD) measurements for the lumbar spine (L1–L4)were obtained using DEXA.

Results: The mean age of the 44 patients was 7.55± 4.18 years. Twenty-one (47.7%) were male. Thirty-nine patients were receiving enzyme replacement therapy. (4 with MPS-I, 2 with MPS-II, 2 with MPS-III, 11 with MPS-IVA, and 25 with MPS-VI). At the last control of the patients, height-SDS weight-SDS,BMI-SDS were as follows:-3.96±3.00,-2.22±2.36,0.65±1.20.Height-SDS was statistically lower than pre-treatment height-SDS(p=0.016). In total thirty-two(%72.72) patients had a short-stature, and twenty-two(50%) of them were underweight for their age. twenty-five(%56.8) had deficiency and insufficient level of 25(OH)D3. DEXA was performed in thirty-eight of these patients. BMD z-score of patients was-3.15±2.25. In twenty-five(%67,57) patients, it was <-2. However, after correction for height-for-age z score (HAZ),adjusted BMD z score was -1.02±1.28. In eight(21.6%) patients, it was <-2.The mean 25(OH)D3 level of the patients in whom DEXA could be performed was 19.64±8.43(<10-44.65)ng/ mL. While the 25(OH)D3 level was 17.57±6.56 in patients with an age adjusted DEXA z-score below normal, it was 20.09±9.17 in those with a normal DEXA z-score. Although 25(OH)D3 level was found to be lower in those with a DEXA z-score below normal, the difference was not statistically significant (p =0.39).Conclusion:The low BMD z-score prevalence reported with DEXA was misleadingly higher in children with MPS and short stature. To prevent exposure to unnecessary antiresorptive treatments in these children, the effect of severe short. No serious dysfunction was seen in other endocrine organs.

Pituitary, neuroendocrinology and puberty

P2-23

Evaluation of etiology and clinical feature of precocious puberty among children presenting in a pediatric endocrinology department in a tertiary care hospital

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Keywords: Central Precocious Puberty, Girls, Peripheral, Idiopathic

Background: Precocious puberty is thought to occur in 1 in 5000–10,000 people. Precocious puberty is a neglected topic in Pakistan, and little research has been done so far to examine its aetiology in our population, despite its importance and relative prevalence

Objective: To find the frequency of precocious puberty in children and to compare the clinical and laboratory parameters of central and peripheral precocious puberty.

Methods: This cross-sectional study was carried out in Karachi's National Institute of Child Health's paediatric endocrinology division between December 2016 and 2021. All patients with precocious puberty will be taken from files through non-probability convenience sampling method. Data was analyzed on SPSS version 22.0.

Results: Total 65 patients were included. The mean age was 6+3.35years. Precocious puberty was classified as peripheral precocious puberty in 38 (58.4%), central precocious puberty in 20 (30.76%), premature thelarche in 5(7.69%) and premature pubarche in 2 (3.07%). In the peripheral precocious puberty group, CAH was found in 22(78.5%), out of which 2 patients were of rare mutation of CAH presenting with peripheral precocious puberty (DAX mutation and 11 B hydroxylase mutation,adenocarcinoma was observed in 2(7.14%) followed by Mu-cane- Albright syndrome was in 4(14.28%) and van wykgrumbach syndrome in 10 patients. Central precocious puberty was found in 20 patients hypothalamicharmartoma in 4(20%), craniopharyngioma 3(15%), hypothalamic astrocytoma 1(5.0%), genetically proven neurofibromatosis in 1(5.0%) patient and hydrocephalus 1(5.0%) and in 10(50%) patients no cause was found. All the parameters were significantly comparable with p-value < 0.05.

Conclusion: Peripheral precocious puberty was more common than central precocious puberty in this study. Etiology in majority of cases with peripheral precocious puberty was CAH and idiopathic in central precocious puberty. Central precocious puberty children showed higher height SDS, weight SDS, FSH, LH than those with peripheral precocious puberty.

P2-24

Familial growth hormone deficiency associated with a *PROKR2* gene variant

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A 16 year old boy initially presented with short stature at age 6, with height <0.4th centile (HSDS -2.78). Bone age was 1.9 years delayed, and growth hormone deficiency was diagnosed after 2 stimulation tests. The rest of his pituitary function was normal. He never had pituitary imaging. Growth hormone treatment was started, and he had an excellent growth response with HSDS improving to -1.57 by 10 years. The growth hormone treatment was discontinued when the family relocated to UAE, but his growth velocity slowed to only 2.3 cm/year, and a year later the treatment was recommenced (HSDS -1.86). His current height at age 16 years is 164 cm (HSDS -1.24) and he is still growing well with height velocity 5.4 cm/year and predicted adult height of 168.1 cm. He had spontaneous puberty and the rest of his pituitary function remains normal.

His father (158cm) and father's brother (161cm) both received hormone treatment with HCG in adolescence for short stature but were diagnosed with growth hormone deficiency. His mother is 158cm, MPH 164.5 cm (-2.01 SD).

His younger brother who is now 7 years, was initially seen from age 3 with short stature, height on 0.4th centile (HSDS -2.70) and height velocity 4.4 cm/year (-2.49 SD). He had the typical appearance of growth hormone deficiency with mid-facial crowding and increased adiposity. His bone age was 1.1 years delayed with low growth factors. He was confirmed to have growth hormone deficiency on stimulation testing with peak GH 5.36 ng/ml. MRI showed normal pituitary but identified a pineal gland cyst. He was commenced on growth hormone therapy at 4.5 years with a fantastic growth response, current HSDS -0.97 and HV 6.8 cm/year.

As there were four individuals in the family with growth hormone deficiency, whole exome sequencing was undertaken in the older brother which revealed a previously undescribed heterozygous variant in the *PROKR2* gene, which is a G protein-coupled receptor essential for the development of the olfactory bulb and sexual maturation and also neuronal migration. This gene has been associated with Kallman syndrome and variants have been found in patients with multiple pituitary hormone deficiencies. The older brother has had normal spontaneous puberty and both the father and the uncle were able to father children without any intervention, although they both had pubertal delay. We hypothesise that *PROKR2* may also be relevant in familial isolated growth hormone deficiency.

P2-25

Coexistence of Pituitary Stalk Interruption Syndrome, Sacrococcygeal Teratoma and Horseshoe Kidney

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Introduction: Pituitary stalk interruption syndrome is a rare congenital abnormality of the pituitary gland manifesting with varying degree of anterior pituitary insufficiency. It is presented with isolated growth hormone deficiency or multiple anterior pituitary hormone deficiencies. It is characterized by the triad of thin or interrupted pituitary stalk, hypoplasia or aplasia of adenohypophysis and ectopic or absent neurohypophysis. It is manifested with hypoglycemia, prolonged jaundice, cryptorchidism and micropenis during neonatal period; with short stature in older children. Either genetic mutations in HESX1, LHX4, OTX2, SOX3 and PROKR2 genes or other factors that can cause neonatal hypoxia such as breech delivery, cesarean delivery or neonatal distress are proposed to be the etiological culprits of the disease. Here, we present a case with co-ocurring APSHAEN syndrome, sacrococcygeal teratoma, and horseshoe kidney.

Case: A 5-year-old girl was referred for short stature. She was a twin delivered by cesarean section at 30 weeks of gestation, weighing 2090 grams, and the fourth child of healthy consanguineous parents. She was operated for anal atresia and rectovestibular fistula on the postnatal 20th day and for sacrococcygeal teratoma when 13 months old. She had noteworthy facial features; large forehead, deep set eyes, broad nasal bridge, bulbous nasal tip, long philtrum and narrow upper lip. Her height, weight and BMI were 86 cm (-5,28 SD), 11 kg (-4,07 SD) and 14,87 kg/m^2 (-0,4 SD) respectively. Midparental height was 158,5 cm (-0,77 SD). Her bone age was found as 2,5 years. Laboratory investigations (CBC, urea, creatinine, liver enzymes, serum electrolytes, cholesterol and triglycerides) were resulted normal, except anemia and central hypothyroidism. Sodium L-thyroxine and iron supplementation were started. Karyotype was 46, XX with a normal micro-array analysis. IGF-1 was found <-2 SD. Peak serum GH responses to stimulation tests (with clonidine/L-Dopa) are <10µg/dL. ACTH, cortisol and prolactin levels were normal. Skeletal survey revealed J-shaped sella, Harris-lines in the metaphysis of long bones and absence of the sacrum due to the surgery. Abdominal ultrasound revealed a horseshoe kidney and grade II hyperechogenic liver. No abnormalities were identified in the etiological tests for steatohepatitis. MRI of the pituitary region uncovered ABSHAEN. Growth hormone supplementation was initiated. Growth velocity for 3 months length increment is 3,5 cm.

Conclusion: We presented a case with the coexistence of developmental midline malformations that was not formerly presented in the literature. This co-ocurrence may be due to genetic and environmental causes or coincidental.

P2-26

Craniopharyngioma-related hypothalamic obesity: efficacy of bariatric surgery in two adolescents

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Although craniopharyngiomas are low-grade tumours, long-term survivors frequently suffer from severe morbidity due to hypothalamic lesions, such as hypothalamic obesity, that is largely resistant to lifestyle modification and pharmacotherapy. We investigated the efficacy of bariatric surgery in two patients with craniopharyngioma-related hypothalamic obesity during 18 months of follow-up.

Patient n1, diagnosed with craniopharyngioma and treated with complete surgical excision at 11 years of age. Subsequently, she developed panhypopituitarism, hypothalamic obesity (BMI>40 kg/m2 at 15 years of age), diabetes mellitus (HbA1c 48 mmol/mol, fasting blood sugar 102 mg/dl), dyslipidaemia (triglycerides 296 mg/dl), NAFLD with hepatic steatosis and elevated transaminases. Dietary intervention and exercise were ineffective as she kept gaining weight; hence, she was started on Metformin and Semaglutide, without success. At the age of 21 her bodyweight was 180 kg (BMI 54 kg/m2); therefore, according to the European guidelines (severe obesity associated with comorbidities), she was candidate for bariatric surgery and underwent sleeve gastrectomy. Within 6 months after the surgery, she achieved a weight loss of 40 kg, 22% of her initial weight. During the follow-up the blood tests showed complete remission of diabetes mellitus (HbA1c 33 mmol/mol, fasting glycaemia 77 mg/dl) allowing discontinuation of the antidiabetic therapy; the laboratory testing also revealed normal lipidic profile and liver function. No complications were observed.

Patient n2, surgically treated for craniopharyngioma with complete removal at the age of 12. Afterward he developed panhypopituitarism, severe hypothalamic obesity (BMI>40 kg/m2 at 15 years of age), insulin-resistance (HOMA-IR 4.6), dyslipidaemia (HDL 28 mg/dl, triglycerides 194 mg/dl), OSA. Lifestyle modification was inadequate for weight loss; hence, after multidisciplinary evaluation, sleeve gastrectomy was applied at the age of 19 (BMI 56 kg/m2, weight 190 kg). After bariatric surgery he lost weight markedly and continuously, with a substantial weight loss of 33% of bodyweight (64 kg). The BMI has reduced by 18 units. Moreover, levels of glycated haemoglobin and insulin declined during the first month (HOMA-IR 2.4); hypoglycaemic therapy was discontinued. An improvement of lipid profile was achieved (HDL 57 mg/dl, triglycerides 98 mg/dl). These results were consistent during 18 months of follow-up. No major complications occurred.

This double case-report revealed that dietary interventions and pharmacotherapy could be unsuccessful in patients with craniopharyngioma-related hypothalamic obesity. Bariatric surgery could be a promising therapeutic option to promote weight loss and improve or even resolve comorbid conditions such as diabetes mellitus and dyslipidaemia.

P2-27

Use of the arginine-stimulated copeptin test in polyuric syndrome in paediatrics. Experience in three patients

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Introduction: Differential diagnosis of partial arginine vasopressin deficiency (P-AVPD) and primary polydipsia (PP) can be challenging. Arginine-stimulated copeptin concentrations have been used to differentiate between arginine vasopressin deficiency (AVPD) and PP, setting a copeptin value of 3.8pmol/L at 60 min as a cut-off point in adults.

Objective: To evaluate the efficacy and safety of the arginine-stimulated test in paediatrics.

Methods: Descriptive and prospective study on a diagnostic method in six paediatric patients with polydipsia-polyuria syndrome (PPS).

Inclusion Criteria: Patients under 18 years with polyuria (>2mL/kg/h), normal glycaemia and no electrolytic changes. The arginine-copeptin test is performed with analytical control and vital signs (Times: basal, 0', 30', 60', 90', 120').

Patients description and results (Table 1 and 2):

-Patient 1: 5-year-old boy with sudden PPS and MRI showing hypoplastic adenohypophysis and absence of neurohypophysis signal. Arginine-copeptin test <3.8pmol/L.

-Patient 2: 12-year-old boy with long-standing PPS and syntelencephaly without alterations in the hypothalamic-pituitary region. Arginine-copeptin test >3.8pmol/L.

-Patient 3: 13-year-old boy with sudden PPS. MRI showed an absence of the neurohypophysis and thickening of the pituitary stalk, etiological study pending. Arginine-copeptin test <3.8pmol/L.

-Patient 4: 3-year-old girl with SGA, monosomy X, and Kabuki-like syndrome with long-standing PPS. MRI without alterations in the hypothalamic-pituitary axis. Arginine-copeptin test >3.8pmol/L.

-Patient 5: 4-year-old girl with long-standing PPS. Arginine-copeptin test >3.8pmol/L.

-Patient 6: 10-year-old boy with GH deficiency under treatment and MRI showing interruption of the pituitary stalk and ectopic neurohypophysis. He presents long-standing PPS. Arginine-copeptin test >3.8pmol/L.

All patients were asymptomatic and hemodynamically stable during the procedure. Blood tests at the beginning and end of the test show no alterations.

Conclusion: The arginine-stimulated copeptin test is a safe procedure and can represent an alternative to the diagnosis of AVPD.

Table 1. Water-restriction test

	1	2	3	4
Duration (hours)	15	17	Basal (without restriction; plasma osmolality of 303mOsm/Kg)	10
Urinary osmolarity before Desmopressin (mOsm/kg)	601	495	98	304
Urinary osmolarity after Desmopressin (mOsm/kg)	845	687	507	415

Table 2. Arginine-copeptin test

	1	2	3	4	5	6
	Copeptin (pmol/L)					
Basal	2,4	3,8	1,61	4.42	2.7	3,94
30'	2,5	4	1,48	5.24	3	5,3
60'	2,3	4,13	1,78	8.44	4.8	5,2
90'	1,8	3,8	1,98		4.5	6
120'	2,4		1,47	9.72	3.7	5,8
180'					3.7	4,5
Diagnosis	P-AVPD	PP	AVPD	PP	PP	PP

P2-28

Hipothalamic syndrome in craniopharyngioma: pre and post-surgery

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Introduction: Craniopharyngioma (CP) is a histologically benign rare tumor from the sellar and parasellar region. Its invasion into adjacent structures, namely optic nerve and hypothalamic-pituitary axis brings significant morbidity and warrants surgical treatment.

Hypothalamic Syndrome (HS) can occur in different conditions affecting this structure, comprising a cluster of symptoms like pituitary dysfunction, obesity, temperature dysregulation, sleep disturbances, and behavioral problems. According to these domains, diagnostic criteria for HS in childhood were recently proposed.

Aim: To access HS in childhood-onset CP, before and after surgical treatment.

Methods: Retrospective observational study of CP patients followed in a tertiary pediatric hospital from January 2008 until

December 2022. Collected variables: sex, age at diagnose, clinical presentation, therapeutical approach, clinical outcome.

Results: 10 individuals with CP were reviewed: 80% males, median age at onset of 6,5y (range: 0,8 - 15y).The most frequent onset signs were headache and vomiting (59%), visual impairment (50%), and pituitary hormonal deficits (50%). Of these, TSH and ACTH were diminished in 50% and 30% of the cases, respectively. Seizures (20%), hypersomnia (20%), cold intolerance (20%), failure to thrive (20%), and hyperphagia and obesity (10%) were also documented. 50% were approached endoscopically. All CP were of the adamantinomatous subtype. HS was present in 30% of the cases, all of them MRI Muller grading 2, recurring and needing posterior radiotherapy intervention. Until now, there is 100% survival.

After surgery, HS was diagnosed in 60% of the cases: all of whom either needing open transcranial approach or adjunctive radiotherapy, or having a relapse. Hormonal deficits were present in all patients (TSH: 100%; ACTH: 80%; LH/FSH: 70%; ADH: 70%; GH: 60%). Central precocious puberty was not observed. Hyperphagia and obesity were present in 60% of the cases, all of them with documented insulin resistance and reports of temper outbursts related to food restriction. One child had sleep disturbances.

There were no reports of cognitive impairment either before or after surgery.

Discussion: More severe cases increased the prevalence of HS after treatment. Whilst neuroendocrine consequences of craniopharyngiomas are well established, neuropsychological ones are less frequently reported and can be as important in these patients management. We hypothesize that some of these symptoms may be underrepresented and therefore its incidence might be undervalued. Further prospective studies and a multidisciplinary protocolled approach to these patients might improve these outcomes.

P2-35

A case of congenital central hypothyroidism with complete growth hormone deficiency caused by a novel nonsense mutation in the *IGSF1* gene

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The *Ig superfamily member 1*(*IGSF1*) gene encodes a plasma membrane immunoglobulin superfamily glycoprotein, that is highly expressed in Rathke's pouch and the adult pituitary gland and testis. It is now known that a loss-of-function mutation in this gene causes X-linked syndromic disorders including congenital central hypothyroidism, macroorchidism, prolactin deficiency, partial and transient growth hormone (GH) deficiency, disharmonious pubertal development and overweight. We report a case of congenital central hypothyroidism due to a novel nonsense mutation in the *IGSF1* gene complicated with complete GH deficiency.

The male patient was incidentally diagnosed with central hypothyroidism during the newborn period when he was referred for neonatal seizure, and levothyroxine was started. At 6 years of age, a genetic test revealed a novel hemizygous nonsense mutation c.2548C>T (p.R850*) in *IGSF1* gene and the diagnosis was confirmed. Due to decreased growth velocity, his pituitary function was examined at 10 years of age. His height was 126.0 cm (-1.81SD) and his body weight was 33.9kg (body mass index, 21.4 kg/m^2; 91.4 percentile). The patient's Tanner stages were G1 and PH1, and the volume of each testicle was 2 ml. His thyroid function was normal on levothyroxine (FT$_4$, 0.96 ng/dl; TSH, <0.01 μIU/ml). His insulin-like growth factor-1 value was 148 ng/ml, which was within normal range for his age. His adrenal function was normal and his gonadal function was at the prepubertal stage. His hypothalamic-pituitary function was more examined by stimulation tests. GH stimulation tests showed extremely poor responses; the peak levels of GH were 0.68 ng/ml with arginine and 2.19 ng/ml with l-dopa, indicating complete GH deficiency. The peak levels of TSH and PRL on a TRH test were 0.01 μIU/ml and 8.08 ng/ml, respectively, which were consistent with the genetic diagnosis. An LHRH test showed prepubertal LH and FSH responses; the peak levels of LH and FSH were 2.01 mIU/ml and 18.89 mIU/ml, respectively. The pituitary-adrenal axis was normal on a CRH test.

The present case differed from previous reports, in that the patient's GH deficiency was not partial, but complete. Because his growth velocity had been gradually decreased since the young infant period, complete GH deficiency might be one of features of IGSF1 deficiency. From the viewpoint of GH therapy in adult life, long-term follow-up is needed to know whether his GH deficiency is transient or persistent.

P2-36

Unusual presentation of pheochromocytoma (PCC) and paraganglioma (PGL) in two sisters with von Hippel Lindau disease (VHL)

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Introduction: Von Hippel-Lindau disease(VHL) is an autosomal dominantly inherited tumor syndrome that predisposes to development benign and malignant tumors.The prevalence of VHL disease is one in 36,000, and the penetrance is higher than 90%.PCC occur in up to 20% of VHL patients. Classically, it is characterized by having an adrenal location, mostly bilateral and being derived from the sympathetic nervous system, resulting in the releases of catecholamines with norepinephrine predominance.Rarely transform into malignant tumors.

Patients: The index case was a 6-year-old girl who was diagnosed with a retinal hemagioma. A year later, she developed hypertension and enlargement of both adrenal glands. The catecholamine profile showed a predominance of norepinephrine (Eur: 3.8mg/24h, NEur:1150mg/24h (11-75), VMA: 23.7ug/24h

(1.2-0.5). Left adrenalectomy and the resection of a right paraadrenal tumor were performed.Histophatology studies confirmed left PCC and right PGL. The molecular biology study identified a pathogenic variant in the VHL gene:p.Gly92Ser, confirming the diagnosis of VHL disease. She continued with periodic clinical and biochemical controls, finding a new increased catecholamines in 24-h urine.(E:13.6mg/24h (0-21), NE: 288.7 mg/24hl18-110),MN: 54.6 nmol/L(<130), NMN: 957 nmol/L(<334).

Imaging studies of the abdomen were normal and a nodular image (21x24.5 mm) with intense enhancement in the left costovertebral angle was found in the computed axial tomography.

The tumour was confirmed with MIBG-I131 scintigram, that showed a lesion with increased uptake in left upper lobe of the lung.

After surgical resection, histopathology studies confirmed well-differentiated PGL. 24h urinary catecholamine levels normalized(NEur: 50.9 ug/24hs) after surgery.

After index case diagnosis, her sister began clinical and biochemical control. When she was 11years-old a tumor in adrenal gland was found in abdominal MNR. Catecholamine levels were normal in two opportunities (E:2.3mg/24hs (0-21), NE:22.5 mg/24hs(18-110), VMA:3 ug/24hs(<8.5),MN: 54.6nmol/L(<130), NMN: 142nmol/L(<334) Adrenal cortex hormones were also in normal ranges. It was decided to maintain expectant management. One year later, an abdominal CT was performed and the nodule in the right adrenal gland had increased by 50%(47.7x37x42mm). Catecholamines were still in normal ranges. Surgical resection was performed and PCC was confirmed in an anatomopathological study.

Conclusions: We found two atypical presentations of CCP/PGL in patients with VHL disease that emphasize the importance of close clinical follow-up in these patients, and the possibility of achieving early detection of other unusual clinical manifestations, avoiding possible complications and greater survival.

P2-37

A male case of peripheral precocious puberty caused by testotoxicosis

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Introduction: Familial male-limited precocious puberty (or testotoxicosis) is a very rare genetic disorder with autosomal dominant transmission that causes gonadotropin-independent precocious puberty due to mutations activating the lutropin-chorionic gonadotropin receptor (LHCGR), which lead to elevated testosterone levels and suppressed gonadotropins. The age of onset is between 2-5 years essentially with penis and testes enlargement, linear growth acceleration, progressive bone age advancement and growth of pubic hair. Premature epiphyseal fusion results in reduced adult stature. Current treatment consists of a combination therapy with nonsteroidal antiandrogen agents and aromatase inhibitors.

Case Presentation: A 4-years and 6-months-old male came to our clinic for appearance of pubic hair for months. Familiarity for precocious puberty (paternal line). The growth curves documented a progressive acceleration of staturoponderal growth from 2-years-old (50th to 95th percentile). On physical examination: herculean appearance, presence of café-au-lait spot on right flank, increased penis size, testicles 6-8 cc bilaterally, dark curly pubic hair. No headache or visual changes. There was tall stature (+3.39 SD) and advancement of bone maturation (7.9 years). GnRH test was performed which documented peripheral precocious puberty (elevated testosterone values with suppressed basal and post-stimulus gonadotropin levels). Thyroid function, serum and urinary electrolytes, 17-OH-P, ACTH, cortisol, PRL, alpha-fetoprotein and beta-HCG were normal. Testicular ultrasonography didn't show morpho-structural changes. Head MRI and adrenal ultrasound were negative. Excluding tumor causes, genetic investigation showed a c.1193T>C mutation of the LHCGR gene in heterozygosity, confirming the diagnosis of testotoxicosis. In contrast, molecular investigation for McCune-Albright syndrome was negative. After starting antiandrogenic therapy (ketoconazole) associated with cyproterone acetate, the child presented a significant reduction in testosterone levels (from 355 ng/dl to 14 ng/ml during the first year of follow-up). However, after 1 year of treatment, because of the onset of iatrogenic adrenal insufficiency, the therapy was modified with the combination of letrozole and spironolactone. At 6.6 years-old GnRH test documented activation of the pituitary-gonadal axis with diagnosis of central precocious puberty. Therefore, therapy with GnRH analogs was initiated.

Conclusions: Male peripheral precocious puberty is a very rare condition. After excluding neoplastic causes and congenital adrenal hyperplasia from 21-OH deficiency, rarer causes such as McCune-Albright syndrome or testotoxicosis should be considered. Testotoxicosis should be treated early with antiandrogenic drugs to mitigate the effect of testosterone on stature and bone maturation. Therapeutic management, however, requires the use of off-label drugs that may lead to side effects. Close clinical-auxological and laboratory follow-up appears essential.

P2-38

Combined pituitary hormone deficiency caused by a missense *de novo* variant in *FGFR1*

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Background: Heterozygous loss-of-function variants of fibroblast growth factor receptor 1 (FGFR1) are genetic causes of Combined Pituitary Hormone Deficiency (CPHD), Kallmann syndrome (KS) with anosmia/iposmia, Congenital Hypogonadotropic Hypogonadism (CHH) with normosmia and Septo-Optic Dysplasia. It is well-known that these variants are the main genetic factor underlying the development of CHH and KS; however, they have only occasionally been identified in CPHD.

Case Presentation: A 14-year-old boy was admitted to Outpatient Clinic of Pediatric Endocrinology for short stature (-2.6 SDS) and pubertal delay. He had a personal history of cleft lip and palate and cryptorchidism surgically corrected during childhood.

During follow-up he had significantly deficient height growth rate (1.4 cm/year) and failure to spontaneous onset of puberty despite evidently puberogenic bone age (14 years). In consideration of the abovementioned findings, the patient underwent endocrinological investigation, including endocrine dynamic function test, that documented a growth hormone deficiency and hypogonadotropic hypogonadism (HH). The other pituitary tropins were within normal range. Brain MRI delineated a complex midline and maxillofacial bones malformation, with hypoplastic olfactory sulci, caudal dislocation of the fronto-basal cortical gyri, impaired cranio-caudal development of the nasal pits, nasal septal deviation, defect of the alveolar process of the maxillary bone, maxillary and frontal sinuses hypoplasia and one palatalized supernumerary tooth. The pituitary gland was normal and the pituitary stalk in axis. Despite the complex alteration affecting the olfactory structures, the patient presented normosmia.

The patient underwent array-CGH, which resulted negative for microduplications or microdeletions, and trio exome sequencing. The latter identified a de novo heterozygous missense variant c.2002G>A in FGFR1 gene, that determines the aminoacidic change p.Glu668Lys. This missense variant is classified as pathogenic (class 5 according to ACMG criteria) and is associated with autosomal dominant HH.

Since the age of 15 years the patient was treated with daily growth hormone therapy, which resulted in significant height recovery (from -2.6 SDS to -1.66 SDS), and testosterone, which promoted the appearance of secondary sexual characteristics. GnRh and gonadotropin therapy was considered to promote increased testicular volume and future fertility.

Conclusions: This case highlights the role of missense variants of FGFR1 in the development of combined pituitary hormone deficiency associated with complex brain malformation even without anosmia. In the diagnostic workup of HH, the role of comprehensive pituitary function study, brain MRI, and genetic analysis is crucial in clarifying the etiology of HH and any possible associated comorbidities.

P2-39

A Case Report of a 10-Year-Old Girl with Pituitary Abscess

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Background: Pituitary abscess is a rare disorder, representing less than 1% of pituitary lesions. Preoperative diagnosis is often difficult due to non-specific symptoms and image findings.

Case Report: Here, we report the case of a 10-year-old girl with a pituitary abscess. She presented with polyuria and polydipsia and headache for the past year. Magnetic resonance imaging revealed polycystic lesion in the sella turcica to suprasellar lesion, which extended to the pituitary stalk and compressed the optic chiasm. The lesion was hypointense on T1, and high intensity on T2, and peripheral rim enhancement following gadolinium injection. Computed Tomography showed no calcification. Laboratory test showed no elevation of C-reactive protein level. Hormonal evaluation revealed central diabetes insipidus, moderate growth hormone deficiency, hypogonadotropic hypogonadism, central hypothyroidism, and mild adrenal insufficiency. Thyroid hormone and antidiuretic hormone replacement initiated. Craniopharyngioma was initially suspected, and a transsphenoidal surgery was performed. Hydrocortisone was administered perioperatively. Intraoperatively, an abscess was seen and diagnosed as a pituitary abscess. Pathology did not reveal any neoplastic lesions. Culture of the abscess was negative. She was treated with antibiotics for 4 weeks after surgery; CTRX was used but was switched to MEPM during the course of the treatment because of a skin rash that was suspicious of drug eruption. Hypopituitarism persists after 4 weeks of antibiotic therapy and thyroid hormone and antidiuretic hormone replacement therapy is continued and growth hormone replacement was initiated.

Conclusion: Pituitary abscess are rare, especially in children, but should be differentiated when MRI show rim-enhancing pituitary mass even in the absence of signs of infection.

P2-91

Peripheral Precocious Puberty due to Exogenous Estradiol in a 3-Year-Old Girl: A Case Report

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Introduction: Transdermal estrogen replacement therapy in girls with hypogonadism is well known for induction of the puberty. Sexual development due to exogenous exposure for sex steroids in food, environment or medication is known, but is rare and sparsely reported. We present a case of peripheral precocious puberty in a 3-year-old girl due to inadvertent exposure to an estradiol gel used by her father as gender affirming hormone therapy (GAHT).

Case description: A 3-year-old girl was referred to our pediatric outpatient clinic with breast development and vaginal discharge over a period of 6 months. The GAHT of her transgender father was estradiol spray 6.12 mg applied to both forearms daily. After 6 months this was changed to estradiol gel 3.75 mg daily for 7 months. The gel was manually applied to the chest, abdomen, shoulders, and thighs. The father reported skin to skin contact on a daily basis. A physical examination of the girl revealed a Tanner stage III for breast and Tanner stage I for pubic hair development. Height was 108.1 cm (+3,2 SD), weight 19.7 kg (+0,54 SD) and bone age advanced to 6.9 years (Greulich and Pyle). Pelvic ultrasound demonstrated increased size for age of both uterus and endometrium corresponding to Tanner stage III-IV. Estradiol was 0.04 nmol/l and GnRH stimulation test revealed a peak LH of 2.0 IU/l with a LH/FSH ratio of 0.77. MRI of the pituitary gland was normal. These clinical, radiologic and laboratory findings were consistent with a diagnosis of peripheral precocious puberty due to exogenous estradiol. The hormone therapy of the father was changed from a gel to a transdermal patch, and the girl experienced regression of breast development, normalization of growth velocity, pelvic ultrasound and GnRH stimulation test.

Conclusions: Exposure to exogenous estradiol can lead to precocious puberty in prepubertal girls. Transgender persons should be thoroughly informed of the risk of transmission of transdermal hormones and be advised to wash hands, use gloves and avoid skin contact shortly after hormone application. Patients with children must be warned of the risk and Gender Clinics should consider the possibility of prescribing alternative routes of administration such as tablets or patches in high-risk patients.

P2-92

A case of pituitary stalk interruption syndrome of normal height with chronic fatigue and delayed puberty

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Pituitary stalk interruption syndrome (PSIS) is a rare congenital pituitary anatomical defect with endocrine abnormalities. The triad of this syndrome comprises thin or interrupted pituitary stalk, absent or ectopic posterior lobe, and hypoplastic or aplastic anterior pituitary lobe. We diagnosed a 16-year-old female patient with combined pituitary hormone deficiency (CPHD) due to PSIS. The patient complained of chronic fatigue and was Tanner stage 1 with no signs of puberty. However, her height, which was 5 percentile at the age of 7, was 163.5cm (75 percentile) at the age of 16. It was rather taller than her mid-parental height (MPH), 160cm. Pelvic ultrasonography and MRI showed hypoplasia of the uterus and ovaries, and chromosomal analysis showed a normal 46,XX karyotype. The combined pituitary stimulation test revealed CPHD and hyper-responsiveness of prolactin to TRH, suggesting hypothalamic-pituitary disconnection. MRI of the pituitary gland revealed the absence of the pituitary stalk, a small anterior pituitary, and an ectopic posterior pituitary located in the hypothalamic area. Replacement therapies with corticosteroid, levothyroxine, estrogen priming and growth hormone were initiated. Herein, we report a case in which a PSIS-induced CPHD patient reached her final height above MPH despite delayed puberty and severe growth hormone deficiency. Although of rare incidence, pituitary stalk interruption syndrome (PSIS) should be kept in mind while investigating a child with delayed puberty. Furthermore, in case of suspicion for early diagnosis and treatment, it is necessary to actively utilize imaging test and recognize characteristic MRI findings.

P2-93

Diabetes insipidous and non langerhans histiocitosis, a challenging diagnosis

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A 5-years-old boy was admitted because of polydipsia and polyuria. His family history was unremarkable. After water deprivation test (10h), laboratory test showed high levels of serum sodium (150.1 mmol/L), low urine osmolarity (88 mOsm/kg) and high serum osmolarity (301 mOsm/kg) consistent with the diagnosis of central diabetes insipidus (CDI). He started therapy with oral desmopressin with clinical improvement.

Brain MRI revealed pituitary stalk thickening (3 mm), no hyperintense signal in the neurohypophysis. CBC and inflammatory markers were negative. No other pituitary defects.

In order to highlight the underlying aetiology of CDI, a close follow-up was started and the patient underwent subsequent clinical-instrumental evaluations and further examinations. Autoimmune and infectious diseases were excluded. Tumour markers (AFP, beta-HCG) on serum and CSF were negative.

Imaging (chest and total body X-ray, abdominal ultrasound) was normal. No pituitary biopsy was performed because of the risks of the procedure and the absence of urgent indications.

Two years after the presentation, the patient reported a skin nodule on the left cheek. During a complete physical examination, sparse nodules were observed in multiple locations. Two lesions were biopsied and the histology showed dermal proliferation of histiocytic cells. Immunoperoxidase studies showed the cells to be CD1a, S-100 and CD207/langerin negative, CD68, CD163, CD14 positive, suggestive for non-Langerhans histiocytosis (non-LHC). Immunohistochemistry also detected the presence of BRAF V600E point mutation. These findings oriented the diagnosis within a clinicopathologic spectrum including extracutaneous juvenile xanthogranuloma and Erdheim-Chester disease. Due to the diagnostic difficulty, after multidisciplinary evaluation, the lesion has been currently defined as non-X histiocytosis, no further classified. No mutation of BRAF was found in peripheral blood and CSF.

The patient follow-up is currently ongoing with regular check-ups: MRI shows reduction of the pituitary stalk thickening. To date, the tumour markers are negative, the instrumental examinations are normal.

The diagnosis of isolated CDI raises the question of its aetiology: patients must undergo complete clinical examinations, routine surveillance for new lesions, periodic blood tests and brain MRI.

Non-LCH is a rare entity in paediatric age, with predominantly cutaneous manifestations; however few cases of non-LCH are reported with internal organ involvement, including CNS and CDI. In this case, the clinical course, the radiological and histopathological features, could suggest a form of non-LCH with CNS involvement, but it's an hypothesis to be confirmed. For avoiding pituitary biopsy, further evaluation and follow-up is needed to determine a definitive diagnosis.

P2-94

Diagnostic and predictive value of brain magnetic resonance imaging in Algerian children with growth hormone deficiency

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Background: Growth hormone deficiency (GHD) in children is a rare condition. It may be idiopathic or may develop as a consequence of congenital or acquired organic pathology of the hypothalamic-pituitary axis. GHD can be partial or part of a combined pituitary deficiency. Brain magnetic resonance imaging (MRI) is very useful in establishing the etiology of GHD and predicting its severity.

Study Aims: To investigate the relationship between the detection of organic pathologies with MRI of the pituitary gland and the clinical and laboratory findings in a group of patients followed for GHD.

Materials and Methods: The study included a total of 131 Algerian children with confirmed GHD, who have been followed up in the pediatric departement of CHU Nafissa Hamoud, Pediatrics « A » in Algiers over a period of five years from (2017 - 2022) and whose pituitary MRI images were available. The patients were divided into tow groups: those with and without pathology demenstrabale on brain MRI. Clinical and laboratory features were compared between these tow groups.

Results: Mean (range) age at diagnosis was 08,4 (0,8 - 16,8) years, sex ratio: 2,3 :1 (94M – 41F). Mean (range) height standard deviation score (SDS) was 2.6 (- 4,66 DS - 0,47) with severe short stature (- 4 DS) noted in 2,7 % of patients. GH deficiency was total (< 3,5 ng/ml) in 45,6 % of cases and partial (3,5 – 7 ng/ml) in 45,40 % of cases. Abnormal MRI was found in 47 (38 %) children, with pituitary hypoplasia (n = 22: 16,7 %) and empty sella (n = 12 ; 9,2 %) being the most frequent findings, MRI was normal in 84 (64 %) of cases. Patients with anatomical abnormalities had more severe characteristics of GHD ($p < 0,05$) and MRI abnormalities were more frequent in multiple GH deficiency than in the isolated forme ($P = 0,05$).

Discussion: The use of brain MRI remains a significant contribution to the assessment of pituitary pathology in children. It is the investigation of choice in the exploration of this region and especially in the context of GH deficiency. GHD is associated with a wide variety of neuroanatomical abnormalities which can be identified by MRI, which should be carried out according to a structural algorithm. Our study shows a clear association between anatomical and functional abnormalities of the pituitary.

Conclusion: Brain magnetic resonance imaging is a useful tool in assessing GH deficiency pathogenesis and in predicting its evolution.

P2-95

Short-term impact of therapy with GNRH analogues on the growth of female children with central precocious puberty: a retrospective study of the last 20 years

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Introduction: Since the 1980s, long-acting gonadotropin-releasing hormone analogues (GnRHa) have been the standard treatment for central precocious puberty (CPP).

Aims: To evaluate the short-term response (at 6 and 12 months) of treatment with GnRHa in female children diagnosed with CPP, regarding growth, bone maturation (Greulich and Pyle method), predicted adult height (PAH) and pubertal development (Tanner stages).

Methods: A retrospective, observational, descriptive and analytical study was conducted in female children diagnosed with CPP, followed at a Pediatric Endocrinology Unit in a tertiary hospital. The sample was divided into 3 groups: group A – 21 children with CPP treated with GnRHa (main study group); group B – 10 children with CPP who did not undergo treatment; group C – 19 children without CPP (control group). Data was collected at baseline (t0), 6 months (t1) and 12 months (t2) of follow-up. In group A, the differences in the studied variables were analyzed between those timings. Later, the same data was compared throughout the follow-up period and between groups.

Results: In group A, there was a decrease in height and corrected height z-scores between t0 and t2 ($p=0.007$), as well as a decrease in growth rate (GR) between the 3 moments ($p<0.001$). Bone age z-score decreased while corrected PAH z-score increased, but the results had no statistical significance. There were no differences in Tanner stages for breast development between moments. At t0, group A GR was significantly higher when compared to groups B and C ($p=0.003$ and $p<0.001$, respectively). Group A GR at t1 and t2 decreased to values similar to group C, which are prepubertal values. Group A GR at t2 was significantly lower than group B ($p=0.013$). There were differences between groups A and C at all timings, regarding z-score of weight, body mass index and height, which were significantly higher in group A.

Conclusions: Short-term treatment with GnRHa was effective in slowing down linear growth and preventing breast development. However, short-term treatment does not seem to significantly decrease bone maturation and, consequently, to increase PAH significantly, suggesting that a longer treatment may be necessary to achieve these goals. These results allow a better understanding of the short-term effects of GnRHa treatment, which may be useful in the clinical management of pediatric patients with CPP.

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P2-145

Clinical observation of post-menarche in idiopathic central precocious puberty or rapidly progressive puberty treated by GnRHa and GnRHa+rhGH

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Objective: To investigate the clinical efficacy of GnRHa in the treatment of girls with post-menarche in ICPP or rapidly progressive puberty (RPP).

To analyze the effect of GnRHa combined with rhGH on growth velocity (GV) and predicted adult height (PAH) in the process of GnRHa treatment with too low growth velocity.

Methods: Retrospective analysis of the clinical data of 55 post-menarche ICPP/RPP girls within 3 months of menarche,all girls to receive treatment ,the 27 girls were treated with GnRHa alone(GnRHa group), another 28 girls received GnRHa+rhGH treatment when GV fell below 4 cm/year. all patients were treated regularly and followed up 1 year,the height, BA, GV, PAH, HtSDSBA, ΔPAH and ΔHtSDSBA were compared between the two group after 1 year of treatment, and the changes in GV, height, BA, HtSDSBA and PAH were observed before and after the combination treatment was observed.

Results: Among the 87 girls in GnRHa group, 31 girls chose to discontinue after 1~1.5 years of GnRHa therapy and were followed up to nearly FAH (158.01±2.73 cm), which was slightly higher than the PAH at the start of treatment (157.08±2.70 cm), but the difference was not statistically significant ($P>0.05$)

55 post-menarche ICPP/RPP girls ,the 27 girls were treated with GnRHa alone,another 28 girls received GnRHa+rhGH treatment when GV fell below 4 cm/year.after treat for one year,the height were 149.60±2.98 cm and 147.75±3.08 cm,PAH were 157.49±2.78 cm and 155.98±2.47 cm, ΔHtSDSBA were 0.93±0.26 and 0.58±0.24, ΔPAH were 5.08±1.48 cm and 3.10±1.35 cm, the GV were 6.00±1.38 cm/year and 4.71±0.99 cm/year respectively in rhGH+GnRHa group and GnRHa group.There were statistically significant differences in GV, height, PAH, ΔHtSDSBA and ΔPAH between the two group ($P < 0.05$).

Conclusions: ICPP/RPP girls within 3 months after menarche experienced significant growth retardation during the GnRHa treatment, the risk of below normal annual growth velocity was more pronounced in the second half year, especially the girls with older bone age, higher IGF-1 and LH basal value.

GnRHa treatment could improve FAH in ICPP/RPP girls within 3 months after menarche,but the effect was limited.

If the ICPP/RPP girls after menarche within 3 months showed low growth velocity (GV<4cm/year) during GnRHa treatment, combined rhGH therapy could improve GV and PAH, and no obvious adverse effects occured.

P2-146

Some descriptive characteristics of hypopituitarism in children and adolescents in Armenia

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Background: Hypopituitarism is a rare condition characterized by the insufficiency of 2 and more hormones produced by anterior pituitary gland. The major causes of hypopituitarism are brain tumors located near or in the pituitary gland and/or hypothalamus, cranial radiation, chemo- or surgical therapy, cranial traumas, neuroinfections, autoimmune hypophysitis (immune-mediated inflammation of pituitary gland) etc. Brain tumors are the second most frequent type of all pediatric malignancies. Depending on their localization patients with brain tumors may present neurological and/or ophthalmological symptoms, as well as weight anomalies and endocrine disorders ranging from growth hormone deficiency (GHD), hypogonadism (delayed puberty) to panhypopituitarism and diabetes insipidus (DI), alternately called arginine vasopressin deficiency (AVP-D). Antidiuretic hormone is not synthesized in the anterior pituitary but is stored and released into the blood from the posterior pituitary, and thus not every hypopituitarism is associated with DI/AVP-D.

Objectives: The aim of the current work is to evaluate and describe the some characteristics of patients <18 years of age with hypopituitarism in Armenia.

Methods and Results: 16 patients with hypopituitarism were enrolled in this study, from which 9 boys and 7 girls. The average age of patients at diagnosis was 8.6 years (4-15), in 56% of patients hypopituitarism occurred in prepuberty - before the age of 8y. Out of 16 patients 5 had meduloblastoma, 1 - craniopharyngioma, 1 – Hodgkin's' lymphoma, 1 – pituitary macroadenoma, and 8 – other cause of hypopituitarism, including septo-optic dysplasia. Hypopituitarism was associated with DI/AVP-D in 8 patients (50%), from which only 3 was post-surgical. Almost all cases (94%) of hypopituitarism were accompanied by secondary hypothyroidism, and 88% - by GHD, and only 75% - by secondary hypocorticism. Interestingly, 7 out of 8 (87.5%) tumor cases are treated with GH after surgical and/or chemotherapy without tumor re-occurrence.

Conclusion: DI/AVP-D is not a common disorder in post-operative hypopituitarism, but the most common is hypothyroidism, then GHD and then hypocorticism. All the children with cranial tumors, regardless the type of it, should be followed by the pediatric endocrinologist before and after the tumor treatment.

P2-147

Posterior Sellar Spine - an unusual cause of precocious puberty

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A 7 year old girl presented with breast development, mood changes and rapid growth spurt from 6.5 years. Clinically she was tall for her family and had Tanner stage 2 breast development and pubic hair. Bone age was 3 years advanced and pelvic ultrasound demonstrated globular anteverted uterus with endometrial lining and enlargement of the ovaries with follicles. LHRH test confirmed central precocious puberty with peak LH 44mIU/ml and FSH 19mIU/ml, with baseline estradiol of 92pmol/l. The pituitary function was otherwise normal. MRI pituitary demonstrated a 4x2mm hypodense lesion in the right side of the pituitary gland, with rim of enhancement suggestive of a pituitary adenoma. She was commenced on GnRH analogue treatment with good effect, with no further pubertal progression.

Repeat MRI after 6 months did not show any interval change in the appearance of the adenoma. Repeat baseline pituitary function and tumour markers were normal aside from raised IGF1 +3SD. By age 9 there was pubertal progression with more breast enlargement, vaginal discharge and emotional lability. She had incomplete suppression of the LH and FSH, but unmeasurable estradiol. The IGF1 remained elevated and HCG was normal. The bone age was now 2.6 years advanced and the pelvic ultrasound confirmed further uterine and ovarian development. It became clear that she had received the previous GnRH analogue injection 4 weeks late due to travelling.

The MRI was repeated and the same hypodense lesion was seen in the right side of the pituitary gland but this time the sagittal images were suggestive of a bony spur protruding into the pituitary gland and disrupting the pituitary shape with displacement of the posterior pituitary, which on coronal images was giving the appearance of a hypodense lesion with rim of enhancement. A CT brain showed the bony 'thorn' which was confirmed as a posterior sellar spine growth.

A posterior sellar spine is a rare congenital finding, arising from ossification of the cephalic end of the notochord. They have been reported as asymptomatic incidental findings or in association with pituitary disease e.g. galactorrhoea, hypopituitarism, Cushing's syndrome and amenorrhoea. There is one previous report in the literature of a posterior sellar spine with precocious puberty. On imaging the osseous spur is seen arising from the posterior sellar wall and extending into the pituitary fossa. They can be misdiagnosed as pituitary neoplasms, leading to further interventions, hence recognition and accurate diagnosis are critical.

P2-148

Diagnostic dilemma in an adolescent boy with hypopituitarism – pituitary apoplexy or Rathke cleft cyst?

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Background: Pituitary apoplexy (PA) is a rare clinical emergency in pediatric population. In patients with apoplexy-like symptoms, clinical and imaging features of PA, caused by hemorrhage in a pre-existing macroadenoma, are sometimes difficult to distinguish from Rathke cleft cyst (RCC).

Case Presentation: A 14.5-year-old boy, with an uneventful past medical history except for mild COVID-19 infection six months earlier, presented with fatigue, weakness and exercise intolerance lasting for several months. Over the last few weeks he had lost some weight, had nausea and vomited occasionally. Several days prior to admission, he started complaining of occipital and retro-orbital headache. At physical examination he appeared adynamic with Glasgow coma scale (GCS) score 15/15, and without neurological or visual disturbances. He was hypotensive (90/60 mmHg) with bradycardia (46 beats per minute). Patient's linear growth and pubertal development were appropriate for chronological age. At admission blood glucose was 3.9 mmol/L, serum sodium 132 mmol/l. Endocrine testing revealed secondary adrenal insufficiency, central hypothyroidism and hypogonadotropic hypogonadism with significantly elevated prolactin. Pituitary magnetic resonance imaging (MRI) detected a sellar mass with a suprasellar extension (1.6x1.3x1.7 cm), a caudal displacement of anterior pituitary, and slight pituitary stalk and optic chiasm displacement. Radimorphological characteristics of the mass were in accordance with PA. Ophthalmological testing showed no visual deficits. As a part of nonsurgical treatment strategy, hydrocortisone was immediately introduced, followed by levothyroxine and testosterone, which led to rapid clinical improvement, although excessive fatigue persisted despite ongoing hormone replacement therapy. Follow up MRIs after 3 and 9 months revealed no changes in size of the lesion, while the signal intensities appeared more heterogeneous on T2-weighted imaging, with a visible posterior hypointense area, which is suggestive of a RCC.

Conclusion: RCC may mimic PA, presenting with sudden onset of headache, endocrine dysfunction and, more rarely, visual or neurological disturbances. At the time of diagnosis, pituitary MRI may not be able to differentiate between PA and RCC. In the absence of visual or neurological deficits, conservative therapeutic approach is a valid option. Prompt introduction of corticosteroid therapy is required in patients with signs or symptoms suggestive of adrenal insufficiency. Substitution of other deficient hormones should be employed as needed. In non-surgically treated patients, repeated imaging can provide clues for more accurate distinction between RCC and PA.

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P2-149

Growth arrest due to multiple hormonal deficiencies caused by hemorrhagic apoplex of a Rathke cleft cyst - a rare difefrential diagnosis of acquired childhood pituitary insufficiency

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Among the acquired causes of growth hormone deficiency (GHD) in childhood, the most common reasons are benign or semimalign pituitary tumors - first and foremost craniopharyngiomas or dysgerminomas. We report on a very rare differential diagnosis in a 11-year-old, prepubertal boy with a growth arrest (1.1 cm in 2 years, height - 2.38 SDS). 2 growth hormone stimulation tests confirmed GHD (2,7 and 2,3 ng/ml after priming). There was mild central hypothyroidism (fT4 1.04 ng/dl, T3 0.9 ng/ml) and normal morning cortisol (10.9 mcg/dl) - thyroxin was substituted and a cortisol stress dose was prescribed. Nocturia was reported, but there was no polydipsia. Cranial MRI showed a 12x8x7mm cystic pituitary lesion with the strong suspicion of craniopharyngeoma. As calcifications were absent in the lesion on MRI, dysgerminoma was excluded by lumbar puncture and a short-term control MRI was arranged. The likely consequence of surgical removal was explained to the family. 3 months later a regression in size (10x7x6mm) was documented on MRI-consequently surgery was postponed and repeated MRIs performed. Over the course of 2 years the lesion showed further regression (5x3x3mm 9 months after presentation), the protein rich (hemorrhagic) areas were resorbed. The latest MRI- 2 years after first presentation- only showed minor residual enlargement of the pituitary stalk. Retrospectively, radiologists and neurooncologists consider hemorrhagic apoplex of a Rathke cleft cyst (RCC) as the most likely diagnosis. Over the observation period, therapy with thyroxin was continued, GH was substituted starting 6 months after diagnosis, together with ADH which improved persistent nocturia, and puberty was induced at age 14,5 years.

Summary and Conclusion: Rathke cleft cysts (RCC) are benign sellar and suprasellar lesions found in as many as 1 out of 6 healthy people, they are often asymptomatic and found incidentally. In the literature there are very few case series of describing hemorrhagic apoplexy oft the RCC with consecutive pituitary insufficiency. All diagnoses had been made histologically upon surgery.

In our patient we interprete the growth arrest prior to diagnosis as developing pituitary insufficiency caused by a RCC with asymptomatic hemorrhagic apoplex. Interestingly, there was significant regression over time with almost normal findings upon the latest MRI thus saving the child from pituitary surgery. The endocrine long-term outcome still hast to be evaluated after attainment of final height.

P2-164

Precocious puberty: let's talk about the north of Algeria!!

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La puberté précoce est définie comme le développement des caractéristiques sexuelles avant l'âge de 8 ans chez les filles et de 9,5 ans chez les garçons. L'objectif de notre étude était de calculer la prévalence de la puberté précoce en consultation spécialisée et de décrire le profil clinique, paraclinique, étiologique et de prise en charge ainsi que la qualité de vie des patients et de leurs parents.

Méthodes: Il s'agit d'une étude transversale descriptive de 2018 à 2020 dans le service d'endocrinologie pédiatrique de l'Hôpital d'Enfants de Sétif.

Résultats: quarante-neuf (49) enfants ont été inclus. La prévalence était de 6,68 %. L'âge moyen des patients était de 6,08 ± 2,39 ans. Nous avons noté une prédominance féminine à 91,8% (45 filles) avec un sex ratio F/G : 11,25. La tranche d'âge la plus touchée chez les filles était de 6-9 ans dans 64,4% et chez les garçons de 3-6 ans dans 50%. Les signes révélateurs chez les filles étaient dominés par le développement mammaire (61,6%) avec la présence de ménarche chez 37,8%. L'âge osseux moyen était de 8,14 ± 2,67 ans. Biologiquement, dans la puberté précoce centrale, le taux moyen de LH initial était de 0,93 Mui/L, le taux moyen de LH maximal après stimulation par la GnRHa était de 8,99 UI/L avec un rapport moyen entre LH et FSH de 1,33. Les étiologies étaient les suivantes chez les filles: la puberté précoce centrale 75,6% dominée par les causes idiopathiques à 79,4% et dans les causes périphériques le syndrome de McCune Albright était à 27,2%. Chez les garçons, la puberté précoce centrale 50% et l'autre moitié était représentée par la cause périphérique. Toutes les causes centrales ont été traitées avec un analogue de la GnRH. La qualité de vie notée avant et après le traitement n'a montré aucune différence significative chez les enfants avant et après le traitement, cependant, chez les parents,

Conclusion: Notre étude confirme qu'il y a une augmentation du nombre de cas de puberté précoce centrale, et qu'elle est plus fréquente chez les filles, et dominée par des causes idiopathiques ; et que la qualité de vie peut être significativement altérée tant chez les patients que chez les parents.

P2-165

Peripheral precocious puberty in a hospital in eastern Algeria

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Introduction: Peripheral or gonadotropin-independent PP is due to the production of sex steroids by gonadal or adrenal tissues independently of gonadotropins (which are usually suppressed). Peripheral PP may result from gonadal, adrenal or hCG-producing tumors (in boys) and exposure to exogenous sex steroids.

Peripheral PP may rarely lead to activation of pulsatile GnRH secretion and PPC due to prolonged priming of the HPG axis.

The pattern of pubertal development in peripheral PP may be asynchronous, in contrast to normal puberty or PPC, for example, with menarche occurring at an early stage of breast development. Autonomous ovarian cysts may manifest as vaginal bleeding and breast development.

Materials and Methods: during the study period from January 01, 2018 to December 31, 2020, we collected all cases of precocious puberty referred to our specialized pediatric endocrinology consultation, pole pédiatrique de Sétif, Algeria.

Results: We collected 45 cases of precocious puberty in girls. Peripheral causes accounted for 11 cases (24.4%).

The mean age of onset of symptoms was 3.77 years, with a consultation age of 4.69 years. The mean height was 110.54cm, i.e. +0.81 SDS, with a BMI of 16.45 Kg/M2, i.e. -0.35SDS. Mean bone age was 6.81 years with a delta BA/CA: 2.65. Mean baseline LH was 0.5 Mui/l, baseline E2 187.03pg/ml. Mean peak LH 0.53mui/l.

Causes were dominated by McCune Albright syndrome 3 cases, indeterminate 3 cases, 1 case hypothyroidism, 1 case ovarian cyst, 1 case granulosa tumor and 2 cases HCS.

Conclusion: Peripheral precocious puberty represents an important part of precocious puberty, in our series it was McCune Albright syndrome that dominated followed by indeterminate causes or a careful search made but alas no cause was found.

P2-197

Precocious thelarche and menarche in 5 years old girl – McCune - Albright syndrome – our experience

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Introduction: McCune - Albright syndrome is rare genetic disorder characterized by periphereal precocious puberty, fibrous bone dysplasia and cafe au lait skin spots.

Case: Almost 5 years old girl was sent to Endocrinological department due to precocious thelarche and menarche. At the time of first examination, patient had breast M 3 and large cafe au lait macule on the right tight, no pubic and axilar hair was present, no visible skeletal deformities were seen. Laboratory tests revelaled low gonadotropins and high estrogens levels, pubertal IGF 1 concentration and euthyroid condition. Her bone age was advanced. Pelvic ultrasonography showed bilateral ovarian follicles, hypophysis hyperplasia was confirmed on MRI scan. Due to advanced pubertal signs in order to reduce estrogen activity she was given LH RH agonists treatment while we were waiting for results of genetic analysis. Afetr short period of breast size regression and vaginal bleeding suppression under LH RH agonists administration both symptoms (vaginal bleeding and thelarche enlargement) occured again. Laboratory tests confirmed not only basal but also stimulated (LH RH test) low gonadotropins and very high estrogens levels. MRI pelvic scan confirmed pubertal type of uterus, bilateral large ovarian follicles with almost cystic formation on the right ovarium and fibrous dysplasia of proximal rigt femur. Although DNA analysis of peripheral blood did not confirm the presence of activating mutation of the stimulatory G-protein alpha subunit gene, we conclued diagnosis of McCune - Albright syndrome based on clinical features. The patient started aromatase inhibitor treatment - letrozole – 2,5 mg per day at the age of 5,5 years of life. After short period of treatment (10 days), massive but short time lasting vaginal bleeding accompanied by decreased levels of estrogens and collapsing of ovarian follicles occured. At the present time girl does not have signs of vaginal bleeding and breast size is reduced to stage M1, puberty is supressed. Unfortunately, she had pathological bone fracture, X ray confirmed multiple cystic lesions mostly on right arm and forarm. She started bisfosfonate treatment with pamidronate acid.

Conclusion: McCune - Albright syndrome is a rare sporadic disorder. Although DNA analysis do not reveal GNAS mutations, the final diagnosis might by made due to clinical features, the most frequent endocrine disorders is precocious puberty due to large ovarian cysts with estrogen hyperproduction. In her case long term letrozol and bisfosfonate treatment as well endocrinological follow up of other hyperfunctional endocrinopathies is needed.

P2-198

Idiopathic diabetes insipidus: beyond the initial diagnosis

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Introduction: Diabetes insipidus (DI) is a rare disease in children. In most cases it is acquired and central in origin (CDI). The most frequent cause of acquired CDI is brain tumor and idiopathic forms represent between 20-50% of cases, depending on the series. Autoimmune hypophysitis is a rare cause of DI and is a presumptive diagnosis with a suggestive brain MRI and ACTH and TSH deficiencies as the most common hormonal involvement, although it can manifest with diabetes insipidus in the case of predominant involvement of the pituitary stalk. Anti-pituitary autoantibodies are not sensitive nor specific. We present the case of a 6-year-old boy with an initial diagnosis of idiopathic DIC that was later diagnosed as possible autoimmune hypophysitis.

Clinical Case: 6-year-old boy referred to the ER due to polyuria and polydipsia. During his admission a water restriction test is carried out and CDI is diagnosed. Desmopressin is started with a good response. Pituitary hormones and tumor markers are normal and brain MRI shows the absence of the typical bright spot of the neurohypophysis. The MRI control 4 months later reveals a thickening of the pituitary stalk with extension to the neurohypophysis without local compression of adjacent anatomical structures. The diagnosis of idiopathic DIC is ruled out and the patient is admitted at the referral centre to complete the study. Tumor markers in the CSF are negative and rule out dysgerminoma; the imaging study rules out osteolytic lesions or other stigmas of histiocytosis. Hormonal control shows TSH 3.5 mIU/L, FT4 0.59 ng/dl, Cortisol 6.4 mcg/dl and IGF-I 70 ng/ml (-0.6 SD). Adrenal insufficiency is ruled out with an ACTH stimulation test and treatment with levothyroxine is started. It is oriented as possible autoimmune hypophysitis and a conservative management is decided through clinical, analytical and radiological follow-up. 12 months after the onset of the clinical symptoms there has been a decrease in the growth velocity and treatment with GH is planned to be started soon given the stability of MRI images.

Conclusions: Idiopathic DI is rare in children and requires periodic follow-up to rule out underlying organic lesions. Autoimmune hypophysitis is a rare entity whose diagnosis must be accompanied by strict follow-up through ophthalmologic control, brain MRI, pituitary hormones and tumor markers. There are no conclusive studies regarding treatment in the pediatric age group, but conservative management is a good alternative if there are no compression symptoms.

P2-232

Diabetes insipidus in pediatric onset langerhans cell histiocytosis with excellent response to treatment

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Introduction: Langerhans cell histiocytosis is a neoplastic disorder characterized by proliferation of myeloid dendritic cells. It can involve single system or multisystem with commonly involving sites including skin, bone, central nervous system, lung, hematopoietic system, liver and spleen. It also involves the endocrine system with diabetes insipidus a common presentation in 15-50% cases. It has a broad spectrum of presentation ranging from a relatively benign course to a fulminant progressive disease.

Case Report: We present a case of 4 years old male child presented to us with rash on scalp and multiple lumps on head for 3 months and history of polyuria for 2 months. On physical examination findings were consistent with Langerhans cell histiocytosis in the form of swellings involving frontal and temporoparietal bone which were firm and smooth with no tenderness, greasy erythematous scaly rash involving scalp, and neck region and hepatosplenomegaly. Child was investigated on which he had microcytic hypochromic anemia with atypical lymphocytes on peripheral smear and normal metabolic panel and liver function tests. Histopathological analysis of the lump biopsy showed findings consistent with Langerhans cell histiocytosis. His urine had decreased specific gravity (1.000) spot urine osmolality of 254 mOsmoles/kg and spot serum osmolality 280mOsmoles/kg. So we proceeded further with water deprivation test which was consistent with central diabetes insipidus and other endocrinological investigations including thyroid profile, serum cortisol, serum prolactin and MRI brain pituitary protocol which were all normal. His bone marrow examination was normal with no evidence of malignant cell infiltration. So the child was started on chemotherapy after which size of the swellings decreased, rash improved with overall symptomatic improvement and tab desmopressin for diabetes insipidus was started.

Discussion: Langerhans cell histiocytosis is a malignant disorder which is mainly treated with chemotherapy and management of complications. Poor prognostic indicators include presentation in age less than 2 years, multisystem disease, risk organ involvement (bone marrow, blood, liver, spleen) and unsatisfactory response to initial treatment.

P2-233

McCune-Albright Syndrome: knowing how to think about it

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Introduction: McCune-Albright syndrome (MAS) is characterized by fibrous dysplasia (FD), cafe-au-lait skin spots and precocious puberty (PP). SAM is a rare disease and its prevalence is estimated between 1/100,000 and 1/1,000,000. Somatic activating mutations of the GNAS gene located on chromosome 20q13 encoding the α subunit of the regulatory protein Gsα are responsible for the entity.

Case Report: This is a patient referred by her attending physician at the age of 6 years and 5 months for treatment of precocious puberty. She is 1m22 tall and weighs 23 kg. The patient has already presented a pubertal episode at 5 years of life, characterized by pink leucorrhoea. She then presented an S2 status breast augmentation. Developed and pigmented lips, and type P2 pubic hair. The biology shows an E2 increased to 75 pg/ml with the indosable gonadotropins. Pelvic ultrasound shows a stimulated uterus with polycystic ovaries. She also has a unique, irregular patch of café-au-lait skin on her right flank. Bone age is overmature 1 year. The thyroid balance is normal as well as the androgens. treatment with an aromatase inhibitor was initiated.

Discussion: Diagnosis is usually clinical. Evaluation of patients with MAS should be guided by knowledge of all possible impairments and appropriate investigations. Genetic testing is possible, but not routinely available.

Conclusion: MAS is a rare disease. Genetic counseling should be offered although SAM is not hereditary. Malignant transformation of DF lesions is rare and probably occurs in less than 1% of cases.

P2-236

Congenital Hypopituitarism: a pathology not to be ignored

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Introduction: Pituitary deficiency, or hypopituitarism, is defined by insufficient synthesis of one or more anterior pituitary hormones (growth hormone, TSH, ACTH, LHFSH, prolactin) associated or not with diabetes insipidus (ADH deficiency). In children it is more frequently congenital, due to abnormal pituitary development; it is then a rare disease with an estimated prevalence of between 1/16.000 and 1/150.000.

Case Report: A 2-month-old female infant, the first full-term born of a consanguineous couple. The diagnosis is revealed by the presence since the neonatal period: of hypotonia, prolonged jaundice as well as recurrent hypoglycaemia suggestive of a hypotalamo pituitary deficit. Hormonal exploration revealed combined pituitary damage: adrenal insufficiency, central hypothyroidism with GH deficiency. RMI showed hypoplasia of the anterior pituitary. the malformative assessment returned to normal.

Discussion: Our patient presented a severe anterior pituitary deficit explaining the clinical picture. the diagnosis of congenital hypopituitarism is important from birth to avoid hypoglycaemia and adrenal insufficiency and their cerebral and vital risks. the prognosis is good if diagnosed and treated early.

Conclusion: Congenital hypopituitarism is a rare disease. responsible for an isolated or combined deficit. MRI is currently the most efficient means for diagnosis and a prognostic approach. Treatment is based on hormone replacement therapy. Between 80 and 90% of congenital hypopituitarism cases remain unresolved in terms of molecular genetics.

Sex differentiation, gonads and gynaecology or sex endocrinology

P2-40

Mass of the inguinal region, from casual finding to genetic diagnosis

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The SRD5A2 gene (MIM607306) codes for the type 2 5α-reductase enzyme that catalyzes the conversion of testosterone to its active metabolite, dihydrotestosterone (DHT), essential for the development of the male external genitalia. Pathogenic variants in homozygosis or compound heterozygosis may be responsible for a 46XY Disorder of Sex Development.

Case: A 5-year-old girl who was referred to us after the mother noticed lumps on both labia majora when adopting the genuflecting position. No family or personal history of interest, clinical examinations at birth record genital examination at birth and in successive health check-ups as a normal-configured female phenotype.

- Clinical examination: 5.2 years old, 19.5 kg (p45, +0.1 SD), 115cm (p72, +0.61 SD), BMI: 14.7 kg/m2 (p31, -0.2SD), female phenotype. Rounded masses in the bilateral inguinal area, close to the pubis measuring 1.5 x 1.5 cm, cremasteric reflex detectable in genuflection. Thickened labia majora, labia minora decreased in size with posterior fusion, vaginal introitus, normal-shaped non-hypertrophic clitoris. Prader 3/5.
- Abdominal ultrasound: testes are observed in the inguinal canal, 13x4 mm and 12x4mm, epididymis is identified. There is no evidence of the uterus or ovaries.
- Abdominal MRI: normal-sized testes with epididymis and minimal amount of fluid around them are observed in the inguinal canal. No ovary, uterus, or prostate is identified. In the labia majora, a small vaginal introitus can be sensed, without connection to any anatomical structure.
- 46, XY karyotype. SRY gene positive.
- Prepubertal gonadal profile with LH 0.12 mIU/ml, FSH 0.7 mIU/ml, Antimüllerian Hormone 107 ng/ml, Inhibin B 101 pg/ml. Estradiol <24 pg/ml, Prolactin 9.2 ng/ml, Cortisol 9 ug/dl.

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ACTH STIMULATION TEST	Base Line	30 minutes	60 minutes
17 OH Progesterone (ng/ml)	0.26	1.37	1.53
17 Oh Pregnenolone(ng/ml)	1.1	2.36	2.8
11 deoxycortisol(ng/ml)	2.7	3.4	3.6
Androstenedione (ng/ml)	0.03	0.03	0.05
S-DHEA (ug/dl)	6.2	6.6	7
hCG STIMULUS TEST	Pre	Post	T/DHT Rate
Testosterone (ng/dl) –T	0.69	377	23
Dihidrotestosterone (ng/dl) -DHT	0.03	1	377

- A homozygous variant was detected, c.377A>G; (p.Gln126Arg) in exon 2 of the SRD5A2 gene, already previously described as pathogenic; heterozygous parents (INGEMM, SDSeq_v3.0).

Conclusions: Genital feminization is a clinical challenge that requires a correct gender assignment, taking into account factors such as identity, the possibility of fertility, the need for masculinizing genitoplasty or gonadectomy and hormone replacement treatment, being of vital importance to have a multidisciplinary team.

P2-41

5α-Reductase Type 2 Deficiency over three decades in a single center

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Female phenotype and sex reversal are often reported in 46,XY patients with 5α-Reductase Type 2 Deficiency (5αRD2). In case of late diagnosis, at puberty, virilization occurs. Over the years, sex assignment in case of early diagnosis evolved from female to male. We report four cases of 5αRD2, managed differently over three decades.

All children presented with a female phenotype (EGS 3-4), palpable gonads, absent uterus, and 46,XY karyotype. All patients were assigned female at birth. All were from consanguineous families, except for patient 1.

Patient 1, of Spanish origin, was 3-months-old when referred in 1992. Six years later, the molecular diagnosis was confirmed: p.(Gly115Asp)/p.(Ala207Asp) *SRD5A2* compound heterozygous mutations. At puberty, she expressed female identity, and started treatment with GnRH analogues. At 19, vaginoplasty and gonadectomy were performed.

Patient 2, of Italian origin, was 9-days-old when referred in 1996. Two years later, the molecular diagnosis was confirmed: p.(Gly115Asp) *SRD5A2* homozygous mutation. Parents preferred to keep the female-sex orientation. The child underwent gonadectomy at 4. Estrogen treatment started at 12. At 19, after sexual intercourses with her boyfriend, a vaginal depth of 5 cm was noted and dilatations were discussed. She currently expresses no doubts about her female identity.

Patient 3, of Moroccan origin, was 2-days-old when referred in 2002. Two weeks later, the molecular diagnosis was confirmed: p.(Lys41ThrfsTer94) *SRD5A2* homozygous mutation. Parents opted for female-sex orientation, bilateral gonadectomy at one year, vaginoplasty at 2, clitoro-vulvoplasty at 3. Estrogen replacement therapy began at 12. She currently seems to cope well with her situation.

Patient 4, of Pakistani origin, was 1-day-old when referred in 2022. Four weeks later, the molecular diagnosis was confirmed: p.(Gly196Ser) *SRD5A2* homozygous mutation. After the declaration of male sex at 3 months, topical DHT was applied from 3 to 9 months resulting in modest genital bud growth.

For all patients and their families, psychological and multidisciplinary supports were provided throughout follow-up.

Growing evidence suggests male sex assignment in 46,XY newborns with 5αRD2 to avoid gender dysphoria among those assigned female. This evidence is based on varying clinical management ranging from early female sex assignment with gonadectomy (surgical or pharmacological) or without gonadectomy and pubertal virilization, to early male sex assignment with DHT topical treatment. More precise long-term data, including adults' quality of life evaluation, are required to refine the clinical approach of this condition. Psychological support along with multidisciplinary management remain pivotal.

P2-43

Persistent Müllerian duct syndrome and the identification of a yet unreported homozygous mutation in AMHR2 gene

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Introduction: Persistent Müllerian duct syndrome (PMDS) is a rare disorder of sex development (DSD) characterized by the persistence of Müllerian derivatives, the uterus and/or fallopian tubes, in otherwise normally virilized boys. PMDS is caused by mutations in the genes coding anti-Müllerian hormone (AMH, PMDS type 1) or the AMH receptor (AMHR2 gene, PMDS type 2) and it usually presents as undescended testes (cryptorchidism) or inguinal hernias.

Case Report: We present the case of a 13-year-old boy, with a history of bilateral cryptorchidism. Several attempts of right orchidopexy were performed in 2013 and 2014. Exploratory laparoscopy was performed in search of the left testis that was identified intraabdominally and a fibrous structure extending from the left testis to the deep inguinal ring was identified (Mullerian duct remnants) and also a medially located abdominal mass, bilaterally fixated to the parietal peritoneum (uterine remnant). The mass was dissected and left orchidopexy was performed. Testicular biopsy revealed immature prepubertal testicular tissue. The karyotype was 46XY, without other numerical or structural chromosomal abnormalities. Reinterventions for left testis ectopy were performed in 2018 and subsequently in 2021, when a left testicular remnant was identified in the inguinal canal and removed (histopathologic examination was consistent with testicular agenesis). Three months after the left orchidectomy surgery, ultrasound followed by abdominopelvic RMI identified a structure resembling a testis in the left inguinal canal. Another laparoscopic exploration was undergone and a biopsy from the suspected mass was performed. The histopathologic examination showed characteristics of immature testis. The patient was later referred to our clinic with the suspicion of sexual differentiation disorder. Serum AMH and inhibin B were normal. Therefore, the diagnosis of PMDS was suspected. Genetic testing was performed using Next Generation Sequencing in a gene panel that included AMH and AMHR2 genes. A homozygous variant classified as likely pathogenic in AMHR2 gene was identified, yet unreported in the literature.

Conclusion: High degree of suspicion and awareness is needed to diagnose this condition. Early treatment is needed to maintain fertility and to prevent the occurrence of malignancy in remnant Müllerian structures.

P2-44

New variant in DHX37 associated to 46,XY gonadal dysgenesis

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Introduction: 46,XY gonadal dysgenesis (GD) represents a heterogeneous group of disorders/differences of sex development (DSD) characterized by abnormal gonadal development leading to a wide phenotypic spectrum. Variable degrees of external genitalia undervirilization are observed, ranging from micropenis to female-like genitalia and partially or fully-developed Mullerian derivatives.

Case Report: A 6 years-old boy followed-up in our Pediatric Endocrinology clinic consultation due to bilateral cryptorchidism. At neonatal period, was evaluated by testicular hydrocele where testicular sonography reported as normal bilateral testis structure. There was not any personal or family history of interest.

At physical examination testis were found in inguinal channel entrance of 0.5 cm3 with normal penis and no other dysmorphic features. Basal levels FSH were elevated, Inhibine-B and AHM were low consistent with low reserve of gonadal tissue. Karyotype show 46XY. Laparoscopic examinations were performed and no mullerian structure were found, in scrotum were observed hipotrophic testis (04.cc) and spermatic cords, also a left testis fragment was collected for histological study and spermatogonia was absent.

A massive sequencing analysis of genes and regions associated with DSD in index case and parents aws performed and an heterozygous variant in the DHX37 gene, c.1261C>T; p.(Arg421Trp) in exon 9 with maternal origin was detected. This variant, missense, affects a highly conserved amino acid and has been classified as probably deleterious by bioinformatics tools. Following the ACMG variant classification recommendations, this variant was classified as a variant of uncertain significance (VOUS), but probably related to the phenotype present, although for the moment without sufficient evidence.

DHX37 (DHEA-Box-Helicase-37) is an RNA helicase that plays a prominent role in the biogenesis of ribosomes. In relation to sexual development, DHX37 has been described as specifically expressed in the somatic cells of the gonads during testicular determination and development, although the exact role of DHX37 in testicular development is currently unknown. Recently, heterozygous variants have been identified in non-syndromic gonadal dysgenesis 46,XY and testicular regression syndrome. Therefore, DSD 46,XY due to heterozygous variants in DHX37 are characterized by absence or low reserve of gonadal tissue. The development and function of the ovary is apparently normal in mothers carrying pathogenic variants in DHX37.

Conclusion: DHX37 pathogenic variants are a new cause of an autosomal dominant form of 46,XY DSD, including gonadal dysgenesis and TRS, showing that these conditions are part of a clinical spectrum. This raises the possibility that some forms of DSD may be a ribosomopathy.

P2-49

Case series: WT 1 mutation- an important differential in 46, XY disorders of sexual development (DSD)

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The Wilms' Tumour (WT1) gene is thought to play an important role in nephrogenesis, genitourinary development, and sex determination.

We report three cases followed up in a tertiary care center in Sri Lanka. All three patients were referred for evaluation of ambiguous genitalia (stretched penile length <= 2cm, penoscrotal hypospadiasis in all three patients. Patient one had bilateral palpable testes in inguinal canal. Patients two and three did not have any palpable testes) in the neonatal period. Their karyotypes revealed 46, XY.

After exclusion of other conditions, the patient 1 was screened and was positive for WT1 mutation. Later, he developed nephrotic range proteinuria and hypertension. His renal biopsy showed moderate tubular atrophy with glomerulosclerosis. He is currently on multiple immunosuppressants, including biologics and is followed up closely by a Paediatric nephrologist.

In patient 2, an ultrasound scan (USS) revealed the presence of Mullerian structures and pelvic testes. Echocardiogram showed evidence of osteum secondum atrial septal defect. He was lost to follow up for a short period and he presented with edema and proteinuria after a respiratory tract infection and a clinical diagnosis of WT1 mutation association was made. He unfortunately succumbed to acute renal failure.

Patient 3 had USS findings of persistent Mullerian structures and undescended testes. Gonadal biopsy revealed bilateral testicular tissues and it was decided to register him as a boy. Bilateral orchidopexy was done. Routine screening revealed microalbuminuria. His proteinuria is currently being managed conservatively under a Paediatric Nephrologist. Genetic testing is pending for patients 2 and 3. None of these patients had Wilms tumor on serial USS monitoring of kidneys.

WT1 mutation is a rare, but important differential diagnosis in 46 XY, disorders of sexual development (DSD). Routine periodical clinical and biochemical screening as well as serial radiological assessment for this association may be lifesaving in patients with 46 XY, DSD where genetic testing is not feasible.

P2-50

A Rare Diagnosis in a Virilized Adolescent with a 46,XX Karyotype: Gonadoblastoma with Dysgerminoma

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Keywords: Dysgerminoma, gonadoblastoma, virilization

Introduction: Gonadoblastoma is a rare ovarian tumor composed of sex cord cells and primitive germ cells. Although it is frequently seen in patients with 46,XY gonadal dysgenesis, it is also rarely seen in patients with a 46,XX karyotype. Here, we report a girl with a 46,XX karyotype presenting due to an uncommon cause of virilization, which was caused by bilateral gonadoblastoma and dysgerminoma.

Case: A 14.5-year-old girl with significant hirsutism for the last 2 months was admitted to outpatient clinic. She was born at term, with appropriate weight for gestational age to first-degree consanguineous parents, and her family history was unremarkable. Puberty started at the age of 10.5 years and menarche has not occurred yet. At the initial evaluation, her weight, height, and body mass index were 42.7 kg (-1.95 SDS), 158.1 cm (-0.5 SDS), and 17.08 kg/m2 (1.85 SDS), respectively. Pubertal stage was Tanner stage 4. On genital examination, a 1.5 cm measured clitoromegaly was noted and, gonads were unpalpable. The modified Ferriman Gallwey (mFG) score was calculated as 16 and a deepening of the voice was also remarkable. Hormonal evaluation was consistent with hypergonadotropic hypogonadism (FSH 87.6 mIU/L, LH 43.4 mIU/L). Total testosterone level was high (1.07 ng/mL). Adrenal androgen levels were within normal ranges and congenital adrenal hyperplasia was excluded with ACTH stimulation test, and no adrenal mass was observed on imaging. On pelvic imaging, uterus and ovarian volumes were consistent with the pubertal stage. Tumor markers including β-hCG, α-fetoprotein, and lactate dehydrogenase were normal. Karyotype analysis revealed 46,XX, and PCR analysis showed the absence of the *SRY* gene. The patient, who did not come to follow-up for about 2 years was reevaluated at the age of 16.3 years with the complaint of progressive hirsutism. The mFG score was 22, clitoromegaly was measured as 3 cm. Abdominopelvic MRI showed that bilateral ovaries were fibrotic, however, no abdominal or gonadal mass was visualized. A laparoscopic gonad biopsy revealed bilateral gonadoblastoma and dysgerminoma on the right ovary, and bilateral gonadectomy was performed ultimately. There was no pathological FDG uptake on PET/CT and she did not require chemotherapy. Following the gonadectomy, hormone replacement therapy was started.

Conclusion: Malignant gonadal tumors should be kept in mind in cases with primary gonadal insufficiency with a 46,XX karyotype and progressive virilization. Even when laboratory and imaging tests show no abnormalities, gonadal biopsy should be considered.

P2-96

Clinical outcomes and genotype-phenotype correlations in patients with complete and partial androgen insensitivity syndromes

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Purpose: Androgen insensitivity syndrome (AIS) is a rare X-linked recessive disorder caused by unresponsiveness to androgen because of mutations in the AR gene. Here, we investigated the clinical outcomes and molecular spectrum of AR variants in patients with AIS attending a single academic center.

Methods: This study included 19 patients with AIS who were confirmed by molecular analysis of AR. Clinical features and endocrinological findings were retrospectively collected, including presenting features, external genitalia, sex of rearing, timing of gonadectomy, pubertal outcomes, and sex hormone levels. Molecular analysis of AR was performed using Sanger, targeted gene panel, or whole exome sequencing.

Results: Among all 19 patients, 14 (74%) were classified as having complete AIS (CAIS), whereas five (26%) had partial AIS (PAIS). All patients with CAIS and three patients with PAIS were reared as female. One patient with CAIS manifested mixed germ cell tumor at the age of 30 years. Molecular analysis of AR identified 19 different sequence variants; 12 (63%) were previously reported, and the remaining seven (37%) were novel. Missense mutations were the most common (12/19, 63%), followed by small deletions, nonsense mutations, an insertion, and a splice site mutation.

Conclusions: Here, we describe the clinical outcomes and molecular characteristics of 19 Korean patients with AIS. Patients with PAIS manifested various degrees of masculinization of the external genitalia. Nonsense and frameshift mutations were frequent in patients with CAIS, whereas patients with PAIS harbored exclusively missense mutations.

P2-97

Single Center Experience in Patients with Mixed Gonadal Dysgenesis

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Objective: Mixed gonadal dysgenesis (MGD) (45,X,46,XY mosaicism) is a rare chromosomal disorders of sexual development (DSD). In this article, single center data were evaluated.

Material and Method: From the files of ten patients followed up with the diagnosis of mixed gonadal dysgenesis, complaints and physical examination findings, laboratory tests, chromosome analysis, FISH results, ultrasound, laparoscopy, pathology reports, multidisciplinary council decisions were reviewed. According to the gonadal dysgenesis classification; it was defined as bilateral streak gonad complete gonadal dysgenesis (CGD), one gonad streak one gonad dysplastic gonad mixed gonadal dysgenesis (MGD), bilateral dysplastic testis partial gonadal dysgenesis (PGD) (1). The treatment dose, duration and height gains of the patients receiving growth hormone therapy were evaluated.

Results: The mean age at presentation of the patients was 6.15 (±6.05) years, and the age at presentation ranged from 6 months to 17.5 years. The mean height sds of the patients was -1.34 (±1.56), mean body weight sds -0.23 (±1.43), mean BMI sds was 0.47 (±1.02). Five patients presented with ambiguous genitalia, four patients had short stature, and one patient had amenorrhea. Five patients were completely female phenotype, and five patients were insufficiently virilized male phenotype. External masculinization score (EMS) changes between 1 and 6.5 (2). Seven patients underwent gonadal biopsy. Four of these patients were classified as CGD, two as MGD, and one as PGD. With the decision of the multidisciplinary council, it was decided to raise six patients as girls and four patients as boys. Gonadectomy was performed on the patients who were decided to be raised as girls. Since four of these patients had short stature, growth hormone (45 mcg/kg/day) treatment was started after gonadectomy (3). One patient did not have short stature, and one patient did not come for regular follow-ups. Height gain of the patients was 29.4 (±14.67)cm, height SDS gain was 0.42 (±0.49). Additional estradiol treatment was given to five patients. Short stature was not detected in patients who were planned to be raised as males.

Conclusion: The mixed gonadal dysgenesis phenotype is very diverse. Gender decision of cases with ambiguous genitalia should be made by the multidisciplinary council at an early stage. Growth hormone therapy improves adult height in short girls (3). Therefore, early diagnosis is important for appropriate treatment and follow-up.

P2-98

Novel genetic variant in NR5A1 (SF1) gene with clinical presentation of Hypergonadotropic hypogonadism

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Background/Objectives: Hypergonadotropic hypogonadism (HH) is characterised by primary gonadal failure with excess of pituitary gonadotropin secretion. The causes can be congenital or acquired. Herein, we report a case of a 10-years-old-boy with obesity, development of HH during follow-up and a novel genetic variant in NR5A1 (SF1) gene with de novo origin.

Methods: The child presented with obesity (started at the age of 5 years with gradual increase of the weight) and development of eunochoid body shape. At the age of 10 years his BMI was 28.19 kg/m2, with normal height of 138 cm. The pubertal development was Tanner stage 3 with testes' size of 4 ml. In the next 3 years his BMI increased to 32 kg/m2 despite recommended change in the lifestyle. Pubarche advanced to stage 4 with no increase of testes' size. Gradually he developed lab constellation of HH with elevated pituitary goandotropins and estradiol levels, decreased testosterone and borderline SHBG levels. The karyotype was 46,XY. Treatment with testosterone has been started at the age of 13 years with reducing of weight with 10 kg for 6 months. DNA from K2EDTA blood was extracted from the proband and his parents. Sanger sequencing of coding regions and intron-exon boundaries of NR5A1(SF1) gene was performed after PCR amplification.

Results: A heterozygous genetic variant NR5A1:c.371_374del (p.Pro124ArgfsTer171) with de novo origin was identified in the patient.

Conclusion: SF-1 regulates a constellation of genes that are required for gonadotrope function. Further studies are needed to identify the mechanisms by which these effects are mediated. In our opinion NR5A1(SF1) mutation screening needs to be included in differential diagnosis of HH.

P2-99

Three cases of Leydig cell tumor with different clinical presentation

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Leydig cell tumors(LCTs) are rare testicular tumors, representing 1-3% of them. They are usually unilateral but can be bilateral up to 3%. Its incidence is bimodal, peaking at 5-10 years (20%) and 25-35 year (80%). Malignant transformation has not been clearly proven in children, whereas in adults they are malignant in 10% of cases. The main clinical manifestation is a palpable, painless testicular mass associated in a variable percentage with endocrinological manifestations that vary according to the age of onset. In prepubertal patients, signs of early virilization are nearly constant and may occur before the testicular abnormality. During puberty, the diagnosis is often difficult as the symptoms are masked by the normal pubertal development. Orchiectomy has been the classical treatment, however, the testicular sparing surgery can be performed on those who meet the criteria for benignity of the testicular mass. Surgical excision of the tumor is frequently curative, with arrest and partial regression of clinical signs.

We describe three patients with LCTs with different clinical presentation.

Patients(P) characteristics

			Physical examination			
P	**Age at diagnosis (years)**	**Reason for consultation**	**Tanner stage**	**Testis volume with mass**	**Contralateral testis volume**	**Bone age**
1	8,33	Precocious puberty	PH 3 G 2	6ml	2ml	13,5
2	11,16	Testicular pain (hydatid torsion)	PH 4 G 3	6ml	8ml	14
3	11,5	Follow up for history of precocious pubarche	PH 4 G 3	6 ml	8-10ml	14

PH: pubic hair, G: genitalia

Laboratory test and treatment

	Pre surgery levels					**Surgery**	**Post surgery levels**		
P	LH mUI/ml	FSH mUI/ml	To ng/dl	β-HCG	AFP		LH mUI/ml	FSH mUI/ml	To ng/dl
1	<0,1 (0,7- 2)	<0,2 (0,16-3,5)	190 (10- 32)	N	N	tumorectomy	3,6	3,5	97,7
2				N	N	orchiectomy	11,2	2,2	183
3	2,04 (0,3- 4,4)	4,54 (0,4-6)	406 (15- 280)	N	N	tumorectomy			

LH: luteinizing hormone, FSH: follicle-stimulating hormone, To: testosterone, AFP: alpha-fetoprotein, β-HCG: β-human chorionic gonadotropin

Post surgery treatment	**Post- GnRH analog treatment**		
	LH mUI/ml	FSH mUI/ml	To ng/dl
triptorelin aromatase inhibitor	0,7	0,3	<2,5

We report three patients with LCTs who consulted for diferent reasons. We found in the anamnesis that all had a history of signs of early virilization. These cases highlight the importance of investigating the presence of testicular tumors using complementary imaging methods in boys with early virilization, especially in prepubertal patients but also in those with early puberty.

P2-100

Diverse Phenotypes of Three Cases of Partial Androgen Insensitivity Syndrome with Androgen Receptor Gene Variants

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Background: Partial Androgen Insensitivity Syndrome (PAIS) is characterized by varying degrees of masculinization defects due to impaired androgen action, resulting in a wide range of physical and psychological phenotypes.

Case 1: 18-year-old with a male social gender. The patient presented with hypospadias, micropenis, and cryptorchidism during the neonatal period, and received testosterone therapy during infancy, but showed no increase in penile length. At 13 years old, the patient exhibited hypergonadotropinemia with normal testosterone levels. A silent mutation in the androgen receptor (AR) gene with a previous report of pathogenicity was identified. Due to the presence of marked gynecomastia, the patient's male gender identity was thoroughly confirmed, and a bilateral mastectomy was performed at 14 years old in accordance with the patient's wishes.

Case 2: 14-year-old with a male social gender. The patient presented with hypospadias and micropenis during the neonatal period and received testosterone therapy during infancy, resulting in a slight increase in penile length. The patient preferred wearing skirts during early childhood and developed gynecomastia at 13 years old. Subsequently, the patient expressed discomfort with either male and female gender identity, a desire for longer hair and an interest in cosmetics. A de novo missense mutation in the AR gene was identified.

Case 3: 16-year-old with a female social gender. At the one-year age medical checkup, bilateral inguinal masses were noticed, leading to the diagnosis of clitoromegaly and the presence of 46,XY. Ultrasonography suggested the presence of testes in both inguinal regions, and MRI revealed the absence of a uterus and ovaries. Bilateral orchiectomy was performed at five years old, and vulvoplasty at seven years old. Female hormone replacement therapy was initiated at 11 years old, but medication adherence was poor. The patient has predominantly male friends, prefers dark-colored clothing, and the family suspects a more masculine gender role. A previously reported pathogenic missense mutation in the AR gene was identified.

Conclusion: We presented three cases of PAIS with diverse clinical courses. It is essential to be aware of the need for various physical and psychological care in these patients.

P2-101

Change in timbre of voice as one of the signs of hyperandrogenism in a 11-year-old girl- a Case report

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Background: Partial gonadal dysgenesis with a 46,XY karyotype (46,XY PGD) is a disorder of sex development (DSD) associated with abnormal development of the gonads. It is characterized by abnormally developed external genitalia with or without Mullerian structures. The degree of abnormality varies from a female phenotype with clitoral hyperplasia to a male phenotype with isolated hypospadias. The incidence is unknown. In 20-30% of patients, gonadoblastoma or invasive germ cell neoplasm develops.

Case Report: A 11- year- 4 month-old girl was admitted to the Department of Pediatrics, Endocrinology, Diabetology with Cardiology Devision of the Medical University of Bialystok for diagnosis of a change in voice timbre that had been present for about six months. On physical examination, except for a low voice and hypertrophied clitoris, there were no significant abnormalities. Hormonal studies confirmed high levels of androgens and gonadotropins. Due to the high level of testosterone, the diagnosis was expanded with genetic testing - a normal male karyotype was obtained - 46,XY. Pelvic imaging studies showed a small uterus, a gonad in the right groin suggestive of a testis, and a non-specific tissue structure in the left inguinal region. The patient had the abnormal gonads removed and hormonal treatment was administered.

Results:

1. Patients with abnormal genitalia require genetic diagnosis.
2. Hormonal treatment for patients with a uterus present is estrogen and progesterone, and in girls without a uterus, only estrogen is used.
3. Prophylactic gonadectomy before puberty should be performed in patients with a 46,XY karyotype to avoid androgenization and the development of gonadal malignancies.

P2-102

Ovotesticular Disorder of Sexual Development Diagnosed in Adolescence – a Twins Case Report

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Introduction: Individuals with ovotesticular disorders of sexual development (OT-DSD) have both seminiferous tubules and ovarian follicles. The combination of gonads could be separated (ovary-testis), unilateral (ovotestis-ovary or ovotestis-testis), or bilateral (ovotestis-ovotestis). The last one is the rarest variant (24.5%). In 60% of cases, the karyotype is 46, XX.

Case Report: 15-year-old, monochorionic-monoamniotic, Prader IV, male phenotype twins.

- **Twin 1**

Hypospadias with two correction surgeries performed during the first year of life. At 15y, he began multiple monthly episodes of alternating right and left testicular painful swelling. Ultrasound confirmed scrotal hematocele and small for-age "testicles". These episodes were interpreted as an acute scrotal syndrome. Six months later, a testicular biopsy was performed documenting an area with interrupted spermatogenesis and a fragment of the corpus luteum. Lab work revealed hypergonadotropic hypogonadism. Genetically he was 46, XX, and SRY-negative. Bilateral excision of the ovarian tissue and Müllerian remnants was performed, and testosterone was started.

- **Twin 2**

Hypospadias with three correction surgeries during the first year of life. At 8y, just before the closure of urethral fistulas, an ultrasound scan documented small for-age "testicles": the right one in the scrotum and the left one in the inguinal canal. Gynecomastia was detected at 13y. At 15y, after his brother's diagnosis, a scrotal ultrasound was performed followed by a left orchidectomy due to the risk of neoplasia. Similarly, an ovotestis was identified. After analysis and karyotype matching those of his brother, he underwent excision of the right ovarian tissue and Müllerian remnants, with a succeeding start of testosterone.

Discussion: The diagnosis of OT-DSD in adolescence is very rare and clinics depend on the underlying karyotype. In male phenotype individuals, the most frequent hints are gynecomastia and recurrent hematuria. In the reported cases, hypospadias was the first sign of sexual ambiguity. However, diagnostic suspicion arose only when there were female pubertal manifestations: breast enlargement and acute scrotum secondary to ovulation.

Despite the possibility of oogenesis, the testicular component of ovotestis spermatogenesis is often compromised. On the other hand, as there is a risk of gonadoblastoma and dysgerminoma development, prophylactic gonadectomy should be performed.

P2-103

Clitoromegaly as a manifestation of neurofibromatosis type 1

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Background: Clitoromegaly usually is a sign of virilization, and should lead to prompt evaluation in order to allow adequate treatment. Neurofibromatosis (NF) is a syndrome characterized by pigmentary changes, development of benign tumors of peripheral nerve and increased risk of other malignant tumors.

Clinical Case: A five year old female patient was referred to the pediatric clinic of Hospital de Clínicas de Porto Alegre due to the investigation of NF. She had NF family history, cutaneous and pigmentary changes and a previous healthy past history with no medication use. An advice consultation was required for the endocrinology team due to atypical genital appearance. It was even thought of a disorder of sex differentiation (DDS), but her mother stated the difference appeared post-birth. On physical examination of the external genitalia there was a clítoris measuring 3,5cm x 1,5cm, in an otherwise female non-virilized genitalia with vaginal and urethral meatus, no pubic hair and non-palpable gonads. Furthermore, there was at least six café-au-lait skin macules. In order to evaluate virilization, laboratory tests were performed showing no alterations in gonadotropin levels, estradiol, thyroid function and androgens like DHEAS, testosterone, androstenedione and 17OHprogesterone. There was no hormone contact history or exposure to endocrine-disrupting chemicals.

Complementary evaluation included a bone age X-ray compatible with an age of 4 years and 2 months, besides an abdominal and pelvic ultrasound and a karyotype XX. The ultrasound demonstrated a clitoromegaly due to a huge neurofibroma located adjacent to the clítoris and others neurofibromas next to the bladder causing urinary obstruction and grossly bladder thickened walls, compatible with neurofibromatosis. The uterus was normal for her age, with a volume of 1.8cm, ovaries were identified. The right ovary with 0.5 cm^3 and 3 follicles smaller than 0.5 cm in diameter. The left ovary with 0.5 cm^3 and contains 2 follicles smaller than 0.5 cm in diameter.

The diagnosis was clitoromegaly caused by a neurofibroma in a NF girl.

Discussion: Even with a falus that made the pediatricians suspect of a DDS it is possible that a clitoromegaly is not associated with virilization. Notwithstanding there are some cases of NF presenting with genital indifference, neurofibromas as a manifestation of clitoromegaly are still rare. A differential diagnosis of clitoromegaly in children may include the diagnosis of neurofibromatosis by the pediatric endocrinologist.

Reference

1. Early presentation of neurofibromatosis type I patient with clitoromegaly and café au lait spots: A case report. 2021.

P2-104

Gender dysphoria, social transition, mental health and metabolites of cortisol among transgender and gender non-conforming youth in one of Polish hospitals

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Introduction: In the body of available literature, the information on the relationship between the level of gender dysphoria (GD), social transition and mental health and hormone levels is scant.

Methods: The data has been obtained from medical records of 120 transgender and gender non-conforming (TG/GNC) young patients of the pediatric and endocrinological ward of the Upper Silesian Center of Youth's Health in Katowice, Poland. The information contains scores of our own gender dysphoria scale, socio-demographic data, steroid metabolon/urine and information pertaining to the patients' mental health.

Results: Depressive disorders were diagnosed in 37.5% of patients, bipolar disorders in 7.5%, anxiety disorders in 26.7%, adjustment disorders in 6.7%, psychotic disorders in 5.0%, conduct/disruptive disorders in 0.8%, substance use disorders in 0.8%, eating disorders in 6.7%, personality disorders in 15.8%, attention deficit hyperactivity disorder in 5.0%, autism spectrum disorders in 10.8%,

Our analysis has revealed negative associations between GD and levels of α-cortolone and β-cortolone as well as a positive association with length of the period of gender expression adjustment. Onset of gender incongruence has been positively associated with length of the period of gender expression adjustment, onset of gender dysphoria, length of the period after coming out to family and friends, length of the period after social transition, and negatively associated with mental health. The study has revealed that GD is a negative predictor of α-cortolone and β-cortolone.

The results of the intergroup differences analysis have shown that young patients who identify as non-binary report significantly higher levels of GD in comparison to those who identify as binary. Young patients who experience GD related to chest and voice are diagnosed with more disorders than those who do not experience GD related to chest and voice.

Conclusions: The results presented in the study indicate that the importance of alleviating GD among TG/GNC youth and facilitating their social transition and coming out as the potential levels of distress might possibly have a significant impact on their mental and somatic health.

P2-105

Self-perception of voice in trans girls adolescents depends on pubertal stage blockage

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Introduction: A transgender individual's voice may contribute to the negative psychosocial outcomes. Some studies have shown that an incongruence between one's voice and internal gender identity can be a potential source of ongoing psychological distress and could impact on their social interactions, employment outcomes, and invite verbal or physical harassment.

This study was aimed to examine whether early puberal blockage (PB) impacts on self perception of voice in trangender girls in adolescence.

Methods: A cross-sectional study was performed including trans girls younger than 18 years old followed in our transgender reference unit that has started puberal blockage. Transsexual Voice Questionnaire (TVQ), Voice Handicap Index (VHI-30) and acoustic analysis with /a/ for F0 obtained from all participants after sign informed consent by them and the main caregiver. We classified in 2 groups: Early PB (pubertal stage <3) and late PB (Pubertal stage > 3). Non-parametric test were

Results: 28 trans adolescents were included, 7 with Early pubertal blockage and 21 with late pubertal blockage. Age at BP initiation was found but No difference in blockage duration between groups was found at voice questionnaire and acoustic analysis time. Higher score on VHI-30 and TVQ (worst voice perception) and lower F0 was observed on late BP with difference statistically significant.

Conclusion: Trans adolescents with early pubertal blockage show lower score in VHI-30 and TVQ questionnaire and Higher F0 in acoustic analysis, which support a good voice perception. This study supports that testosterone has acted irreversibly virilizing to the voice if they already went through male puberty.

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	Early PB	Late PB	p-value
N	7	21	-
Current Age (years)	14.3 (13.3-14.5)	17.6 (16.6-18.5)	<0.001
BP age initiation (years)	11 (10.8 - 12.7)	15.4 (14.2 -16.3)	0.475
BP duration (years)	3.3 (2.2-4.1)	2.7 (1.9-3)	0.475
VHI-30 score	4 (0-26)	31 (11-56)	0.023
TVQ score	31 (30-39)	70 (55-87)	<0.001
F0	227 (216-257)	135 (120-140)	0.001

P2-106

Evaluation of trends and care of transgender young assisted in a reference unit

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Introduction: Transgender people and the gender transition process requires a series of processes with psychosocial, legal and physical implications. In our community, with the establishment of the care plan for trans youth, reference units were created in 2015. We had an interest to analyze the different epidemiological variables and the type of care demand of this population cared for in our unit.

Methodology: An observational, descriptive, longitudinal and retrospective study of a series of cases that attend the provincial care unit for transsexual people under 14 years of age has been designed, from June 2015 to June 2022. With the main objective of comparing the differences in regarding gender.

Results: 119 transgender you were recruited, of which 53.8% were trans girls and the rest were tran boys. There is an upward trend in demand over the years, with changes in the trend with a higher proportion of trans boys. The average age of social transition was 9.10(3.2) years. They attended the unit for the first time with a median age of 10.7 (2.7), with differences between transsexual girls and transsexual boys (9.8(3) vs 11.7(1.9), respectively; p-value: <0.01). As of June 2022, 80 (67.2%) have started BP, 44 (36.9%) have started THC, mastectomy (older 18 years old) in trans boys 3 (5.5%) and genitoplasty(older 18 yo) in trans girls 3 (4.7 %). There are significant differences between girls and boys, among which it stands out that transsexual boys are older, have a higher Tanner stage, a higher proportion with onset of pubertal block, and an older age at the start of hormonal therapy. crusade regarding transgender girls..

Conclusions: The demand of care for trans people has increased in recent years. In our environment, the ratio between transsexual girls and boys has been reversed. The transsexual boys who attended the unit were older and had a more advanced Tanner stage, which could explain the higher proportion of people with pubertal block compared to trans girls.

P2-114

Tailored daily transdermal testosterone treatment before hypospadias surgical repairing: preliminary data of a single center study

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Background: Hypospadias is one of the most common congenital anomalies in males. Surgical repairing aims to improve the aesthetic and functional outcome. The success rate of hypospadias repairing is variable according to the severity of the malformation with a complication rate(CR) of almost 60% in proximal forms. Testosterone treatment before surgery is still controversial and its impact on surgical outcomes, and the best regimen for administration, is unclear. This study aims to evaluate the penile tissue response and the surgical short-term outcomes in patients with severe hypospadias treated with preoperative transdermal testosterone(TT).

Methods: Medical and surgical records of patients treated with TT before hypospadias repairing between December 2020 and February 2023 were reviewed. Patients with proximal or midshaft hypospadias with glans circumference(GC)<14 mm and/or clinically relevant ventral curvature at preoperative assessment were included. Daily treatment with topical testosterone gel (2%) at a standard dose of 2 mg/day was administered in all patients for 30 to 60 days, according to the clinical response. Penile length (PL), GC and secondary effects of testosterone treatment (painful erection, scrotal hyperpigmentation, pubic hair, skin irritation) were recorded before and after therapy by the same Pediatric Endocrinologist. All patients were treated by the same surgeon who also checked for short term post-operative complications. Data are expressed as mean ± standard deviation (SD).

Results: Ten patients (aged 2.67 ± 1.60 years) were included: 4 (40%) with mid-shaft and 6 (60%) with proximal hypospadias. The mean interval between the topical testosterone stimulation and the surgical intervention was 52 ± 23 days. A two-stage repair was performed in 5 patients with Bracka (20%), Duckett (10%) or TIP technique (20%), while the others underwent a single stage repair with TIP technique. TT prior to the first surgical time was performed in 80% of the cases. No secondary due to the hormonal

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treatment were reported. A mean increase of 0.76 ± 0.27 cm (+37%) for PL and of 0.42 ± 0.26 cm (+ 40%) for GC were measured. Urethrocutaneous fistula or glandular dehiscence were reported in three patients with proximal hypospadias (50%), while no short-term surgical complications were developed in mid-shaft cases, with a CR of 30% in the overall population.

Conclusions: In our experience, TT is a noninvasive and well-accepted treatment which might help improving hypospadias surgical repair outcome. Standardised dosing protocols and randomized controlled trials are necessary to confirm these preliminary results and to develop future treatment guidelines.

P2-150

46,XY disorders of sex development associated with MAP3K1variants: Case and review of the literature

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The genetic causes of 46, XY disorders of sex development (DSD) are mostly unknown, having been identified in only 20-35%. Mitogen-activated protein kinase 1, part of the MAPK signaling pathway, which controls testicular development, is one of the etiological genetic pathways. Here, we present a case of 46, XY DSD with heterozygous MAP3K1 variant.

A 6-month-old baby was referred to pediatric endocrinology because of ambiguous genitalia. They were born by C-section at 28 weeks with birthweight 790g (-2.42SDS). The parents were not consanguineous and pregnancy history was unremarkable. The family were informed of female gender during antenatal ultrasound, and chose a girl's name. On examination, there was bifid scrotum, gonads were bilaterally palpable under the labioscrotal folds, incomplete posterior fusion, perineoscrotal hypospadias, and phallus 12 mm with chordee. The severity ofambiguous genitalia was assessed as 3b (Sinnecker classification), external genital score (EGS) was 5/12 Pelvic and abdominal ultrasound showed no internal female genital structures. Electrolytes were compatible with patient age. Follicle-stimulating hormone (FSH) was 1.71mIU/mL, luteinizing hormone (LH) was 4.13mIU/mL, testosterone (T) was 0.94μg/L, dehydroepiandrosterone sulfate (DHEAS) was 9.7μmol/L (2.93-16.5), and androstenedione was 11nmol/L (1-11.5).Adrenocorticotropic hormone (ACTH) was 32.8pmol/L (5-111) and 17- hydroxyprogesterone was 13.4pmol/L (0–10). Anti-Müllerian hormone (AMH) was 68.8pmol/L (4–174.4). Beta-human chorionic gonadotropin (β-hCG) stimulation test was performed (500 IU). T increased to 10.6μg/L and dihydrotestosterone (DHT) was 3206pg/mL with a T/DHT ratio of 13.3. Following the β-hCG test, the phallus increased from 1.0 to 5,5 cm in length. The karyotype was 46, XY. A heterozygous mutation of MAP3K1(NM_005921/2) c.3418A&gt; G (p. Met1140Val) was detected by WES. Cystoscopy was performed and a closed-end vaginal structure was seen. The case was discussed at the DSD council and corrective surgery was recommended. The patient's family was consulted and decided to raise the patient as male.

The clinical presentation of the MAP3K1 mutation ranges from a normal external female phenotype to hypospadias phenotype, as well as complete or partial gonadal dysgenesis associated with a risk of gonadoblastoma. There are very few studies of this mutation but patients tend to be raised in the female gender and diagnosed late. The presented case was diagnosed in the first year. Although the EGS was in the female half of the range, there was increased testosterone in response to β-hCG stimulation and the choice to raise as male may be appropriate.

P2-158

A case of male pseudoermaphroditism (46,XY DSD) in an adolescent with a novel *de novo NR5A1* gene variant

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Introduction-Purpose: In addition to chromosomal abnormalities, a number of genes have been implicated as causes of Disorders of Sexual Development (DSD). The NR5A1 (SF-1) gene expresses a transcription factor that plays a role in steroidogenesis by controlling multiple stages of adrenal and gonadal development, and its mutations have been reported in cases of DSD.

Case Presentation: A $15^{2/12}$-year-old teenager was admitted to the Children's ICU of the University Hospital of Patras, Greece, due to acute encephalitis. On physical examination labia majora and minora, open vaginal opening, and a 4.8cm phallus (stretched length) in the anatomical position of the clitoris, were identified. In addition, the patient presented with hirsutism with intense hair growth on the chest, abdomen, thighs and cheeks, breast development was Tanner stage I, and pubic hair was Tanner V. Medical history revealed primary amenorrhea. Extensive hormonal investigations demonstrated: LH: 8.2 mIU/ml, FSH: 24.8 mIU/ml, E2 (estradiol): 36.67 pg/ml, Testosterone: 118.1 ng/dl, SHBG: 25.9 nmol/l, Δ4-Androstenedione: 2.6ng/ml, DHEA-SO4: 141.4 μg/dl, 17-OH-Progesterone: 0.7ng/ml, Progesterone: <0.05ng/ml, Cortisol: 16.61 μg/dl, ACTH: 18.9 pg/ml, Renin: 28.4 μU/ml, Aldosterone: 60.2 pg/ml, AMH: 0.37 ng/ml, INH-B : 6 pg/ml, β-hCG: < 2.30 IU/ml, CEA: 1.19 ng/ml, αFP: < 2 ng/ml, Prolactin: 22.3 ng /ml, TSH (mIU/L): 2.59, FT4: 1.30 ng/dl, Anti-TPO: 12.1 mIU/L, anti-TG: 10.6 mIU/L.

On ultrasound of the lower abdomen, a 3.31x0.85 cm lesion was identified posterior to the bladder, indicating residual duct of Muller. MRI scan of the lower abdomen revealed oval formations with limited diffusion and magnetic signals primarily compatible with testicular parenchyma in the anatomical location of the inguinal ducts bilaterally. The karyotype revealed a 46,XY individual and whole exome sequencing (WES) revealed the presence of the heterozygous splice site variant of the NR5A1 gene (NM_004959.5), c.990G>C, p.Glu330Asp, which on further genetic testing of the parents was proven to be de novo. Based on the ACGM criteria, the mutation is classified as Pathogenic. According to psychiatric assessment, the patient self-identifies as female. A gonadectomy and laparoscopic exploration of possible residual Mullerian ducts were performed, and hormone replacement therapy with estrogens was initiated.

Conclusions: We describe a very rare case of male pseudomaphroditism (46.XY DSD) in an adolescent phenotypically female patient carrying the novel de novo p.Glu330Asp variant of the NR5A1 gene. We also highlight the delay in diagnosis of ambiguous external genitalia.

P2-166

Value of antimullerian hormone (AMH) in the diagnosis of precocious puberty: revaluation of the covid-19 post-pandemic cohort

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During the pandemic, an increase in the cases of premature thelarche consultations was observed. Our group published a series in 2021 of 75 cases. This effect could have been caused by an increase in body fat mass in girls, suggesting a "trigger effect" in the activation of the gonadal axis, causing an increase in the number of cases of early puberty (SEEP Oviedo 2022). AMH has been correlated as a predictor of the moment of menarche (doi: 10.1515/jpem-2014-0521)

Objectives: To assess the existing correlation between AMH values in premature thelarche and the actual evolution to precocious puberty.

Patients and Methods: 75 cases of girls assessed for premature thelarche in 2019 and 97 cases in 2020 were analyzed.

variables were analyzed for each patient, such as somatometry, hormones, echo, AMH, treatment... and follow-up was performed. Clinical reassessment in 2022. SPSS studies 19.0 non-parametric studies for n<30.

Results: In 2019, 75 first visits by girls were due to premature thelarche; 55% 41/75 presented lipomastia and normal puberty (PN), 40% (30/75) were diagnosed with early puberty (PT), and 4/75 (5%) had evidence of central precocious puberty (PPC).. On the contrary, in 2020, of the 97 consultations, 62% 60/97 presented lipomastia and PN, 32% (31/97) were diagnosed with TP, and PPC was found in 6/97 (5%). Total Central precocious puberty 10/172 cases, advanced thelarche 61/172 and 101/172 lipomastia -others. AMH data 21 patients (13+8).

The mean AMH levels (n:21) of the PPC group (6/21) were significantly lower than those of the PT group (10/21) (18.7±9.8 pmol/L and 42.42±12.7 pmol /L, respectively, p=0.022). The PT and PN (5/19) group was similar.

Conclusion: Although the n studied is low (we plan to increase the n in the future), these results suggest that AMH levels decrease when the hypothalamic-pituitary-ovarian axis is activated. We think that AMH could/can be a marker to distinguish between CPP and PT and could be considered for inclusion in clinical practice.

P2-180

SRY-positive 45, X male with monoorchism and hypospadias

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A rare case of a 4-year-old boy with a SRY-positive 45, X karyotype was presented. Family history of the child was not remarkable. His height and weight were -2.1 SD and -1.4 SD, respectively. Physical examination revealed a well-developed penis with hypospadias. His right testis was in the scrotum and the left testis was not palpable. In previous inguinal exploration recordings, unilateral testicular agenesis on the left side were noted. The right testis was biopsied and prepubertal testis tissue was pathologically confirmed. There was no ovarian tissue in the material. Also, no ovary was found in the laparotomy examination. Chromosomal analysis was carried out on peripheral blood of the patient with unilateral testicular agenesis and hypospadias on his first admission to the hospital, which demonstrated a 45X karyotype. In FISH analysis, SRY positivity was found to be 10%. SRY gene is a single-exon gene. It is important role as primary testis- determining gene in normal testis development. The presence of SRY gene in Turner syndrome is necessary to prevent the development of tumoral or nontumoral gonadal lesion, even if karyotyping does not detect Y chromosome material.

P2-199

Adolescent girl with premature ovarian insufficiency due to X-chromosome deletion

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Objective: Premature ovarian insufficiency (POI) is rare in adolescents, most commonly caused by genetic defects or cytotoxic therapy. The aim is to present the case of an adolescent girl with normal pubertal progress and irregular menstrual cycle, followed by amenorrhea.

Case Presentation: A 15 9/12-years-old girl presented because of lack of menses for the previous 21 months. She reported that she had menarche at the age of twelve years followed by three normal menstrual cycles since then, with the last one being at the age of 14 years. Her past medical history was uneventful. Her family medical history was unremarkable as well. The physical examination revealed no dysmorphic features, body weight was 62,8 kg (75th-90th percentile) and height 156 cm (25th-50th percentile), within her target height range. She had normal pubertal development, with Tanner stages (Breast IV, Axillary hair III, Pubic hair V). Laboratory investigations revealed elevated gonadotropins FSH:96,64 mIU/ml, LH:60 mIU/ml, undetectable estradiol: <5 pg/ml and anti-mullerian hormone:0,01ng/ml. Thyroid function and prolactin levels were within normal range. Pelvic ultrasound showed prepubertal development of the uterus with a maximum diameter of 36,4 mm and small ovaries (Right volume: 1cm^3, left volume: 1,1cm^3). In the MRI scan, the ovaries were recognized as cystic structures with a maximum diameter of 11mm and 16mm respectively. With the diagnosis of secondary amenorrhea due to hypergonadotropic hypogonadism of unknown etiology, genetic consultation was suggested and a karyotype analysis followed. Karyotype using a conventional cytogenetic analysis detected a deletion in the long arm of chromosome X, resulting in female 46, X, del(X)(pter→q21.2:) karyotype. The finding was considered de novo as parental karyotypes were normal. Her bone density was -1,1 z-score by Dual-energy x-ray absorptiometry, at the lower normal limit, prior to the beginning of the therapy. After the identification of the POI cause, estradiol replacement therapy was initiated and she's followed since then on a regular basis, while pelvic ultrasound shows progression from prepubertal to pubertal development of the uterus (uterus size: 7,41×2,29×1,91 cm).

Conclusion: Chromosomal changes regarding the Xq are associated with abnormal menstruation and infertility. Great variability of phenotype is appreciated in women with Xq deletions, thus genetic counselling is still challenging. In more distal Xq deletions premature ovarian failure seems to be more common than primary amenorrhea. Regular monitoring of the patients is required in order to elucidate the evolution of the phenotype.

P2-200

Familial Male-limited Precocious Puberty. Case report from Mexico City

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Familial Male-limited Precocious Puberty is a rare form of gonadotropin-independent precocious puberty. It is inherited in an autosomal dominant manner and it is caused by mutation in the LH/chorionic gonadotropin receptor (LHCGR) that promotes the production of cAMP without the hormone ligand, causing increased androgen production that determines the onset of puberty. The prevalence reported is less than 1/ 1 000 000.

As there are few cases reported in the literature, information related to the disease is required. The objective is to provide data that can guide clinicians to reach the diagnosis in a timely manner and improve the quality of life and height prognosis of patients.

Our 5 year-old male patient began at 3 years with pubarche, one year later, he presented with a pubertal growth spurt, 30 cm in a year (2-3 cm / month); increase in muscle mass and body hair. He also began with sexual interest and a rebellious attitude. Upon presentation his weight was 28.4 kg (Z score + 2.6 SD), height 130.6 cm (Z score + 4.64 SD), the physical examination revealed pubertal testes, Tanner stage 3, with a bilateral testicular volume of 8 cc, pubic hair at Tanner stage 3. The bone age was reported as 13 years.

An approach was performed for precocious puberty, in which the central variety was ruled out with the measurement of baseline LH and stimulation curve with GnRH analogue.

Genetic testing was done and the patient presents a heterozygous state of the pathogenic variant c.1118C>T (p.Ala373Val) located in the LHCGR gene (MIM *152790), which may be responsible for the patient's phenotype. As of now he is in treatment with anastrozole, bicalutamide, triptorelin and growth hormone.

Being a very rare disease, the diagnosis can be delayed affecting the quality of life and prognosis of height of patients, so diagnostic suspicion and opportune management is important.

P2-224

Spectrum of phenotypic features variation in XY DSD patients with NR5A1 mutation: case series

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Background: Disorder of sex development (DSD) includes a wide spectrum of clinical disorders affecting gonadal and genital development. Many causative gene mutations are involved in these disorders. One of these genes is nuclear receptor subfamily 5 group A member 1 (NR5A1) encoding Steroidogenic factor-1 (SF-1) located on chr 9q33.3. This gene is expressed in many tissues such as Sertoli cell and Leydig cell in testes, ovaries, placenta, adrenal cortex, hypothalamus and anterior pituitary taking part in the regulation of their functions. There are lots of detected mutations in this gene those can cause a variety of phenotypic features in patients with XY DSD.

Objectives: This study describes a spectrum of phenotypic features of four patients with XY DSD who have different mutations in NR5A1 gene.

Cases Description: It is a case series of four patients with XY DSD having different heterozygous mutations in NR5A1 gene. Two patients were presented at birth by ambiguous genitalia. No internal female genitalia were found. One of them had extra-genital manifestations such as arrested hydrocephalus, renal anomalies, ear tag, short stature and learning disabilities. This patient had spontaneous virilization at puberty. The third patient was normal baby girl at birth and reared as a female. Then, spontaneous virilization of external genitalia occurred at pubertal age with no breast maturation. This patient had increased hair distribution in extremities, abdomen and chest at pubertal age. He had no internal female genitals. The fourth one was presented by cliteromegaly, but she was reared as a female till puberty. This patient had no internal female genitals, normal hair distribution and no breast development. The first two patients were assigned as males and the remaining patients were assigned as females and received tapered feminizing hormonal treatment as an induction of puberty. All of them had normal adrenal function. Furthermore, testicular function was evaluated in all patients. the karyotype was 46,XY for all patients. The syndromic one had additional mutation in FRAS1 gene besides NR5A1 mutation which might cause the associated renal manifestations. additionally, the last two patients had the same NR5A1 novel mutation.

Conclusion: Although, NR5A1 gene mutation is a common cause of XY DSD, it has a wide spectrum of phenotypic features. This may be due to different mutations in the same gene or due to associated gene mutations.

P2-225

Oligomenorrhea in two girls with familial mediterranean fever: how chronic inflammation can impair ovarian cycle

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Introduction: Familial Mediterranean Fever (FMF) is an inherited auto-inflammatory disorder still extremely underdiagnosed in the Mediterranean area.

The disease is secondary to a gain of function mutation of the MEFV gene, classically defined as "autosomal recessive", with possible symptoms also in heterozygous patients. The mutation induces a hyperexpression of IL-1 beta and a chronic inflammation. Clinical manifestations are characterized by recurrent attacks of fever, polyserositis, abdominal, thoracic, articular pain, fatigue, rash, oral aphthae, myalgia, etc. Some young girls suffer of oligomenorrhea or amenorrhea, especially in cases of unsatisfactory control of chronic inflammation.

Treatment is based on colchicine and, in non-responders, anti-IL-1 biological drugs.

Materials and Methods: We describe the case of two sisters, 16 and 18 years-old, affected by FMF (hererozygous MEFV gene mutation: A744S), with a limited number of attacks characterized by fever, abdominal pain, oral aphthae. Both showed a persistent increase of serum amyloid A (SAA) (> 13 mg/l) in the attacks-free intervals. Treatment with colchicine was followed by a rapid SAA level normalization. Following the well-being status, the patients decided to stop colchicine treatment. In the following years, both showed a persistent increase of SAA levels, with oligomenorrhea and anovulatory menses, with increased LH/FSH ratio.

They started again the treatment with colchicine (1 mg/day), with the reduction and normalization of SAA levels and the recovery of menses cycles within 6 months.

Conclusions: FMF can interfere with the gonadic function, compromising hypothalamic-hypophyseal-gonadic axis. The pathogenesis is linked to chronic subclinical inflammation and treatment with colchicine can normalize SAA, with the improvement of gonadic function. We highlight the importance of endocrine follow-up in patients with autoinflammatory syndromes, as FMF, to prevent gonadic impairment and infertility.

P2-226

Classical CAH girls having early intervention and puberty development

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Introduction: CAH (congenital adrenal hyperplasia) is the most common cause of ambiguous genitalia among girls. 21 Hydroxylase deficiency is the most common type of CAH. If the CAH girls have early intervention and they have started early treatment then they will achieve normal puberty. IF CAH girls have started treatment later in the life then they will present either with precocious puberty or delayed puberty.

Methodology: We have collected data from 27 girls who are diagnosed as classical CAH in our Endo OPD. Inclusion Criteria includes All girls who have ambiguous genitalia and diagnosed as 21-hydroxylase deficiency and are 46XX, these girls are 15 years or older. Exclusion Criteria Includes non classical CAH, CAH girls reared as boys,46XY. Detail history, physical examination, lab investigation and medication record were noted and verified from the parents as well.A questionnaire was made which includes age of presentation in endo clinic, age of start of treatment, compliance, age of pubic hairs appearance, breast development and menarche and how many surgeries done so far. By using SPSS calculator we will get results.

Results: Out of 27, only 5 girls (18%) have pseudo precocious puberty with the pubic hairs appear earlier but they have achieved menarche around 14 years and had regular cycles.Among these 5 girls, 4 were presented very late in endo clinic and treatment started after 1st year of life and 1 girl had very poor compliance for medicines. Remaining 23 girls have good compliance to medicines and they achieve puberty at appropriate ages and have regular menstrual cycle and breast development as well. All have undergone 1 or 2 surgeries as well.

Discussion: If CAH girls have early intervention and regular follow ups, they will have normal puberty and have regular menstrual cycles.

Thyroid

P2-45

Evaluation of the clinical progress of hashimoto thyroiditis in childhood

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Keywords: Hashimoto's thyroiditis, autoimmune thyroiditis, hypothyroidism

Objective: In our study, it was aimed to determine the clinical course of the disease by evaluating the cases diagnosed with Hashimoto's thyroiditis (HT) periodically, clinically, laboratory, and radiologically.

Material and Method: Patients diagnosed with HT without chronic systemic disease, drug use history, and syndromic disease, who applied between 07.10.2019 and 15.03.2021, were included in this prospective study.The cases were divided into euthyroid, subclinical hypothyroidism, overt hypothyroidism, and hyperthyroidism groups at diagnosis and were followed up clinically, laboratory, and radiologically until the 18th month.

Results: Of the 35 cases with HT, 29 (82.9%) were female, 6 (17.1%) were male, the mean age was 12.5±3.64 (3.4-18) years, and 26 (74.3%) were pubertal. At diagnosis, 31.43% (n=11) euthyroid, 37.14% (n=13) subclinical hypothyroidism, 22.86% (n=8) overt hypothyroidism, 8.57% (n=3) hyperthyroidism were found. 45.7% (n=16) of the cases were asymptomatic; goiter was present in 18 (51.4%) cases. Anti-TPO levels 5202.2±17843.8 IU/ml in 94.3% of cases (n=33), anti-Tg levels 165.1±192.5 IU/ml in 67.6% of cases (n=23) were positive. At diagnosis, height, height SDS, body weight (BW), BW SDS, BMI, BMI SDS, heart rate, systolic, diastolic blood pressure, goiter rate, anti-TPO, and anti-Tg positivity rate, and levels were similar in all groups. On ultrasonography, 82.4% parenchyma heterogeneity and 67.6% hypoechogenicity were found, which were similar between the groups.In the euthyroid group, 2 patients developed subclinical hypothyroidism (1 patient at 6 months, and 1 patient at 18 months), and 1 patient developed hyperthyroidism (at 3 months).Clinical, laboratory, and radiological findings were similar in diagnosis and follow-up in the euthyroid group.Levothyroxine (LT4) treatment was started in 22 (62.8%) of 35 cases (8 cases with overt hypothyroidism, 13 cases with subclinical hypothyroidism, and 1 case with euthyroidism). Clinical, laboratory, and radiological findings were similar in diagnosis and follow-up in both subclinical and overt hypothyroid groups. The anti-Tg positivity rate was statistically significantly decreased only in the subclinical hypothyroid group in the follow-ups after diagnosis (p=0.029).

Conclusion: It was seen that approximately half of the cases with HT were asymptomatic at diagnosis. Most of the cases (60%) were diagnosed with hypothyroidism, followed by euthyroidism and hyperthyroidism. All of the hypothyroid cases required treatment. It was determined that thyroid autoantibody levels fluctuated and although a decrease in thyroid volume was observed, this decrease did not reach the level of significancein the one-and-a-half-year follow-up in the treatment group.

P2-46

Admission Characteristics and Rates of Transient/Permanent Hypothyroidism in Infants from Congenital Hypothyroidism Screening

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Introduction and Aim: In this study, we aimed to investigate the admission characteristics, the ratio of permanent/transient hypothyroidism, and the predictors of permanent or transient hypothyroidism at initial evaluation in newborns admitted in 2013 and 2014 from neonatal TSH screening program. .

Method and Results: During two years period, 985 babies were admitted to our clinic with screening results for evaluation, and L-T4 treatment was started for 73 patients (7.4%). The median age at admission was 21 days (25p-75p;14-33). The median age at presentation and treatment initiation were 20 days (25p-75p;15.5-30.5) and 30 days (25p-75p;17-63), respectively. There was no statistical difference between the TSH screening values from heel prick between 912 babies recalled from screened and no treatment was required and 73 patients who needed treatment (p:0.80). The TSH values in the 1st and 2nd heel pricks blood in treated group were 14.7 mIU/L (25p-75p;7.2--27.3) and 10 mIU/L (25p-75p;7.1-22.5), respectively.

When the patient were evaluated for etiology after 3 years of L-T4 treatment, 32 (42%) (14 male) patients had permanent hypothyroidism. Thyroid dysgenesis was detected in 7 patients (22.5%) (2 agenesis, 5 ectopic thyroid tissue).

A significant difference was found between the permanent and transient hypothyroidism groups for the 1st(23.5 mIU/L (25p-75p;9,65-43,6) and 12,3 mIU/L (25p-75p; 6,42-22,67) respectively.) and 2nd heel blood TSH(14,85 mIU/L (25p-75p; 7,6-44,75) and 8,6 mIU/L (25p-75p; 6,35-15,85) respectively.) and venous TSHs(23,8 mIU/L (25p-75p; 10,25-118) and 12,29 mIU/L (25p-75p; 8,41-27,84) respectively.)(p:0.009; p:0.0055; p:0.0077, respectively)[ST1]. Additionally, a venous TSH of ≥17.74 mIU/L measured before the initiation of treatment was found to predict permanent CH with 61.2% sensitivity and 66.6% specificity.

Treatment was initiated after checking venous TSH and fT4 for 1.5±0.92/1.8±0.94 times In permanent/transient hypothyroidism groups (p:0.11). While 19 (44%) of 43 patients who were treated according to the first venous TSH and fT4 values had transient hypothyroidism, 23 (76.6%) of 30 patients with treatment intiation after multiple samples had transient hypothyroidism (p:0.0057).

Summary of Results: L-T4 treatment was initiated in 7.4% of infants who were recalled from the newborn TSH screening program, and 42% of these infants were subsequently diiagnosed with permanent hypothyroidism. An initial venous TSH of ≥17.7 before treatment initiation was found to be predictive of permanent CH. In addition, the need for multiple sampling to make a treatment decision was found to be predictive of transient CH.

P2-110

A 5-year study on the incidence of Congenital Hypothyroidism in Gertrude's Children's Hospital Nairobi, Kenya

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Background: Congenital hypothyroidism (CHT) is one of the most common congenital endocrine disorders. The study will determine the incidence of CHT and describe demographic characteristics and developmental outcomes in children attending Gertrude's children's hospital, Nairobi Kenya over 5-year, period.

Objective: To determine the incidence of congenital hypothyroidism, developmental outcome, and demographic characteristics in Gertrude's Children's Hospital, Nairobi Kenya.

Methods: Retrospective descriptive survey analyzed thyroid function test results from May 2015 to May 2020. Data is stratified based on age; medical charts of patients who meet the inclusion criteria with respect to age i.e.,3 days of life up to 2 years were accessed using the hospital's unique identifying number (UHID) of the patients. To compare the study groups in terms of quantitative and qualitative variables, the t-test and Chi-square test were used respectively, using the SPSS25. P-value<0.05 was considered as significant.

Results: Of 1426 children included in study 90 had abnormal TSH out of which 70 have transient TSH elevation with normal thyroxine while 20 were identified with CHT (incidence of 14 per 1000 children). The female-to-male ratio was 1.5:1. The incidence of abnormal TSH across the different age groups was 2.4%, 7.2%, and 10.5% for ages 0-29 days, 1-11 months, and 1-2 years respectively. There was a significant association between the age group and abnormal test results (p=0.0002).

Conclusion: The incidence of congenital hypothyroidism in children attending Gertrude's children hospital over the 5-year study period, is 20/1426(1.4%; 95%CI: 0.9%-2.1%). All cases were Primary CHT. Of which 12(60%) had poor developmental outcomes.

P2-111

Thiamine responsive megaloblastic anemia with hypothroidism, a puzzling association, a case report from LMIC

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Introduction: Thiamine responsive megaloblastic anemia (TRMA) is a rare autosomal recessive condition caused by mutations in SLC19A2 gene and is classically characterized by the triad of diabetes mellitus, sensorineural hearing loss and megaloblastic anemia. It usually presents between infancy and adolescence but the cardinal findings are often not present initially. The anemia, and sometimes the diabetes improves with high doses of thiamine. Apart from the classical characteristics, less common presentations include optic atrophy, congenital heart defects, short stature and stroke.

Case Report: We present the case of a 5-year-old child with known case of IDDM since 1-year of age presented to us at the age of 14 months with complain of polyuria, fever and vomiting. His HBA1c turned out to be 10.64 confirming his diabetes. On doing further examination, we learned that the patient has diminished hearing and vision. Antibody workup was negative and thyroid profile showed hypothyroidism. For diminished hearing and vision we send the patient for BERA and retinal examination which showed bilateral sensorineural hearing loss and maculopathy respectively. Keeping TRMA in view we looked at the patient's complete blood count which revealed megaloblastic anemia. Furthermore, we sent patient's genetic profile showing homozygous mutation in SLC19A2 gene confirming Thiamine responsive megaloblastic anemia (TRMA).

Conclusion: Thiamine responsive megaloblastic anemia (TRMA) is a rare condition which is confirmed by genetic mutation in our patient. The pediatricians should be vigilant with patients having diabetes to look for other features leading towards disease. Timely diagnosis along with genetic confirmation will help in treating the patient early as exogenous thiamine have a good response in these patients. Genetic counseling should also be done so that the families get aware of this disease and it's inheritance patterns.

P2-151

Congenital hypothyroidism in children with Sotos syndrome

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Background: Congenital Hypothyroidism (CH) is the most common neonatal endocrinologic disorder and one of the most preventable causes of mental retardation and neurological alterations in children. The incidence of CH lies between 1 in 2000-3000 newborns. The replacement therapy with levothyroxine (LT4) should be started immediately since studies show that a rapid normalization of TSH and fT4 optimizes the neurodevelopmental outcome. Infants with Down syndrome have a higher risk of developing CH, moreover some congenital malformations, especially affecting the cardiovascular, urogenital, gastrointestinal, and musculoskeletal systems, seem to be mainly associated with CH.

Case Presentation: We described a girl diagnosed with CH identified by neonatal screening. She presented an abnormal gland located in a position higher than usual. She started the replacement therapy on her 6th day of life with levotiroxine 9.5 μg/kg/die. She also had a congenital bilateral hydronephrosis and a mild congenital cardiopathy. During the follow up in her first months of life, she presented several serious infections, which required admission to the pediatric intensive care unit. Moreover, she has also been diagnosed a FPIES. We performed specific laboratory tests that permitted to rule out an immunological defect. When her health conditions improved, she had a rapid growth associated with a progressive psychomotor retardation. Considering all these features: CH, mild cardiopathy, congenital nephropathy, psychomotor delay and recurring infections we suspected a genetic cause for her condition. Genetic analysis evidenced a mutation of NSD1 gene (c.3439G>T p.(Glu1147*)) which permitted the diagnosis of Sotos Syndrome.

Conclusions: Only a previous clinical case describe an association between CH and Sotos syndrome in a patient with a different mutation of the gene NSD1. We confirm this relationship and hypothesize that this relationship is not random. Further studies are needed to better elucidate if CH is casual or a clinic feature of Sotos syndrome. We suggest to suspect a Sotos syndrome in patients with CH, cognitive delay and height acceleration.

P2-167

Subclinical hypothyroidism in children: epidemiological study of 30 patients

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Introduction: Subclinical hypothyroidism (SH) is defined in children by a moderate rise in TSH (TSH: 4.5-10 mU/l) compared to a normal level of free T4. However, the clinical consequences remain a subject of controversy, hence the need to take a position on the relevance of treating it.

Objective: Description of the clinical, biological and evolutionary characteristics of SH in children.

Patients and Methods: It was a descriptive retrospective study including patients under the age of 15 diagnosed and followed for SH in the Pediatrics and Neonatology Department of the Ben Arous Hospital over a period of 8 years (January 2015- December 2022)

Results: 30 patients were collected. The average age at diagnosis was 3 years. The sex ratio was 0.8.The circumstances of discovery of SH were: constipation (11%), goiter (11%), hypotonia (17%), psychomotor retardation (11%), pericardial effusion (3%), systematic screening (60%) in the context of: prematurity (33%), autoimmune disease (7%), growth hormone deficiency (7%) and down syndrome (26%).

The mean TSH level was 8.33 (5.94; 10UI/l) and that of FT4 was 15 (10.8; 24 pmol/l). The biological exploration objectified: a normochrome normocytic aregenerative anemia (38%), positive antithyroid antibodies (20%).

The etiological exploration concluded to: subclinical hypothyroidism associated with Down syndrome (8 cases), associated with growth hormone deficiency (4 cases), associated with congenital adrenal hyperplasia due to 21hydroxylase deficiency (1 case), Hashimoto's thyroiditis (6 cases), transient hypothyroidism of premature infants (7 cases), thyroïd hormone disorder (3 cases), hypothyroidism secondary to hemochromatosis (1 case).

Substitution treatment was started in 18 patients. The others patients, while being asymptomatic, were kept under biological monitoring and etiological treatment.

The evolution was marked by normalization of the TSH level: after an average of 35 days of monitoring for untreated patients and after an average of 41 days for treated patients. The intelligence quotient (IQ) of patients evaluated after the age of two years were:: IQ<70% (30%), 70<IQ<105% (70%); QI>115%(0). Patients with low intelligence had: late start of treatment (50%); poor treatment compliance (66%); other associated pathologies (33%). All patients with untreated SH had an IQ >70%.

Conclusion: The course of subclinical hypothyroidism in children depends on its etiology. Whether primary or secondary, treated or not, it requires clinical and biological monitoring in order to prevent its complications, mainly those affecting neurocognitive development.

P2-178

Total thyroidectomy for thyrotoxicosis in a girl with dysphonia

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Thyrotoxicosis refers to a hypermetabolic state that results in excessive amounts of circulating thyroid hormone. Pediatric patients retain significant thymic tissue that regresses only later in life. This thymic tissue can develop significant hyperplasia during an acute autoimmune process. We describe a case of a 14-year-old girl who presented with dysphonia secondary to severe Graves' disease and a 1-month history of goiter, anxiety, restlessness, and tremor. A 99 mTc thyroid scan and thyroid sono revealed diffuse enlarged thyroid without mass. Treatment was initiated with methimazole and b-blocker, with near complete remission of her thyrotoxic symptom within 3 months. After dose adjustment, she visited sudden dysphonia and mild dyspnea with more increasing goiter size. Her thyroid function test showed recurrent hyperthyroidism and even more severe tachycardia and tremor. Simple neck x-ray showed deviated to right and narrowed airway due to enlarged thyroid. She denied stop or incompliance of medication. She had no vocal cord lesions at laryngeal examination. After 2 weeks full dose methimazole, prednisolone, potassium iodide solution and b-blocker, her biochemical parameters were normalized but dysphonia were persisted. For her age, we recommend thyroidectomy instead of radioactive iodine. After total thyroidectomy, she can phonated well. Also, she is presently euthyroid on thyroid hormone replacement and is asymptomatic. Thus, it is concluded that thyroidectomy is considered for pediatric patients with thyrotoxicosis who have dysphonia which is difficult to manage medically.

P2-179

Papillary thyroid carcinoma of the solitary hot nodule in a pediatric patient

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Keywords: hot nodule, pediatrics, papillary thyroid carcinoma

A nodule over 1 centimeter observed in pediatrics need further evaluation. Not having ultrasound changes during monitoring does not mean being benign. Moreover, normal FNA does not rule out a malignancy and it is necessary to repeat the test every 3-6 months. The case was a 15-year-old girl with a 23 mm fixed nodule on ultrasound and normal FNA. She developed hyperthyroidism after two years; a hot nodule, and PTC were reported during a lobectomy. Hot nodules in pediatrics should be assessed with a lobectomy as soon as possible, regardless of the normal ultrasound and cytology findings of FNA. Constantly elevated thyroglobulin level even at the time of euthyroidism in a hot nodule can be a remarkable predictor of a malignancy.

P2-204

A Case of Neonatal Thyrotoxicosis born to mother after thyroidectomy for Grave's disease

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Neonatal thyrotoxicosis is rare and most of the cases are secondary to maternal Graves' disease. It is usually transient, but can be associated with significant morbidity and mortality if not recognized promptly and treated adequately. We report a case of a 20-day-old female infant who developed thyrotoxicosis with irritability, tachycardia, and relatively poor weight gain. She was born to a mother who took levothyroxine during pregnancy after undergoing a thyroidectomy for Graves' disease, not controlled by antithyroid drugs. She was treated with methimazole, potassium iodide solution, propranolol and hydrocortisone. After 5 month, she maintained euthyroid state without anti-thyroid drug. Neonates born to mothers treated with antithyroid drugs or those who receive maternal thyroid blocking antibodies may exhibit normal thyroid function or even hypothyroidism at birth. Since there may not be any obvious symptoms of hyperthyroidism at birth, it may be overlooked. Therefore, such neonates should be evaluated properly and monitored regularly to prevent serious complications of hyperthyroidism. We have also discussed the importance of careful examination and monitoring to prevent the development of clinical hyperthyroidism.

P2-205

Congenital hypothyroidism – the experience on a group of pediatric patients since diagnosis

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Background: Congenital hypothyroidism (CH) is a treatable thyroid hormone deficiency that causes intellectual disabilities and growth deficiency if not detected and treated early.

Material and Methods: We retrospectively analyzed the medical records of 22 patients, 13 (59%) females and 9 (41%) males, with positive CH screening at birth and confirmed by TSH & FT4 serum concentrations measurements, thyroid ultrasound and physical examination. In unclear cases, a second ultrasound was performed at 6 months of age. The average follow-up period was 19 months. The evolution and compliance under levothyroxine treatment were analysed. TSH & FT4 values and levothyroxine dosage during the follow-up were collected.

Results: The average age of CH diagnosis was 29 days (3-90 d.). Ultrasound detected: thyroid dysgenesis in 16 (72.7%) & dyshormonogenesis in 6 (27.2%) patients. Among dysgenesis: 14 cases (63.6%) of agenesis, one case each of hemiagenesis (4.5%) and hypoplastic thyroid gland (4.5%).

L-T4 starting daily dose varied between 7-15 µg/kg (median 10.2 µg/kg); The maintenance dose was adjusted according to body weight, TSH and FT4 values. During the follow-up, at 12 months mean L-T4 dose was 3 µg/kg/day. Presented below is the average monthly dose in the first 12 months:

Month	Dose
1	10.2
2	7.5
3	5.5
4	4.2
5	3.7
6	3.2
7	3
8	3.3
9	3.2
10	3
11	3
12	3

We found an association between the normalization of TSH and the L-T4 dose: the higher the starting dose, the faster TSH normalised.

No.	Initial dose (mcg/kg)	TSH Normalization (days)	Thyroid ultrasound
1.	12	15	Agenesis
2.	8.8	25	Agenesis
3.	10	9	Dyshormonogenesis
4.	10	17	Agenesis
5.	15	42	Dyshormonogenesis (noncompliant)
6.	7	7	Hypoplastic thyroid
7.	6.9	87	Agenesis
8.	6.1	83	Agenesis
9.	10	29	Agenesis
10.	11.5	78	Agenesis
11.	13.3	13	Agenesis
12.	7.3	34	Dyshormonogenesis
13.	13.2	22	Dyshormonogenesis (goiter)
14.	11.4	20	Agenesis
15.	10.7	48	Agenesis
16.	15.1	16	Agenesis
17.	10	55	Hemiagenesis
18.	9.6	47	Agenesis
19.	10	38	Dyshormonogenesis
20.	10	32	Agenesis
21.	6.2	32	Agenesis
22.	11.4	20	Dyshormonogenesis

Conclusions: We want to highlight the benefits of CH screening: early detection and treatment of CH through neonatal screening prevent irreversible neurodevelopmental delay. L-T4 treatment should be started as soon as possible with a starting dose of up to 15 µg/kg/day, adjusted to the whole spectrum of CH.

P2-206

Hypothyroidism without elevation of thyroid-stimulating hormone associated with oxcarbazepine use in children and adolescents

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Introduction: Hypothyroidism without elevation of thyroid-stimulating hormone level during oxcarbazepine use in children and adolescent. There have been studies on the association of oxcarbazepine, which is used as an anticonvulsant, with hypothyroidism, but studies in children and adolescents have been limited. The authors aimed to determine the effects of long-term oxcarbazepine on thyroid function in children and adolescents.

Methods: This study was a retrospective cohort study of pediatric patients who were treated with oxcarbazepine for the first time in management epilepsy between 2003 and 2020. Changes in serum triiodothyronine (T3), thyroxine (T4), free thyroxine (or fT4), and thyroid-stimulating hormone (TSH) were evaluated during treatment. Thyroid hormone levels were followed up for 5 years after starting the drug.

Results: Changes in TSH levels during the treatment period were insignificant. However, thyroid hormone levels showed a significant decrease for 2 years after the start of treatment and were maintained thereafter. About 6% of the patients observed during the study required levothyroxine administration.

Conclusion: A significant decrease in thyroid function was observed when using oxcarbazepine in children and adolescents. Therefore, regular evaluation of thyroid function is necessary when using oxcarbazepine. Since hypothyroidism without TSH changes is shown, this should be borne in mind when performing the test.

P2-229

What is the risk on intelligence in children with dysthyroiidism ?

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Introduction: Thyroid hormones are essential for early neurocognitive development as well as growth and development throughout childhood. The intelligence of children with dysthyroidism has been little evaluated.

Objective: Assessing of the intelligence in children with dysthyroidism.

Patients and Methods: Descriptive prospective study carried out by applying the IQ in 26 patients aged more than 2 years and followed for dysthyroidism in the pediatric and neonatology department of Ben Arous (Tunisia).

Results: The average age of discovery of the disease was 3 years. The sex ratio was 0.8. The thyroid abnormalities collected were: Subclinical hypothyroidism (SH) (76%), hypothyroidism (15%), hyperthyroidism (7%). 45% of HS were not treated. The other abnormalities were treated within <3 months (82%). Therapeutic compliance was poor in 44% of cases. The IQ assessment objectified: IQ<70% (33%), 70<IQ<105% (66%); QI>115%(0). Patients with low intelligence had: late start of treatment (50%); poor treatment compliance (66%); other associated pathologies (33%). All patients with untreated HS had an IQ >70%.

Conclusion: The delay in starting treatment, therapeutic compliance and the association with damage to the central nervous system represent the main factors influencing intelligence in dysthyroid children.

P2-239

Hyperthyroidism in children

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Introduction: Hyperthyroidism is a rare but potentially serious childhood disorder that, if left unchecked, can lead to a wide range of complications, including effects on growth and development. Medical history, physical examination and thyroid function tests help diagnose hyperthyroidism. Graves' disease is the most common cause of hyperthyroidism in children, accounting for over 95% of cases, and is caused by stimulating antibodies directed against the thyroid-stimulating hormone (TSH) receptor.

Patients and Methods: This is a prospective descriptive study of the records of 11 patients followed in the pediatric department of the Mustapha Bacha University Hospital in Algiers.

The aim of the study is to analyze the epidemiological profile of the patients and the therapeutic possibilities.

Results: The average age of our patients was 10 years old; we found a female predominance with 10 female patients and only 01 male patient.

The disease was symptomatic in all patients (weight loss, tachycardia, insomnia), exophthalmos was present in 03 patients, and clinical examination found goiter in all patients.

Graves' disease was the most frequent cause, found in 09 cases, the other two cases' etiology was a thyroid toxic hot nodule.

Surgical treatment was necessary in a patient with two toxic hot nodules, and radioiodine therapy was performed after the end of puberty for another patient who had poorly controlled Graves' disease under medical treatment (carbimazole).

For the other patients, the disease was well controlled under medical treatment (Carbimazole), with two patients in complete remission.

Conclusion: Hyperthyroidism is a rare but serious childhood disorder, most often occurring as a result of Graves' disease. Treatment options for Graves' disease in children include antithyroid drugs, radioactive iodine, and surgery. Antithyroid drugs are commonly used as first-line treatment in children.

Late Breaking

P2-241

Primary hyperparathyroidism in children

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Keywords: primary hyperparathyroidism, parathyroid gland, genetic study.

Background: Primary hyperparathyroidism (PHPT) is a rare disease with a prevalence up to 2-5:100,000. About 90-95% of cases are isolated adenomas, 5-10% cases are due to hereditary syndromes. Parathyroid carcinomas occur in less than 1%.

Aim: To study clinical features and genetic characteristics of patients with primary hyperparathyroidism.

Materials and Methods: 49 patients with primary hyperparathyroidism was examined. Laboratory, instrumental diagnostic tests and molecular – genetic analysis were provided for all patients.

Results: The median age at the time of the examination was 15.81 [13,1; 16.8] years with median PTH 148.1 [87.0; 532.9] ng/mL, total calcium 2.97 [2.73; 3.2] mmol/L, calcium ionized 1.37 [1.3; 1.49] mmol/L, phosphorus 1.05 [0.91; 1.26] mmol/L. Hypercalciuria was diagnosed in 21 of patients (43%). Topical diagnostics of parathyroid gland was performed by ultrasound investigation and scintigraphy with Tc-99m-technetril, ectopic location was revealed in 5 patients (3 patients - intrathyroidal, 2 patients – mediastinal). The genetic basis of the disease was established in 17 patients (34,7%): MEN1 - 11 (22%), CDC73 - 3 (6%), RET - 2 (4%), SLC9A3R1 - 1 (2%). Surgical treatment was performed in 37 patients. Results of the morphological study revealed 31 adenomas (83,8%), 2 atypical adenomas (5,4%), 3 hyperplasias (8%) and 2 carcinomas (5%) of parathyroid glands. MEN1 pathogenic variants were found in 12,9% cases (4 patients) among the 31 histologically confirmed adenomas.

Conclusion: Molecular genetic analysis is indicated for all patients with PHPT. Pathogenic variants were identified in 17 (34,7%) of cases. MEN1 defects are the most common in PHPT and associated with adenomas.

P2-242

Endocrine manifestations of the COVID-19 pandemic in children and adolescents: a scoping review

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Introduction: There is limited data on endocrine manifestations of the COVID-19 pandemic in children/adolescents. We conducted a scoping review to summarize available evidence.

Method: A literature search was conducted using PubMed, Scopus and Google Scholar databases to identify studies on endocrine manifestations of COVID-19 in children/adolescents, published up to 31/03/2023 using pre-specified keywords, and perusing additional references from relevant articles. Evidence is presented for obesity/insulin resistance, puberty, thyroid disorders, adrenal disorders and pituitary disorders.

Results: A total of 38 studies were reviewed including 2,061,942 subjects, including data on obesity/insulin resistance (n=2,058,876), puberty (n=1868), thyroid dysfunction (n=352), and adrenal disorders (n=846).

A rise in obesity following the pandemic, was reported in many studies (pre-pandemic 10.4%-36.2% vs post-pandemic 12.3%-45.7%), with boys being more affected, together with an increase in incidence of type 2 diabetes in one study (annualized incidence 17.6 vs 48) with younger age of onset (12.9 vs 14.8 years). Associated factors included lockdown restrictions, reduced physical activity, increased screen time, dysregulated sleep patterns, unhealthy diet and stress.

Seven studies reported an increased incidence of central precocious puberty(CPP) (range pre-pandemic 1.4%-26% vs 5.0%-46.8% post-pandemic), predominantly among girls, as well as an accelerated rate of pubertal progression. Reasons postulated include disturbances in hypothalamic-pituitary-gonadal axis due to sleep disturbances, restricted outdoor activities, increased screen time, binge eating and high-calorie intake during the lockdown.

While long-term thyroid dysfunction rates remained stable during the pandemic, an increase in mild transient thyroid dysfunction was reported. Further, worsening of thyroiditis and Graves' disease were not reported among children. However, low free triiodothyronine (fT3) levels were associated with development of multisystem inflammatory syndrome (MIS-C) and need for intensive care among children with COVID-19 infection.

Children with pre-existing adrenal insufficiency showed higher rates of sepsis, need for intubation and mortality when infected with SARS-CoV-2. There were no reports of children developing pituitary apoplexy following COVID-19 or of children with pre-existing hypopituitarism being at increased risk of severe COVID-19 infection.

Conclusion: The COVID-19 pandemic was associated with an increase in overweight/obesity among children/adolescents, especially boys, and an increase in rate and progression of CPP, especially among girls, possibly due to lifestyle changes imposed by lockdown/restrictions during the pandemic. Significant effects of the COVID-19 pandemic on long-term thyroid, adrenal and pituitary dysfunction were not found. Among children with COVID-19 infection, low fT3 levels and pre-existing adrenal insufficiency were associated with severe disease/complications.

P2-243

Endocrine Outcomes in Bardet-Biedl Syndrome from a Large Single-Centre Paediatric Multidisciplinary Clinic

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Introduction: Bardet-Biedl syndrome (BBS) is a rare, autosomal recessive ciliopathy, with a prevalence of 1 in 100,000 – 160,000, caused by mutations across >20 known genes encoding for proteins responsible for the integrity of the primary cilium/basal body complex. Endocrinopathies associated with BBS include hypogonadism, hypothyroidism, and the metabolic complications of obesity. The endocrine characteristics of a large adult BBS cohort have been reported; however, there are fewer data reported in paediatric populations.

Objective: To describe the prevalence of endocrinopathies in BSS from a large paediatric cohort at a single-centre multidisciplinary service.

Method: A retrospective 13-year study of paediatric patients (<18 years) with genetically confirmed BBS at a single-centre paediatric multidisciplinary service. Patient data were collected from electronic records and an independent database, managed and developed by Certus Technology Associates. The study was registered and approved by the Hosptial Trust.

Results: Of 163 patients seen in the paediatric BBS clinic, 139 (50% female) had genetic confirmation and were included in analysis, where data were available. Mutations in BBS1 and BBS10 were most common, in 34% and 22%, respectively.

Patients overweight/obese (BMI >1.34 SDs) totalled 128/136 (94%), and 110/136 (81%) were obese (BMI >2.05 SDs). Of patients >16 years, 26/30 (87%) were overweight/obese and 22/30 (73%) were obese.

Type 2 diabetes was diagnosed in 3/139 (2%). Metformin was prescribed for 4/129 (3%) patients; two for diabetes, two for impaired glucose tolerance, and one for obesity.

For patients >16 years, no patients had needed sex steroid treatment – all had spontaneous onset of puberty and no pubertal arrest. Of males, 8/39 (21%) had delayed puberty. Of females, 3/41 (7%) had delayed puberty, with mean age of menarche 12.9 years.

Thyroid abnormalities were clinical hypothyroidism (on levothyroxine) in 2/125 (2%), subclinical hypothyroidism in 1/125 (1%), and 9/125 (7%) had abnormal thyroid function that self-resolved.

Conclusion: This is the largest analysis of endocrine outcomes for paediatric patients with BBS. Despite dietetic input in an MDT clinic, obesity remains a significant morbidity. Hypogonadism, hypothyroidism, and insulin resistance were not significant morbidities in this cohort and more prevalent in reports from adult cohorts. Longitudinal analysis of growth is ongoing. Longitudinal studies into adulthood could help better understand the timing of endocrinopathies associated with BSS, which could help service development and patient education.

P2-244

The impact of weight for length on the assessment of congenital growth hormone deficiency

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It has been established that a random growth hormone (rGH) level can be obtained and is useful within the first 28 days of life for establishing a diagnosis of congenital growth hormone deficiency (cGHD). However, it remains unclear if weight-for-length (WfL), a surrogate for adiposity, impacts these levels, similar to how body mass index in older subjects impacts peak growth hormone levels derived from provocation testing. The objective of this study is to determine the impact of weight for WfL on rGH levels obtained during the first 28 days of life.

This is a retrospective chart review of subjects who had rGH levels collected during the first 28 days of life. Indications for testing were: hypoglycemia, jaundice, micropenis, abnormal central nervous system imaging and other miscellaneous findings. Deceased subjects and those for whom a WfL could not be calculated due to length < 45 cm were excluded. The primary measure was rGH level. Length, weight, gestational age at delivery, and sex data were also collected. Univariate analyses were performed using Pearson correlation coefficient. Multivariate linear regression analysis was used to determine independent predictors of rGH levels. Covariates such as age, sex, gestational age at delivery which were suspected as potentially having an impact of rGH levels were entered into the model.

The study included 121 neonates with mean age 7.33 +/- 5.40 days, 100 (83%) were born at term gestation and 92 (76%) males. The 2 most common reasons for rGH level testing were hypoglycemia (43.8%) and abnormal central nervous system imaging (25.6%). In the univariate regression WfL z-score was not associated with rGH levels, p =0.0773. Using multivariate analysis, no other variables were found to be significant (all had p-value >0.1)

For neonates who undergo testing based on a suspicion of cGHD, rGH levels do not appear to be impacted by WfL and can be interpreted without caution. This also highlights the contribution of in utero factors on neonatal growth hormone production rather than adiposity which impacts GH levels later in life.

P2-245

Neonatal Hypocalcaemia and association with maternal Magnesium sulphate (MgSO4) administration in a single center neonatal unit

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Introduction: Hypocalcaemia is a biochemical abnormality noted in neonates and considered a possible side effect of maternal MgSO4 administration. Suggested mechanism is MgSO4 treatment increase maternal hypermagnesemia, inhibiting maternal parathyroid hormone secretion leading to maternal and foetal/neonatal hypocalcaemia.

Objectives: This study is aimed to identify common risk factors, presentation, biochemical abnormalities, severity, and treatment given for the neonates with hypocalcaemia on the Neonatal Unit at Walsall Manor Hospital.

Specific Objectives: To identify any correlation between maternal MgSO4 therapy and neonatal hypocalcaemia?

Methodology: Retrospective cohort study for neonates admitted to Neonatal /Transitional Care Unit in Walsall Manor Hospital over 6-month period from 01/01/2022 to 30/06/2022.

Inclusion Criteria: Term and preterm weighing >1500 g: total calcium <2 mmol/L or ionized calcium < 1.1 mmol/L

Very low birth weight weighing <1500 g: total calcium <1.75 mmol/L or ionized calcium <1 mmol/L.

Results: Total live births (TLB) were 1762, 195 admitted to NNU and 78 had biochemical evidence of hypocalcaemia. 96% (76) with hypocalcaemia was symptomatic, 74 had respiratory distress, 2 (4%) had seizures and none had ECG changes. 98% (76) of hypocalcaemia was early onset; late onset and persistent 1 each respectively; and 46 of early onset, settled spontaneously.

Among TLB, 18 neonates were less that 34+6 weeks, 6 less than 30 weeks and 12 were 30+0 to 33+6 weeks.

33+6 weeks and below	Received maternal MGSO4	Did not receive maternal MGSO4
Number of patients	10	8
Number of hypocalcaemic patients	7	7
Number of normocalcaemic patients	3	1
Mean ionized calcium	1.03 mmol/L	0.98 mmol/L
Mean total calcium	2.29 mmol/L	2.53 mmol/L
P value (ionized)	0.256	
P value (total)	0.351	

Discussion, Conclusion, and Recommendation: 74 out of 76 with symptoms having respiratory distress; Hypocalcaemia could be incidental finding in blood gas analysis in neonates with respiratory distress.

Mean ionized calcium for neonates whose mothers received MgSO4(1.03mmol/L) was higher than that of neonates whose mother's did not receive MgSO4 (0.98mmol/L). Mean total calcium for neonates whose mothers received MgSO4 (2.29 mmol/L) was lower than that of neonates whose mother's did not receive MgSO4 (2.53 mmol/L). P value is above 0.05 hence we reject the alternative hypothesis that maternal MgSO4 is correlated with neonatal hypocalcaemia and accept the null hypothesis that MgSO4 has no effect on neonatal calcium levels. The limitation is the small sample size, hence multicenter study is recommended.

P2-246

Results from a Multi-Stakeholder Meeting on Medical Devices in Paediatric Type I Diabetes

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Objectives: To discuss all challenges involved with providing children (including the very young) and adolescents with diabetes (CwD) with the latest appropriate technology, such as automated insulin delivery systems (AIDs), to manage their blood glucose and help improve their quality of life and suggest ways in which access to new types of devices available to adults can be improved for children with T1D.

Methods: In connection to the ATTD (Advanced Technologies & Treatment for Diabetes) congress in 2023 the "conect4children.org" network organized a multi stakeholder meeting to discuss barriers in providing medical devices to children and adolescents with type 1 diabetes with a focus on pre-schoolers. After announcement, stakeholders were asked to apply to this meeting. A coordinating program committee planned the meeting and a balanced selection of participants from relevant interest groups attended, including academics, clinicians, industry, regulators, patient advocates.

Results: 125 participants took part in the hybrid in-person/virtual 1-day meeting, in person and by web portal (interest groups: 50 academia/research, 21 advocates for CwD, 26 industry, 28 regulatory). Three plenary sessions with 16 presenters and 3 panel discussion with 19 participants were held.

Discussion: The most advanced appropriate technology is often unavailable to children with T1D in Europe.

Main issues highlighted were:

- Lack of long-term evidence of benefits/clinical effectiveness and safety of AIDs in very young children
- Regulatory approval processes are very lengthy and expensive for sponsors in EU
- Market access is variable across countries, and even within countries, depending on the proximity of patient to specialist centres (or their ability to travel)
- Reimbursement depends on where the patient lives

Results of this meeting will be published and reported to the EU Commission in order to accelerate access to technology and improve therapy for CwD regardless of their age and place of living.

P2-247

Fluid Selection in The Management of Diabetic Ketoacidosis in Children: A Systematic Review

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Introduction: DKA is the most common cause of hospitalization, morbidity, and death in children with T1DM. Based on the International Society of Pediatric and Adolescent Diabetes (ISPAD) 2022, the biochemical criteria of DKA are: hyperglycemia (blood glucose >200 mg/dL), acidosis (venous pH <7.3 or bicarbonate <18 mmol/L), and ketonemia or moderate/large ketonuria. The principles of ABC (airway, breathing, circulation, and fluid resuscitation) are the first things to be applied while treating DKA patients. Fluid administration to restore the volume of the intravascular, interstitial, and intracellular compartments, is crucial and should be done immediately but with great care to avoid the risk of cerebral edema. However, until now there has been ongoing deliberation regarding fluid treatment strategy compared to the others. Therefore, to discover the best management and outcome for the patients, a systematic review of fluid selection in managing diabetic ketoacidosis in children is required.

Material and Methods: Literature search was performed using keywords with a combination of Boolean connectors (“CHILDREN” OR “PEDIATRIC”) AND (“DIABETIC KETOACIDOSIS”) AND (“FLUID”) with various combinations. The systematic review was carried out based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. The authors used articles from PubMed database. The studies included were limited to articles published in the last 10 years (2013–2023), in English, included children aged 0–18 years with DKA. The exclusion criteria were research using qualitative methods, abstracts from national/international conferences, guidelines, case reports, commentaries, and review articles. All studies which met the criteria were identified using the selected keywords. Then, title screening was done, followed by abstract screening. Complete article screening was done on studies that met the inclusion criteria and did not meet the exclusion criteria. The main outcomes assessed were time to resolution of ketoacidosis, adverse events, duration of hospitalization, and cost.

Conclusion: The evidence to date does not support the use of one over the other options of intravenous fluids for the treatment of DKA: 0.9% saline, 0.45% saline, Ringer’s lactate, Plasma-Lyte, Hypertonic saline. Balanced crystalloid solutions were thought to be superior due to their alkalizing properties, available evidence did not show any clinical benefits over their use compared with normal saline. Although the use of hypertonic saline carries the risk of initial hyperchloremia, there was no significant difference in the incidence of Acute Kidney Injury and development of cerebral edema in comparison with NS.

P2-248

Pediatric Hyperthyroidism in the Time of COVID-19: An Updated Presentation Analysis

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Abstract: The SARS-CoV-2 virus uses ACE2 combined with the transmembrane-protease TMPRSS2 to enter and infect thyroid follicular cells. Studies have reported a higher incidence of hyperthyroidism cases during the COVID-19 pandemic compared to pre-pandemic periods. Studies have also been reported cases of thyroid dysfunction early after mass covid vaccinations. However, there are insufficient data to confirm these associations in children.

Aims: To identify whether presentations of thyroid dysfunction tests suggestive of hyperthyroidism in children to a tertiary paediatric hospital changed as a result of the COVID-19 pandemic and after SARS-CoV-2-mRNA-vaccination.

Methods: A retrospective case note review was conducted of all children with thyroid function tests suggestive of hyperthyroidism between 1stJanuary 2014 and 31stMay 2023 at a tertiary paediatric endocrine center in Barcelona.

Results: The greatest number of thyroid alterations occurred in 2020 (n=7; 40% of total). Prior and after to this, the number of presentations was 1 or 2 cases per year (5.6-11.1%). All cases were female. There were statistically significant differences in fT4, fT3 and TRABs (p<0.05).

Conclusion: The highest number of cases of hypertoidism was observed at the peak of the pandemic. However, thyroid dysfunction since the start of the pandemic appears to be milder and no cases were reported after mass vaccinations.

Table. Characteristics of hyperthyroid patients (n=18) prior to the pandemic and during the pandemic

	Pre-Pandemic n=9 (50%)	**Pandemic n=9 (59%)**	**p-value**
Year	2014-2019	2020-2023	NA
Female sex (%)	9 (100)	9 (100)	NA
Median BMI (Kg/m2) (range)	20.3 (17.1-23.7)	22.8 (18.6-23.7)	0.606**
Median age (years) (range)	12 (11.5-15)	16 (13-16)	0.113*
Median TSH (mU/l) (range)	0.004 (0.004-0.009)	0.004 (0.004-0.027)	1.000*
Median fT4 (pmol/l) (range)	2.54 (2.28-3.1)	1.35 (0.85-2.48)	0.024*
Median fT3 (pmol/l) (range)	3.60 (2.68-6.25)	1.35 (1-1.80)	0.020*
Median TPO antibodies (U/ml) (range)	659 (99-1500)	112 (5-713)	0.222*
Positive TPO antibodies (%)	8 (89)	7 (78)	1**
Median Tg antibodies (U/ml) (range)	166 (17-961)	28 (5-112)	0.161*
Positive Tg antibodies (%)	7 (78)	7 (78)	1**
Median TRABs (U/ml) (range)	5.71 (1.50-11.76)	1.07 (0,03-3.04)	0.031*
Positive TRABs (%)	9 (100)	4 (57)	0.063**
Autoinmune history (%)	1 (11.1)	1 (11.1)	0.765**
Treated (%)	9 (100)	6 (66.7)	0.103**
Thyroid dysfunction prior to SARS-CoV-2-mRNA vaccine	NA	6 (86)	NA
Thyroid dysfunction post to SARS-CoV-2-mRNA vaccine	NA	0 (0)	NA

TSH:Thyroid Stimulating Hormone; fT4:thyroxine; T3:triiodothyronine; TPO:thyroid peroxidase; TRAB:thyroid-receptor antibody. Tg:thyroglobulin. *Mann–Whitney U.test; **Fisher Exact-Test

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Longitudinal Improvements in Health-Related Quality of Life among Children and Adolescents enrolled in Canadian Pediatric Weight Management Programs

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Background: It is critical to understand patient-reported outcomes in pediatric patients enrolled in pediatric weight management (PWM) clinics. Health-related quality of life (HRQoL) is low in children with obesity. Utilizing data from the CANadian Pediatric Weight Management Registry (CANPWR), we examined (1) changes in HRQoL up to 3 years after enrollment in PWM and (2) factors associated with change in HRQoL over time.

Methods: Child-reported (n=957) and parent-proxy reported (n=1111) HRQoL were assessed (PedsQL) at baseline, 6, 12, 24 and 36 months after commencing the PWM program at one of 9 Canadian PWM centers. Associations between demographic, anthropometric, lifestyle behavior and health services characteristics and HRQOL were assessed over 36 months using a linear effects model.

Results: Child self-reported and parent-proxy PedsQL total scores (74.6 ±14.5 vs 69.9±15.2; $p<0.001$ and 68.6±17.0 vs 64.6±17.4; $p<0.001$ respectively) and the scores for each domain (physical, emotional, social and school functioning) improved from baseline. In multivariable models, self-reported total PedsQL score over time was higher in boys, children who identified as non-white, and those with higher household incomes. Lower scores were associated with sleep disturbance, lower physical activity, and higher screen time, independent of BMI z-score. Scores were higher in those with higher hours of clinic attendance. Similar factors predicted parent-proxy scores.

Conclusion: Self-reported and parent-proxy reported HRQoL improved over time in children enrolled in CANPWR. Higher self-reported scores were positively related to the amount of time in PWM clinics. Poor sleep, lower physical activity and higher screen time were associated with poorer HRQoL.

P2-250

Update on the Etiological Diagnosis of Central Precocious Puberty in Both Sexes

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Background: The etiological investigation of central precocious puberty (CPP) has improved with more precise clinical approach, neuroimaging, and genetic studies. CPP can be caused by congenital or acquired conditions, with or without central nervous system (CNS) lesions. More recently, genetic and epigenetic disorders have been identified in children with CPP, previously classified as idiopathic.

Objective: To update the etiological diagnosis of a large cohort of children with CPP.

Methods: We evaluated retrospectively the distinct etiologies of 292 patients (264 girls) followed in a single university hospital from 2000 to 2022. Among them, 182 patients with CPP without CNS lesions were investigated with genetic/epigenetic studies. We performed Sanger DNA sequencing (n=155), target panel sequencing (n=64), exome sequencing (n=64), genome sequencing (n=5), specific DNA methylation analysis (n=111), and genomic microarray (n=30).

Results: Pathological CNS lesions were identified in 51of 292 (17.5%) patients with CPP (17 boys and 34 girls), indicating a prevalence of CNS lesions of 60.7% in boys and 12.9% in girls. These pathological CNS lesions were classified as congenital (n=34) or acquired (n=17). The most common congenital causes were hypothalamic hamartoma (n=20, 11 girls), myelomeningocele (n=4), and neurofibromatosis type 1 (n=2), while the most common acquired causes were hydrocephalus (n=8) and cerebral palsy (n=3). The remaining 241 (82.5%) CPP patients presented without CNS lesions, being classified as apparently idiopathic. In the subset of patients submitted to genetic/epigenetic investigation (n=182; 173 girls, 9 boys), the overall frequency of genetic/epigenetic causes was 12.1% (20 girls, 2 boys); and it was higher in boys (22.2%) than in girls (11.5%). The genetic/epigenetic defects were MKRN3 inactivating mutations (n=8, from 7 families), DLK1 inactivating mutations (n=6, from 2 families), KISS1R activating mutation (n=1), KISS1 activating mutation (n=1), MECP2 mutations (n=2), DDX3X mutation (n=1), and Temple syndrome (n=3). Univariate logistic regression analysis identified positive family history (OR 3.43; 95%CI 1.35-8.69; $p=0.009$) and associated neurodevelopmental abnormalities (OR 3.53; 95%CI 0.99-12.48; $p=0.05$) as possible clinical predictors of congenital CPP in patients without CNS lesions.

Conclusion: The prevalence of pathological CNS lesions was 17.5%, confirming previous data. Genetic or epigenetic defects were identified in 12.1% of patients with CPP without CNS lesions, and family history and neurodevelopmental abnormalities were predictors of these congenital causes. Our findings evidenced the growing role of congenital causes among children with CPP without CNS lesions.

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P2-251

Environmental sustainability of three injection pens used for administration of recombinant human growth hormone

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Background: Growth hormone (GH) therapy typically involves daily administration of recombinant-human growth hormone (r-hGH) injections over many years. Long-term treatment attracts substantial costs due to the regular usage of injector pens. We conducted a study to understand the environmental impact of reusable and disposable GH injector pens.

Aim: To assess environmental sustainability of Aluetta® reusable pen versus other disposable injector pens used for r-hGH treatment.

Method: Three types of GH injector pens namely, Aluetta® (Merck Healthcare KGaA, Darmstadt, Germany; quantity=1), Genotropin® GoQuick® (Pfizer Inc., NY, USA; quantity=1) and Norditropin® FlexPro® (Novo Nordisk A/S, Bagsværd, Denmark; quantity=2) were compared (without product/drug cartridge). A test was performed to assess the total mass of plastic and metal on each injection pen in the Laboratoire National de Métrologie et d'Essais, Trappes at controlled temperature and relative humidity (RH) conditions (23°C±5°C/50% RH ±25% RH) according to test protocol (P228277/DEC1). Balance with a 0.0001 gram resolution was used for mass weighing. Using mass of each pen, an estimate of energy consumed in producing such pens for 3 years of treatment was calculated (assuming use of one Aluetta® pen for 3 years versus one pen/week for other pens). This energy was converted into equivalent days for home power usage, kilometers driven with electric car and number of Aluetta® pens that can be produced.

Results: Total mass of plastic and metal parts on Aluetta® pen is 34.8 grams compared to Genotropin® GoQuick® pen (48 grams) and Norditropin® FlexPro® pen (25.2 grams) in the timeframe assessed. Our analysis indicated that, over 3-year treatment period, total energy consumed in producing Aluetta® pen was lower (1.18 Kilowatt-hour) compared to Genotropin® GoQuick® pens (149.36 Kilowatt-hour) and Norditropin® FlexPro® pens (115.45 Kilowatt-hour). Aluetta® pens produced using this amount of energy can serve another 126 patients as compared to Genotropin® GoQuick® and 98 patients as compared to Norditropin® FlexPro®. Correspondingly, if we calculate the savings with Aluetta® versus Genotropin® GoQuick® or Norditropin® FlexPro® pens, 15.5 or 11.9 house days of power can be utilized, 748 or 577 kilometers can be driven, resulting in 105 or 81 kilograms of CO_2 savings, respectively.

Conclusion: The reusable Aluetta® injector pen lasts over several years of GH treatment, saving considerable amount of energy that can be beneficially used for various purposes considering environmental sustainability. This tangible study highlights an environmentally-conscientious approach with Aluetta® pens and the need of adopting greener solutions.

P2-252

Pump management of genetic and autoimmune diabetes under 1 years old: two case reports

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Handling diabetes at a very early age is difficult, even more when a complementary diet has not yet started. There is increasing evidence supporting the use of CSII in infants but some tricks could be useful.

Infant 1: 10 mo, admitted in cardiac arrest. ROSC after 3 minutes, severe DKA (pH 6,95). Transferred to PICU, received also plasma transfusions.

Day 2: CGM Dexcom G6 was started and tests for pancreatic autoimmunity and genetic of neonatal diabetes were performed.

Day 7: CSII (Tandem t:slim X2 Basal IQ) was started. Genetic and pancreatic autoimmunity tests gave negative results.

Day 14: Control IQ started: TDI 0,9 U/kg/die, bolus for milk meals in extended mode. Control IQ automatically managed meals up to 40 g of CHO. No hypoglycaemia. TIR 52%, TAR 48%, TBR 0%.

Day 90: Considering an interference due to plasma transfusion, autoimmunity was repeated and T1D was confirmed.

Day 180: TIR 85%, TAR 12%, TBR 4% (1% <54 mg/dl). Neurocognitive tests resulted equal to peers.

Infant 2: born at 37 w. Normal pregnancy, SGA. Normal glucose check and metabolic screening.

Day 1: At 34 days of life admitted to ED for fever and hypovalid feeding. At the sepsis workup finding of glycemia 500 mg/dl, ketons 0,3 mmol/L, no acidosis. Rhino-Enterovirus at nasal swab. IV Insulin was started at 0,005-0,01 U/kg/h.

Day 2: C peptide 0,7 ug/L, pancreatic autoimmunity tests and genetic of neonatal diabetes were performed, rtCGM Libre 3 applied, insulin modulated up to 0,07 U/kg/h.

Day 9: CSII was started (Tandem Basal, then Control IQ) using oblique set in high gluteal area. Aspart diluited 1:1, then 1:2, basal rate 0,24 U/h, FSI 1/600, I/CHO 1/180, always-on sleep mode to avoid automatic boluses with stable control.

Days 10-20: the mother was taught how to stop insulin for glycemia 180 in rapid decline and to use oral glucose to manage hypoglycemia. No pancreatic autoimmunity was found.

Day 30: de novo heterozygosis variant in KCNJ11: glibenclamide was started, insulin progressively stopped.

The actual dose is 0,25 mg/kg/die in 6 administrations, TIR 86%, TAR 12%, TBR 2% (<54 mg/dl 0%). The neurological evaluation is normal.

Conclusion: HCL, in an experienced centre, might be useful to manage diabetes also for infants. As regards to neonatal diabetes, it appears fundamental to shift to sulphonylureas as soon as there is the genetic confirmation.

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P2-253

Challenges and Outcomes of Using Insulin Analogues in Children with Diabetes in Low- and Middle-Income Countries

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Introduction: The selection of insulin therapy for children with type 1 diabetes (T1DM) poses a challenge, particularly in low- and middle-income countries. This study aimed to assess the utilization of insulin analogues in diabetic children and identify factors associated with achieving glycemic goals.

Methods: In a retrospective study involving 80 children with T1DM, the impact of transitioning from human insulin to insulin analogues was evaluated. Epidemiological, clinical, and therapeutic parameters, as well as glycemic control, were analyzed before and after the change in insulin therapy.

Results: The average age of patients at the time of switching was 10.9 years, with an average diabetes duration of 3.7 years. Following the transition, there was a significant decrease in fasting blood glucose levels (11.11mol/l vs. 9.62 mmol / l;(p=0.024)) and postprandial glucose levels (20.17 mmol /l to 19.07 mmol /l). The mean HbA1c levels improved with insulin analogues, especially in patients regularly engaging in physical activities (10.40% to 8.61% (p=0.043)). The number of hospital admissions per year significantly reduced after the switch (0.35/year to 0.23 hospital admissions/year (p=0.001)). High costs and the lack of social security coverage led to the majority of patients (82%) reusing needles multiple times per day. Temporary discontinuation of intensive insulin therapy with analogues, resulting in acid-keto decompensation, was primarily due to financial constraints (22%), voluntary decisions (10%), or forgetfulness (68%). Twelve patients switched back to human insulin after an average duration of 1.5 years. Definitive discontinuation of insulin analogues occurred due to the cessation of social security coverage (2 cases) or difficulties in acquiring self-financed micro-fine needles (8 cases).

Conclusion: Insulin analogues exhibit beneficial effects on glycemic control and hospitalization rates, despite the ongoing challenge of attaining optimal glycemic objectives. Personalized therapeutic education plays a pivotal role in preventing therapy discontinuation and should incorporate socioeconomic considerations. By prioritizing affordable physical activities, tailored dietary approaches, and individualized action plans, outcomes can be improved.

P2-254

Decrease in the percentage of eutrophic adolescents in Brazil, temporal evaluation from 2010 to 2022

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Introduction: Adequate nutritional status of adolescents is essential for their healthy development, with health repercussions in both short-term and adult life.

Objective: To analyze the temporal trends of the BMI of Brazilian adolescents (10 to 19 years old) between 2010 and 2022.

Patients and Methods: Descriptive ecological study. Data obtained from e-SUS Primary Care. The BMI categories evaluated were: severe thinness (ST), thinness (T), eutrophy (E), overweight (OW), obesity (OB), and severe obesity (SOB). The prevalence rate, the annual percentage changes (APCs), and its trend were calculated by segmented linear regression. Time series analysis performed in Joinpoint version 4.9.

Results: On average, 4.5 million adolescents were assessed each year of the historical series. In the analyzed period, their BMI showed an increasing character in "T," "OB," and "SOB" (APC:1.52; p=0.002; APC:8.44; p=<0.001 and APC:11.5; p=<0.001, respectively), while "E" presented a decreasing character (APC:1.67; p=<0.001). "ST" showed an increasing character in the Midwest region until 2014 (APC:7.9; p=0.024), changing its nature to a decreasing one between 2014 and 2018 (APC: -10.82; p=0.013) and stationary since then (APC:1.66; p=0.408). Regarding the macro-regions, "OW" showed an increasing character in the North (APC:2.86; p=<0.001) and Southeast (APC:4.14; p=0.003) in the periods from 2010 to 2015 and between 2015 and 2022.

Discussion: The increasing character of "T," "O," and "SOB" in Brazil point to the increase of the extremes of nutritional status since it is possible to observe the simultaneous growth of "obesity" and "thinness" in the country. These data point to inadequate nutrition in this population, either due to the offer of foods with low nutritional value, the increased consumption of ultra-processed foods added to a sedentary lifestyle, or socioeconomic factors, which make it impossible to access a diet with good nutritional value. Thus, it is possible to observe an increase in the healthy vulnerability of this population.

Conclusion: There was a simultaneous increase in adolescents with "T," "O," and "SOB" in Brazil, while the number of "E" adolescents decreased. In the North and Southeast regions, it was also possible to observe an increase in "OW" adolescents. Brazilian Public Health Service should use the BMI trends to guide effective policies for the adolescent population.

P2-255

Phenolic Endocrine Disruptors as Potential Risk Factors for Early Onset Thelarche: Insights from a Population-Based Study

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The diagnosis of early thelarche is common in Pediatric Endocrinology consultations, with many cases lacking an organic cause. It can either spontaneously resolve, remain stable, or progress to precocious puberty. Early exposure to endocrine-disrupting environmental pollutants (EDs) with estrogenic and/or anti-androgenic effects during pregnancy or childhood may affect the timing of thelarche onset and/or puberty in girls. Further research is needed to better understand the influence of EDs on these developmental milestones.

Objective: To examine potential variations in the levels of exposure to a range of phenolic endocrine-disrupting compounds with estrogenic and/or anti-androgenic activity (such as bisphenols, parabens, and benzophenones) between girls with early thelarche (cases) and healthy girls without this condition (controls)

Methodology: A multicenter, geographical variation-based case-control study was conducted in hospitals across different regions of Spain. The cohort, comprising 110 cases and 97 controls, was recruited between 2018 and 2023, and a preliminary analysis was performed. In urine samples collected from participants, concentrations of three bisphenols (bisphenol A (BPA), S (BPS) and F (BPF)), four parabens (methyl- (MPB), ethyl- (EPB), propyl- (PPB) and butyl-paraben (BPP)) and six UV filters from the benzophenone (BP) family (BP1, BP3, BP6, BP8 and 4OHBP). Associations were examined by unconditional logistic regression models adjusted for hospital, age, BMI z-score, and urinary creatinine.

Results: The girls had a mean age of 6.7 (1.6) years. At least one EDs was detected in 99% of all samples tested. In a greater number of case BPA and BP-1 were detected. The cases presented higher concentrations of BPA, BP1 and 4OHBP. These differences were statistically significant. These results are partial, since this study is in the development phase and the association between these exposures and the risk of early thelarche will be evaluated in a larger sample.

Conclusions: Phenolic endocrine disruptors (EDs) have been identified in nearly all of the analyzed samples, suggesting widespread exposure to EDs among school-age girls. Urinary levels of BPA, a compound known for its estrogenic effects, appear to be elevated in girls with early thelarche. Exposure to BPA may increase the risk of early thelarche. Further studies are needed to assess the influence of exposure to phenols and other EDCs on the risk of early thelarche and precocious puberty.

P2-256

Influencing Factors of Growth Hormone Treatment in Short Stature Children Born Small for Gestational Age in China: a single-center, cross-sectional survey

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Keywords: growth hormone, small for gestational age, genetic defects; Silver-Russell syndrome; growth hormone deficiency

Objectives: To evaluate the influencing factors of GH treatment in Chinese short stature children born SGA.

Methods: This was a single-center, retrospective, cross-sectional survey in China. Of 101 patients were identified born SGA and 66 short stature children born SGA were participant in the GH therapy. Forty-one participants were receiving GH treatment and complete at least 6-month of follow-up. Main outcome measures were height standard deviation score (HTSDS), heigh, growth velocity (GV), and change of height standard deviation score (ΔHTSDS). HTSDS was converted by using Chinese reference data. The generalized estimating equation (GEE) was used to identified the potential factors, including GH treatment time, age at GH therapy initiation, sex, SGA related gene mutation, GH deficiency and birth weight, that influencing the effectiveness of GH treatment. Enrolled patients born SGA were categorized into three age groups based on their age at GH treatment initiation (2 to <4 years, 4 to <6 years, and ≥ 6 years). SGA related gene mutations and so as whether the gene mutation was belonged to Silver-Russell syndrome, whether patients were associated with GH deficiency (<10 ng/mL) were also used to evaluate the impact on GH efficacy.

Results: The mean age at GH treatment initiation was 5.6 years old. Results from GEE indicated that GH treatment time were significantly affected HTSDS, height, GV, and ΔHTSDS among patients born SGA. The increase in GV caused by GH treatment was highest in the first half of the year and gradually weakened later. SGA related gene mutation was significantly affected GV (β=-1.25, 95% confidence interval, CI: -2.38, -0.12), and GH deficiency was significantly affected both GV and ΔHTSDS (β=-1.40, 95% CI: -2.21, -0.58, and β=-0.36, 95% CI: -0.66, -0.07, respectively). There was no statistical difference in GV or ΔHTSDS comparison between gene mutation and normal, or SRS gene mutations and not at a single time point. Patients who associated with GH deficiency had significantly higher ΔHTSDS after 2 years and 2.5 years of GH therapy.

Conclusions: Chinese short stature children born SGA without SGA related gene mutations, and those with natural GH secretion deficiency, may have better GH efficacy that those with gene defect and normal natural GH secretion.

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P2-257

A cohort study on growth hormone therapy in Chinese children with Prader-Willi syndrome – the effect of treatment age

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Background: Prader-Willi syndrome (PWS) is a rare multisystemic genetic disorder. Recombinant human growth hormone (rhGH) therapy is the most established form of treatment for PWS. This study aimed to investigate the effect of rhGH treatment age on the treatment outcome of children with PWS.

Methods: A retrospective analysis of 167 genetically confirmed Chinese children with PWS followed between 2017 and 2022. Unadjusted and adjusted generalized estimating equations (GEE) were used to study the long-term trends in anthropometric parameters, insulin-like growth factor-1 (IGF-1), and glucose metabolism parameters during rhGH treatment in PWS. To compare the incidence of hypothyroidism, hip dysplasia, and scoliosis before and after rhGH treatment.

Results: The cohort had a significant increase in height/length standard deviation score (SDS). Compared to the infant group, there was an increase in height/length SDS by 0.42 (P =0.045) and body mass index (BMI) SDS by 1.80 (P =0.037) in the preschool group at year 3 and an increase in weight SDS by 1.09 (P =0.037) and BMI SDS by 1.91 (P =0.008) in the toddler group at year 3. BMI SDS remained stable in the school-age group. IGF-1 was consistently lower in the infant group than in the other groups over time (P <0.05). Both fasting insulin (FINS) and homeostasis model assessment of insulin resistance (HOMA-IR) increased significantly in the school-age group compared to the infant group (P <0.001). The incidence of hypothyroidism was increased in the cohort (P <0.05), independent of treatment age (P >0.05).

Conclusions: rhGH is effective in improving height/length SDS in children with PWS, especially in preschool, as well as weight and BMI-SDS in infancy and toddlerhood. rhGH appears to maintain a stable BMI-SDS in PWS long after school age. It is important to pay attention to changes in HOMA-IR during rhGH treatment. Further monitoring of high IGF-1 levels in older PWS is needed. Watch for hypothyroidism, which is often found in PWS infants, and further investigate whether it is related to long-term rhGH treatment.

P2-258

Long-term Safety and Effectiveness of Growth Hormone in Pediatric Patients with Growth Disorders in Korea: A 10-Year Interim Analysis of the LG Growth Study

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Objectives: This study aimed to evaluate the safety and effectiveness of rhGH treatment, using specific products (Eutropin®, Eutropin®Pen, Eutropin®AQ, Eutropin®Plus and Eutropin®SPen; LG Chem, Ltd.), in pediatric patients with growth disorders in Korea.

Methods: Among the patients who enrolled in LGS (2012–2022, N=5,120), patients received at least one injection of rhGH were included for safety analysis. The effectiveness analysis comprised patients from the safety analysis group who had at least one measurement of height after receiving rhGH treatment. Main outcomes included adverse events (AEs), height velocity (HV) and height standard deviation score (SDS).

Results: During the 10-year study, a total of 5,040 patients (male 53.2%, female 46.8%) were analyzed for safety. Of those patients, 3,332 (66.1%) had GHD, 869 (17.2%) were born SGA, 747 (14.8%) were diagnosed with ISS, 257 (5.1%) had TS and 10 (0.2%) had CRF. The mean age at the screening was 7.6 years and the mean treatment duration was 3.8 years. AEs were reported in 1,725 (34.2%) patients, most AEs were mild.

A total of 41 neoplasms were reported in 36 (0.7%) patients, the majority of which were benign and unrelated to rhGH. Cumulative results of AEs showed that the proportions of patients experiencing adverse drug reactions (ADRs), serious adverse events (SAEs), and serious adverse drug reactions (SADRs) remained relatively stable throughout 10 years of follow-up (7.0%, 3.2% and 0.3% respectively).

The occurrence probability of SADRs remained stable over the 5-year follow-up period. (0.4% for SADRs). This finding suggests that the probability of experiencing SADRs during rhGH treatment was consistently low and relatively consistent throughout long-term duration.

The mean HV increased from 5.3±4.0 cm/year (n=672) at baseline to 9.1±1.7 cm/year after 12 months of rhGH treatment (n=2,070). The greatest mean HV was observed in patients with idiopathic GHD. After treatment with rhGH, the height SDS consistently increased compared to baseline at each assessment. In the effectiveness analysis, the mean height SDS significantly improved

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from -2.58±0.69 at baseline to -1.82±0.74 (n=2,070), -1.43±0.80 (n=1,486), -1.24±0.86 (n=977), and -1.10±1.02 (n=671) at 12, 24, 36, and 48 months, respectively, with stable maintenance thereafter.

Conclusions: Data from the LGS, the largest and longest-running database of rhGH-treated pediatric patients in Korea, support the safety of rhGH treatment and demonstrate significant improvements in mean height SDS.

P2-259

Saudi experience of long term treatment for Laron syndrome with IGF-1 injection over 22 years, cohort study

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Background: Laron syndrome is an autosomal recessive disease caused by molecular defect in GH receptor gene. The patients have severe growth retardation and clinical features of GHD with low IGF-1, high basal GH and failed response to IGF-1 stimulation test. The only proved treatment is daily recombinant IGF-1 administration which showed improvement in linear growth.

Aim: To describe the largest group of patients with laron syndrome Saudi Arabia and asses the efficacy of IGF-1 treatment and complication.

Methodology: We conduct a retrospective chart review to all patients with laron syndrome who are receiving IGF-1 treatment at dosage of 100mcg /kg/dose +/- 20mcg BID in king Faisal specialist hospital and research center from 1998 till 2020. Initial height, basal GH, response to treatment and improvement will be described for every patient currently receives treatment and for those who already completed their treatment. 27 patients with GHIS followed since early childhood were included in the study.

Result: During the first year of therapy a substantial increase in linear growth velocity was witnessed, from a mean 3.4 to 6.5cm/year with the mean difference of 3.1cm ($p < 0.0001$). In the second year the growth velocity was lower, but still suggestively higher than before treatment, from 3.4 to 5cm/year with mean difference of 1.6cm (P:0.0015).

Long term follow-up over 10 years presented an increase in growth velocity compared to the baseline, but changes were statistically significant in the first 5 years. However, weight SDS was expressively greater throughout the treatment as well. Age at starting of the therapy had no particular impact on the results except for the fact that the patient had stayed longer on the treatment.

P2-260

Pseudohypoaldosteronism: a challenging diagnosis with management pitfalls

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Background: PHA is a rare, but life threatening condition, that usually presents with impressive hyperkalemia. It can be initially missed as congenital adrenal hyperplasia (CAH). We present a series of these patients to increase the awareness of treating physicians about misdiagnosis and pitfalls in management.

Case Report: We admitted 4 cases in our institution between 2017-2021. Case one, three and four were all 7 days old males, and case two was 40 days old female. They presented with variable symptoms of vomiting, poor feeding, weight loss, dehydration, and fever. In addition, they all had profound hyperkalemia reaching 10- 11 mmol/l and significanthyponatremia reaching levels of 129 mmol/l. Case one and four both showed initial normal levels of serum aldosteronethat were found to be high after dilution of the samples. During follow-up periods of of 31 months to 4 years, all of these patients required regular adjustment of kayexalate, sodium chloride and sodium bicarbonate doses with weight changes to keep a normal serum sodium level and a potassium level below 5.5 mmol/l.

Discussion: Our patients' series demonstrates challenges that may face physicians during PHA management. PHA mimics CAH in clinical and biochemical presentation. Also, there are technical issues regarding the accuracy of serum aldosterone measurement. Moreover, the use of a potassium chelating agent requires careful and close follow up for optimization of doses to avoid life threatening hyperkalemia. This requires frequent initial follow-up visits to ensure monitoring, dose adjustment and early detection of electrolytes' imbalances when these patients grow out of their doses.

Conclusion: PHA can be associated with a delay in diagnosis and early start of management. An optimal use and adjustment of medications is critical for rapidly growing young children.

P2-261

Rare cause of Endocrine Hypertension - Apparent Mineralocorticoid Excess with a novel mutation

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Introduction: Apparent mineralocorticoid excess (AME) is rare cause of endocrine hypertension. 11 alpha hydroxysteroid dehydrogenase(HSD) type 2 enzyme metabolises cortisol to cortisone, thereby inhibiting cortisol acting at mineralocorticoid receptor(MR). In AME, this enzyme is defective resulting in unmetabolised cortisol causing MR activation with resultant hypokalemic metabolic alkalosis and hypertension.

Case Presentation: Patient is 2 year girl born at 36 weeks gestation with birth weight 1.26 kgs, following pregnancy complicated with severe IUGR and oligohydramnios. Parents were non consanguineous. She presented with 3 day history of lethargy, headache and right hemiparesis. There was a year's history of polyuria and polydipsia. Evaluation revealed short stature (73 cm, -4.15 SDS), poor weight gain (7 kg, -4.12 SDS) BP 157/95 mmHg (> 99th centile). Investigations revealed metabolic alkalosis (pH7.5, bicarb25.9 mmol/l) hypokalemia (3.0 mmol/l), normal serum sodium (145 mmol/l), suppressed renin (<0.5 mIU/ml)and low plasma aldosterone(1.31 ng/dl), no urinary electrolyte losses (Na 29 mmol/l, K 17 mmol/l), normal renal function (urea 24 mg/dl, creatinine 0.3 mg/dl). Echocardiogram -severe left ventricular hypertrophy, Ultrasound-left nephrocalcinosis and MRI brain-acute infarct in left thalamus and capsuloganglionic region. Whole exome sequencing reported homozygous missense variation in exon 3 of HSD11B2 gene (chr16:g.67436005A>G; Depth: 29x) resulting in amino acid substitution of Glycine for Aspartic acid at codon 176 (p.Asp176Gly; ENST00000326152.6). The p.Asp176Gly variant has not been reported in 1000 genomes and gnomAD databases and has minor allele frequency of 0.001% in Medgenome internal database. InIIn silico predictions of the variant are probably damaging by PolyPhen-2 (HumDiv), and damaging by SIFT and LRT. The reference codon is conserved across species. Parents' target gene analysis is awaited. Maximum doses of 3 antihypertensives (Spironolactone 10 mg/kg/day, labetalol and ramipril) were required to control the BP just above 99th centile. Polyuria settled within few days and potassium supplements were stopped after a month. Dexamethasone 0.25 mg had dramatic response and helped to gradually wean down the anti-hypertensives. Blood pressure improved after addition of small dose of Amiloride 0.15 mg/kg/day to Spironolactone 1.5 mg/kg/day

Conclusion: This novel mutation reflects severe phenotype. Hypertension with hypokalemic alkalosis and suppressed plasma renin and aldosterone should make one think of Liddle syndrome or AME. Further delineation can done by urine cortisol/cortisone ratio or genetics. Dexamethasone, Spironolactone and Amiloride are drugs of choice for control of hypertension and hypokalemia.

P2-262

A new case of Malan Syndrome with de novo NFIX sequence variants and a review of the literature

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Background: We report clinical and molecular cytogenetic characterization of a 13-year-7-month-old boy with a Sotos-like phenotype and de novo NFIX deletions and review the literature. Result: A whole exome sequencing revealed in the present patient with unique clinical phenotypes a de novo frameshift mutation c.570-573delATCA (p.S191Ifs*19) in NFIX gene in 19p13.2.

Discussion: The present case with partially overlapping 19p13 microdeletion share the following features: psychomotor and language delay, intellectual disability, seizures, hypotonia, skeletal anomalies and facial dysmorphism. The haploinsufficincy could be the base for the phenotype -genotype correlation. There are striking genotype-phenotype correlations between Malan syndrome and Marshall-Smith syndrome, Sotos syndrome.

P2-263

The gene diagnostic challenge of extrem early-onset obesity before 6 years old

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Purpose: The causes of obesity is so much that the pandemic spread the global. The inherited factors have a profound effect on body fat mass, as well as the environmental factors. Out of these, the foremost is genetic factors that tend to early childhood obesity. The consensus recommended that genetic testing is necessary for serious early onset obesity to identify the pathogenic genes of inherited obesity. In order to improve the positive rate of genetic testing, further screening of the early-onset obesity is needed by clinical parameters. However, the clinical parameters closely related to early onset obesity are not well definite. Therefore, this study aims to distinguish hereditary obesity from non-hereditary obesity by clinical indicators, and provided clinical basis for early diagnosis of hereditary obesity and then genetic screening.

Methods: In generally, We screened the onset obesity before 6 years old by meas of BMI over 95 percent, and then advise hospitalization to evaluate obesity, including physical examination, biochemical testing, hormone levels and gene detection so on. Specifically, gene testing detected point mutations in coding regions, chimeric mutation, mitochondrial mutation, multiplex ligation-dependent probe amplification (MLPA) and whole-exome copy number variations (CNVs) in the study.

Results: After exclusion, the date of 23 children with early onset obesity(17 male and 6 female) was included in our research. We identified 6 (17%) probands carrying different gene mutations, including UCP3, MC4R, NCOA1, SH2B1, BBS1 and 15q11-13, namely positive WES group. At contrast to the group of WES negative, the group of pathogenic gene obesity has a significant increase in differential white blood cell count (WBC), monocyte, serum ALT, AST and cortisol levels so on(P<0.05).

Conclusion: The nonsyndromic and syndromic monofactorial obesity is caused by pathogenic genes. It is especially critical to screen the abnormal obesity that need a further gene test by the differentiation of clinical indices. Through the difference of clinical indicators, this study screened the genetic obesity in early-onset obesity requiring further genetic detection, providing reference for the genetic detection of early-onset obesity in clinical practice.

P2-264

Improvement in the nutritional status of Brazilian children under five years of age, evaluation from 2010 to 2022

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Introduction: The good nutritional status of children in the first years of life is essential for their healthy growth and development. Evaluating the repercussions of nutritional status is fundamental since nutrition can influence both short-term and adult life.

Objective: To analyze the temporal trends of the BMI of Brazilian children aged 0 to 5 between 2010 and 2022.

Patients and Methods: Descriptive ecological study. Data obtained from e-SUS Primary Care. The BMI categories evaluated were: severe thinness (ST), thinness (T), eutrophy (E), overweight risk (OR), overweight (OW), obesity (OB), and severe obesity (SOB). The prevalence rate, the annual percentage changes (APCs), and its trend were calculated by segmented linear regression. Time series analysis performed in Joinpoint version 4.9.

Results: In the whole country, we observed that the BMI of children under five years of age had an increasing character for "E" (APC:0.58; p=<0.001), while "ST" and "OB" showed a decreasing character (APC: -3.77; p=<0.001 and APC: -2.04; p=0.005, respectively). In the Northeast region, "ST" showed an increasing character until 2018 (APC: -5.4; p=<0.001) and a stationary tendency since then. In the Southeast region, "E" was stationary between 2010 and 2013 and increased since then (APC:0.98; p=<0.001), while "T" was stationary until 2018 (APC: -1.06; p=0.108) and increased between 2018 and 2022 (APC:4.87; p=0.012).

Discussion: The improvement in nutritional diagnosis, demonstrated by the reduction of "ST" and "OB" and the increase of "E" in Brazil, suggests an improvement in the quality of life and food supply for children under five years of age. This improvement may indicate the success of implementing public policies and healthcare measures. On the other hand, the analysis by macroregion shows the growing character of "ST" in the Northeast and of "T" in the South, highlighting the essential regional disparities in our country due to economic factors or even bias of health access.

Conclusion: The increasing character in the "E" category and a decreasing character in "ST" and "O" throughout the analyzed period indicates an improvement in the nutritional status of children under five years of age. Nevertheless, the rise in "T" and "ST" in the South and Northeast regions highlights the need for specific intervention in those regions.

P2-265

In vitro metabolic homeostatic activity of brown adipose tissue-derived exosomes

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Introduction: Obesity and related metabolic diseases occur as a chronic imbalance between energy intake and energy expenditure. Due to its high metabolic activity, brown adipose tissue (BAT) has become a promising target for the development of new treatment concepts for metabolic disease. Having a high concentration of mitochondria, BAT is necessary to control the entire energy metabolism of the body. BAT consumes significant amounts of glucose and fatty acids as fuel for energy expenditure by thermogenesis mediated by mitochondrial dissociation protein 1 (UCP1). Exosomes are nanovesicles that share the characteristics of donor cells involved in intercellular communication. BAT-derived exosomes (BAT-Exos) may orchestrate metabolic communication.

Methods: We analyzed the effect of BAT-Exos on cellular metabolism, lipid accumulation, oxidative stress, inflamatory factors in skeletal muscle, adipocytes and liver cell lines. In vitro effects of exosomes were evaluated by cell metabolism analysis. Protein contents of BAT-Exos were analyzed by mass spectrometry.

Results: The results showed that myofibers, hepatocytes, and adipocytes were exposed to BAT-Exos, they showed increased UCP1 protein abundance and cellular metabolism with increased oxygen consumption and proton leakage. These functional responses were associated with browning-like structural changes in mitochondrial and lipid droplet content. Protein profiling of exosomes demonstrated that BAT-Exos were rich in mitochondria components and involved in catalytic processes. Cells in metabolic communication also increased expression of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha and mitochondrial biogenesis, along with a number of BAT selective and beige gene markers.

Conclusion: BAT Exos are important players in mediating cell-to-cell communication as well as interorgan crosstalk between adipose tissue and other distant organs, thereby participating in the regulation of local immune responses, tissue remodeling, systemic insulin sensitivity and energy homeostasis. A more detailed understanding of BAT-Exos as molecular and functional will help increase our metabolic knowledge and facilitate the development of new therapeutics for obesity regulation and the treatment of related metabolic complications.

P2-266

Rabson Mendenhall syndrome (RMS)- Insulin resistance type A. We need to act faster than the disease. Case report

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Background: Rabson Mendenhall syndrome (RMS) is an autosomal disorder where severe insulin resistance is observed. Insulin levels decrease over time and suppress gluconeogenesis in the liver. Fatty acid oxidation is affected leading to frequent episodes of ketoacidosis. The changes in RMS are much faster than in patients with type 2 diabetes. RMS patients have a significantly reduced life expectancy and may die during adolescence or early adulthood.

Case Presentation: A 15-year-old girl with poorly-controlled diabetes. She was diagnosed with RMS at the age of 50 days and her genetic study showed a homozygous mutation for R141W in the INSR gene. Her insulin level was high at 737µIU/mL, IA-2 and GAD antibodies were negative and C-peptide was > 18 ng/ml. There is a strong family history of RMS on her mother's side. For the first six years, her hyperglycaemia was treated with an insulin pump (requiring up to 300 units of insulin/day) and oral Rosiglitazone, after which Rosiglitazone was replaced by oral Insulin-like-growth factor (IGF1). Over the last three years, she had four further episodes of DKA triggered by infections and severe lipodystrophy. A trial of leptin and subcutaneous IGF1 has failed. Currently, the patient is with a closed-loop insulin pump MiniMed 780G with a total daily dose of 261 units (4.6U/kg/day).

Results: During the last 15 years, the patient suffered of so many health, psychological, family and school issues. These issues were due to RMS itself, complications of diabetes, side effects of medications, and technology failure. All issues were tackled by our dedicated multi-disciplinary team by providing the most appropriate care, mediation and technology.

Conclusion: To act faster than the disease progression we need to know the whole list of issues our patient could face as this will help us to look at the entire picture rather than treating different pieces separately. Effective communication and cooperation between the teams is the key point and need to be organized through a family physician or by the team involved the most in patient care. Although technology has some limitations it still helps when used appropriately.

P2-267

Intellectual outcome in children with early treated congenital hypothyroidism

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Background: Congenital hypothyroidism (CH) is one of the preventable causes of intellectual disability. L-thyroxine is a drug of choice for CH treatment to preserve normal brain development and function.

Objective: to evaluate intellectual outcomes at preschool age in early treated CH.

Materials and Methods: This retrospective chart review was conducted on 27 treated children with CH identified by neonatal screening program in Thailand from 1998 to 2017. The IQ test was performed at aged 6-8 years. Clinical data including sex, birth weight, age at the initiation of L-thyroxine, level of Free T4 and TSH before treatment, initial dose of L-thyroxine, type of CH, aged at IQ test, full scale IQ, verbal IQ and performance IQ were reviewed.

Results: Of 27 CH children, 7 patients were initially early treated with L-thyroxine before aged 14 days and 20 patients were treated after aged 14 days. Initial free T4, TSH, weight at treatment and initial dose of L-thyroxine were not different between early and late treatment group. Mean full scale IQ difference between 2 groups was statistic significantly (p=0.01). However, there was no statistically significant difference in the mean of verbal IQ and performance IQ. Thyroid scan results show dyshormonogenesis (n=12), thyroid agenesis/hypoplasia (n=5), and ectopic (n=10) Mean full scale IQ in dyshormonogenesis group was more than thyroid agenesis/hypoplasia and ectopic thyroid group. We found that timing at treatment and type of CH were independent factors significantly influencing the intellectual outcome (full IQ score>90). (p=0.01)

Conclusion: Children with CH treated early after newborn screening within 14 days have better IQ score compare to CH treated after 14 days. Timing of treatment and type of CH have a role in neurodevelopment and intellectual outcome in CH children.

P2-268

Clinical characteristics, molecular genetics analysis results and long-term follow-up of a large cohort of congenital hyperinsulinism from Turkey: A nationwide cross-sectional study

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Objective: Congenital Hyperinsulinism(CHI) is a clinically, genetically, and histologically heterogeneous disease. Turkey is a county with highly prevalent cases of severe CHI due to the high rate of consanguinity and recessively inherited KATP gene mutations. We herein evaluated the clinical characteristics, molecular genetic analysis, and follow-up of a large nationwide cohort of CHI from Turkey.

Patients and Method: This is a nationwide crossectional multicentre retrospective study. Data was collected using a proforma through a web-based data collection tool, CEED-NET for Pediatric Endocrinology. Clinical characteristics, presenting complaints, biochemical features, molecular genetic analysis, treatment strategies, and long-term follow-up outcomes for patients with CHI were collected.

Results: In total 364 patients (female:175), were recruited from tertiary pediatric endocrine centers from around the country. Mutation analysis results were available for 193 patients with a mutation catch-up rate of 91.7%. Mutations in ABCC8 gene(n=120; 62.1%) account for the vast majority of whole mutations which was followed by HADH(n=25; 12.9%), KCNJ11(n=18;9.3%) and GLUD1 gene mutations(n=6;3.1%). Heterozygous mutation in GCK gene(n=3), KMT2D gene(n=1), BWS(n=2), and chromosome 9p deletion syndrome account for the rest of the underlying genetics etiology. The median age of presentation was 2 weeks (Ranges:1 day to 16 years) which did not differ among patients with a K_{ATP} channel gene mutation and mutation-negative group(p=0.168). However, the median age of the first presentation was younger in patients with K_{ATP} channel gene mutations compared to other gene mutations (1 week vs 8 weeks; p<0.001). Besides, patients with K_{ATP} channel gene mutations had a statistically significant higher BW (<0.001). The rate of detection of a mutation was higher in diazoxide-unresponsive cases compared to those of the diazoxide-responsive group(p<0.001).

Conclusion: Recessive mutations in either of the KATP channel genes (ABCC8 and KCNJ11) or HADH genes account for more than 90% of the underlying genetic aetiology of CHI in our large nationwide cohort. In line with recent literature data, our results showed that higher BW and diazoxide unresponsiveness have predictive values in detecting KATP channel gene mutations. In addition, our data suggested that in patients presented later in life detection of non-KATP channel gene mutations might be more likely. The high catch-up rate for detection(92%) of a mutation was attributed to the high rate of consanguinity, and limited sources for genetics analysis thereby performing analysis in selected cases.

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Are Serum MOTS-c Levels and *MOTS-c m.1382A>C* Polymorphism Related to Polycystic Ovary Syndrome?

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Introduction: Mitochondrial-derived peptide (MOTS-c) is originated from the 12S ribosomal region of mitochondrial DNA. MOTS-c functions as an activator of AKT and AMPK, which are involved in the insulin signaling pathway. In experimental studies, MOTS-c administration was shown to reduce insulin resistance and obesity. Besides, MOTS-c levels were decreased and negatively correlated with insulin resistance in obese male children. In male cases, the *MOTS-c* gene *m.1382A>C* polymorphism has been associated with susceptibility to type 2 diabetes. However, there is no research in the literature regarding the *MOTS-c* gene m.1382A>C

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polymorphism and serum MOTS-c levels in subjects with polycystic ovarian syndrome (PCOS).

Objective: We aimed to investigate the relationship of *MOTS-c* gene (*m.1382A>C*) polymorphism and serum MOTS-c levels with PCOS.

Methods: Adolescents aged 12-18 years completed at least two years after the first menarche and were diagnosed with PCOS according to the Rotterdam criteria consisted the PCOS group. The control group was comprised of healthy adolescents with regular menstruation. Anthropometric measurements and body fat analyses of all cases were performed. In addition, metabolic and hormonal tests were carried out in adolescents with PCOS. Serum MOTS-c levels were analyzed by the ELISA method, and *MOTS-c* gene (*m.1382A>C*) polymorphism was evaluated by sequence analysis in all participants' samples.

Results: 121 PCOS and 125 healthy adolescents were included in the study. BMI-SDS, waist circumference, fat mass, fat percentage, and blood pressure values of the PCOS group were higher than the control group. In the PCOS group, 41.6% had obesity, 2.4% had impaired fasting glucose, 24% had insulin resistance, and 18.4% had dyslipidemia. Although the median serum MOTS-c level was higher in the PCOS group, the difference was not statistically significant (p=0.059). MOTS-c levels were not different among obese and non-obese PCOS subjects (median serum MOTS-c levels 101.0 & 80.9 ng/mL, respectively, p=0.160). Serum MOTS-c level was not associated with any of the anthropometric or metabolic parameters in the PCOS group (p>0.05). *MOTS-c m.1382A>C* polymorphism was determined as wild type (A/A) in all study participants.

Conclusion: This study showed that (i) *MOTS-c* gene (*m.1382A>C*) polymorphism is not associated with PCOS, (ii) serum MOTS-c level in PCOS subjects is not different from healthy controls, and (iii) MOTS-c has no role in the etiopathogenesis of PCOS subjects since it does not show a significant relationship with anthropometric or metabolic parameters.

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The effect of dulaglutide (GLP-1agonist) and metformin combination on weight loss in obese patients with and without type 2 diabetes. Gold combination?

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Background: GLP-1 agonists have a special place in the treatment of type 2 diabetes mellitus (T2DM). Dulaglutide is GLP-1agonist with important advantages, it doesn't cause hypoglycemia, reduces weight and decreases HbA1c with sufficient level. GLP-1 agonists are also involved in the treatment of obesity.

Objectives: The purpose of this study was to present the efficacy of Dulaglutide (GLP-1) in obesity with and without T2DM.

Methods and Results: 126 patients were enrolled in the study. 65 of them had both T2DM and obesity. Middle age of the patients of this group was 38.6 years (28.6-61.4), sexual distribution-31 male and 34 female. The duration of T2DM was up to 5 years. In another group 51 patients only with obesity were involved, whose middle age was 36.7years (28.1-54.3), sexual distribution-35 female and 16 male. The study duration was 8 weeks, during which patients of both groups received metformin 2000 mg every day and Dulaglutide 1.5 mg once a week. In the T2DM and obesity group BMI was 34.3 ±2.3 kg/m2, HbA1c-8.1% (7.0-8.9) and only in the group of patients with obesity BMI 36.0 ±2.7 kg/m2, HbA1c-5.2 %(4.3-5.7). As a result of 8 weeks combined treatment in patients with obesity and T2DM reduced BMI with 3.3 kg/m2 or 9.6% (P<0.001). was recorded Weight loss was more evident in other group, about 4.4 kg/m2 or 11.1 %. In the first group decreased HbA1c about 2.6% (P<0.001)was also recorded .

Conclusions: Combination of GLP-1 and metformin is very effective from the point of view of diabetes compensation and weight loss, which reduces the probability of cardiovascular accidents, at the same time, weight loss improves the quality of life.

Reference

Jamy Ard, Angela Fitch, Sharon Fruh, Lawrence Herman Weight Loss and Maintenance Related to the Mechanism of Action of Glucagon-Like Peptide 1 Receptor Agonists Epub 2021 May 11. Adv Ther 2021 Jun;38(6):2821-2839. doi: 10.1007/s12325-021-01710-0.

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Craniosynostosis in Patients With X-Linked Hypophosphatemia: a monocentric experience

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Introduction: X-linked hypophosphatemic rickets (XLHR) represents the most common form of genetic hypophosphatemia and causes rickets in children because of increased FGF23 secretion and renal phosphate wasting. Even though cranial vault an craniovertebral anomalies of potential neurosurgical interest, namely early closure of the cranial sutures and Chiari type I malformation (CM-I), have been observed in children with XLH, their actual incidence and characteristics are not established.

Aim: The main aim of this study was to analyse the prevalence of cranial and CM-I in children with XLH and to identify the predictive factors of these anomalies. The secondary aim of this study was to verify the usefulness of MRI specific scans as an alternative tool to CT for the diagnosis of these anomalies.

Material and Methods: We prospectively performed Neuroradiological evaluation in nine of the eleven XLH children followed at our Pediatric Clinic: 9 Children (five females and four males, mean age 8,5 ± 5 years at the radiological evaluation, all were on burosumab treatment since mean age of 5,8 ± 4,2 years) underwent CT scans of head and skull; moreover three children also underwent MRI "black bone" sequences and two children underwent MR-Angiography (MRA). We found that 44% of XLH children had a complete or partial fusion of the sagittal suture and

33% of XLH children showed protrusion of the cerebellar tonsils. The male sex was associated with craniosynostosis (p<0.01), and craniosynostosis was associated with abnormal descent of cerebellar tonsils (p<0.01). All the patients with radiological diagnosis of CM-I showed symptoms (headache). Three patients with no craniosynostosis underwent MRI with black bone sequences to evaluate the visibility of the sutures: all the cranial sutures were consistently identified on "Black Bone" MRI.

One patient with cranial synostosis and CM-I, diagnosed on skull CT, underwent MRA, showing absence of flow in the transverse venous sinuses.

Conclusions: This study highlights that sagittal suture fusion and CM-I is a frequent complications of XLH. Male sex was a strong predictor of craniosynostosis. All patients were on burosumab and the impact of a very precious start of this treatment on this complication has to be clarified. Because diagnosis of craniovertebral anomalies can be underestimated on a purely clinical basis, radiological studies should be considered in XLHR children. This study highlights that MRI with Black bone sequences are demonstrating considerable clinical potential as a non-ionizing alternative to CT in the diagnosis of craniosynostosis.

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Is screening for vitamin D deficiency reasonable or should we supplement at risk patients?

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Introduction: No consensus on vitamin D (VitD) deficiency screening in children and adolescents exists.

Aim: To evaluate a sample of patients in whom VitD dosing was performed and determine the rationale for this assessment.

Methods: Retrospective, longitudinal study of pediatric patients, from a Portuguese tertiary hospital, who had at least two 25(OH)D level blood sampling between March 2019 and March 2021. Children with less than 12 months were excluded given the routine VitD supplementation in this age group.

Results: From a total 1083 patients, 223 were eligible for analysis: 51% female gender, 82% Caucasians, median age of 12.5 years (IQR 6.5) and median SDS-BMI 1.14 (IQR 2.18). Median 25(OH) D blood level was 51 nmol/L (IQR 26), with 9% having VitD deficiency (<30nmol/L) and 37% insufficiency (30-50nmol/L). The 25(OH)D level was significantly influenced by the reason for testing (higher values in opportunistic screening, p=0.015), season (lower in winter, p<0.001), gender (p=0.04), age (r=-0.21, p=0.001) and by SDS-IMC (r=-0.17, p=0.011). VitD supplementation was offered in 90% and 74% patients with deficiency and insufficiency, respectively, with significant improvement in levels (37 vs. 54nmol/L, p<0,001) after a median of 5 months of therapy (IQR 5).

Most vitD assessments were requested in a screening setting (39%), namely in patients with obesity, type 1 diabetes mellitus, intestinal disease with impaired absorption, use of drugs such as anti-epileptics and corticosteroids. Of the patients screened, 56% had abnormal levels (12% deficiency and 44% insufficiency), and vitD supplementation was prescribed in 42%, with a significant improvement in vitD levels (40 vs. 61mmol/L, p<0.001), and a reduction in the prevalence of VitD deficiency from 20 to 2%. Of the patients screened for vitD deficiency who did not get supplementation, there were no statistically significant differences in the median 25(OH)D value, but the prevalence of the deficit increased from 3 to 5% in a median of 11 months (IQR 8).

Discussion: The dosage of 25(OH)D has important limitations, starting with the determination of normal cut-off levels, to the typical seasonal variation, the influence of obesity, among others. Screening for vitD deficiency in high-risk patients, has a reasonable foundation, however, the cost-effectiveness is questionable. In our study we found a large proportion of at-risk patients with deficit and/or insufficiency, so one may therefore ask whether routine supplementation is not more valuable, at least in the months of less sun exposure.

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Key parameters at puberty onset can help distinguish self-limited delayed puberty from congenital hypogonadotrophic hypogonadism

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Introduction: Delayed puberty (DP), affecting over 2% of adolescents, is defined as pubertal onset 2-2.5 SDs later than the general population. The most common underlying aetiology is self-limited DP (SLDP). However, this can be difficult to differentiate from the more severe condition congenital hypogonadotrophic hypogonadism (HH), especially on first presentation of an adolescent patient with DP. This study sought to elucidate phenotypic and genotypic discrepancies between the two diagnoses to improve diagnostic accuracy and patient treatment.

Methods: This was a retrospective study of a UK DP cohort managed from 2015-2023 identified through the NIHR clinical research network. Patients were diagnosed with SLDP if they had attained Tanner stage G4/B4 by age 18yrs. Otherwise, they were diagnosed with HH if they had not commenced (complete, cHH) or had arrested puberty (partial, pHH) before age 18yrs. Phenotypic data pertaining to auxology, Tanner staging, biochemistry, bone age and hormonal treatment were analysed. Genetic scores, ranging from 1-5, were assigned after whole-exome sequencing and identification of predicted pathogenic variants in genes associated with either SLDP or HH (1=known SLDP variant, 2=likely SLDP

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variant, 3=no or overlap variant, 4=likely HH variant, 5=known HH variant). Statistical analysis was completed using IBM SPSS and R.

Results: 78 patients were included in this study. 52 (66.7%) patients had SLDP and 26 (33.3%) had HH, of whom 17 (65.4%) pHH and 9 (34.6%) cHH patients. Probands were predominantly male (90.4%). Male SLDP patients presented with significantly lower height and weight SD than HH patients (p=0.004, p=0.021). HH patients had lower testicular volumes, particularly cHH patients (p=0.019). 73.1% of patients with SLDP and 43.3% with HH had a family history of DP (p=0.007). 15.4% of SLDP, compared to 38.5% of HH patients, had classical associated features of HH (micropenis, cryptorchidism, anosmia, etc. p=0.023). Mean first recorded LH and inhibin B were lower in males with HH, particularly in cHH patients (p=0.01, p=0.001), but were not discriminatory due to overlapping ranges. Genetic score of SLDP patients was lower than HH patients (3.00±0.55 as compared to 3.47±0.70; p=0.008). No significant differences were identified in FSH, testosterone, AMH or bone age delay.

Discussion: Key clinical markers of auxology, associated signs including micropenis, and serum inhibin B may help distinguish between SLDP and HH. These could be incorporated into an integrated framework or scoring system to aid clinician decision-making and management optimisation. However, the distinction between partial HH and SLDP remains problematic.

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Familial Chylomicronaemia Syndrome; A Challenging Condition in Pre-School Aged Children

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Introduction: Familial chylomicronaemia syndrome (FCS) is a rare autosomal recessive disorder caused by mutations in lipoprotein lipase, resulting in the accumulation of chylomicrons in plasma and therefore hypertriglyceridemia. Elevated triglycerides (TG) cause several complications, the most serious one is recurrent pancreatitis. The mainstream of management is a fat-restricted diet, followed by supplementing with Omega-3 fatty acids. Fenofibrate, and statins, are usually added at an older age.

Case: We report a challenging case of a 6-year-old child who presented initially at the age of 4 years, with acute abdominal pain, found to have acute pancreatitis, further evaluation revealed hypertriglyceridemia. Her biochemical investigations showed: Apolipoprotein A1 (0.92, N:1.08- 2.25 g/L), Apolipoprotein B (1.25, N:0.6- 1.17g/L), Leptin (0.39, N:0.39- 1.86 ug/L for BMI 12 Kg/m2), Triglycerides (68.5, N:0-2.3 mmol/L), Cholesterol (13.8, N:3.5 – 5.2 mmol/L), Cholesterol HDL (0.16), Non- HDL Cholesterol (13.6). Father is obese and his lipid profile showed high cholesterol of 8.8 mmol/L and triglyceride of 3 mmol/L, while the mother had a normal lipid profile. The whole exome sequencing was negative. Clinical examination revealed appropriate growth and development and no distinctive features apart from bilateral lipemia retinalis.

Over the course of her management and despite the extensive education about restricting fat in the diet, the child attained 10 episodes of pancreatitis over a span of 2 years. The highest TG level reached 128 mmol/L. TG usually drops by 50% within 24 hrs of hyperhydrating with 1.5 fluid maintenance and keeping her nil per mouth.

Giving the frequency of her pancreatitis and lipemia retinalis. She was started on fenofibrate 200mg capsules, an antilipemic agent (off-label for the age and the only available formula in Oman so far) to reduce the frequency of pancreatitis.

Conclusion: FCS is a very rare condition, and often either misdiagnosed or not diagnosed at all, hence it is important to raise the awareness of paediatric endocrinologists about this condition. FCS management can be very challenging, especially in young-aged children and when the other family members and surrounding people are not affected and have access to a variety of food. These factors may increase the chance of a young child being exposed to fat-rich food leading to hospitalization to manage acute pancreatitis that can be developed quickly regardless of the ingested amount. Fenofibrate has been used off-label to reduce the frequency of pancreatitis and other complications, with close monitoring of liver enzymes.

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Comparison of efficacy and safety of Leuprolide acetate depot 3.75 mg four-weekly versus 11.25 mg twelve-weekly in girls with central precocious puberty: A randomized-prospective study

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Context: Clinical experience is limited regarding the efficacy of different depot Leuprolide acetate (dLA) treatment protocols in girls with central precocious puberty (CPP).

Aim: To compare the 3.75 mg/4 weeks versus 11.25 mg/12 weeks ıntramuscular injection of dLA in suppressing gonadotropins and pubertal development.

Subjects and Methods: In a prospective study, 92 girls with CPP were randomized to receive ıntramuscular dLA 3.75 mg/4 weeks (Group-1, n=47) or 11.25 mg/12 weeks (Group-2, n=45). A GnRH stimulation test was performed before- and at 6 months of treatment to assess gonadotropin suppression. Basal and 40-minute post-dLA gonadotropins and estradiol were measured at the beginning, at the 3rd and 6th month in both groups and, at the 13th injection in Group-1, and at the 4th injection in Group-2. Clinical and anthropometric parameters of pubertal progression, pelvic ultrasound, bone age assessments were performed at the onset and the 12th month of treatment.

Results: There was no difference in clinical, anthropometric, and hormonal characteristics of Group-1 and Group-2 at the initiation of treatment. Serum gonadotropins and pubertal progression were effectively suppressed in both groups. There was no difference in the parameters examined at all time points during treatment between the groups except slight but significantly higher basal LH levels at 3rd (0,61± 0,35 vs 1,0±0,76), and 6th month (0.7± 0.4 vs 0.9 ±0.4) and at the end and of the study (0,7±0,3 vs 0.9± 0.4) in Group-2 ($p<0.01$). However, mean GnRH-stimulated LH at 6 months or 40-minute post-dLA injection LH at 6th months and at the end of the study did not differ between the groups. Furthermore, Tanner stage of breast development, height SDS, height velocity, bone age advancement, bone age/chronological age ratio, weight SDS, BMI-SDS, uterine and ovarian diameter, and volumes were similar in both groups at the completion of the study. No significant side effects were observed in both groups.

Conclusion: Although basal LH levels are slightly higher in 11.25 mg/4weeks dose, stimulated LH levels and clinical parameters of pubertal suppression are similar during the first year of dLA treatment with 3.75 mg/4 weeks or 11.25 mg/12 weeks doses. The latter offers the further advantage of less injection numbers in treatment of CPP.

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Olfactory bulbs and genetic defects in adolescents with Kallmann syndrome and normosmic hypogonadotropic hypogonadism

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Objective: to assess olfactory bulbs sizes and define the most common molecular defects in adolescents with congenital isolated hypogonadotropic hypogonadism. MATERIALS AND

Methods: Single-centre comparative study. 36 patients were included. The main group consisted of 21 patients with mean age of 15.9 years (17 boys, 4 girls) with congenital isolated hypogonadotropic hypogonadism (IHH): 13 patients with Kallmann syndrome (KS), 8 – with normosmic isolated hypogonadotropic hypogonadism (nIHH). Kallmann syndrome was diagnosed due to complaints of hypo- or anosmia. Olfactory bulbs width and height were assessed via MRI. Molecular-genetic studies were provided in all patients from main group. 15 patients were enrolled as controls (6 girls, 9 boys). Groups were matched for age, height and weight.

Results: Bilateral olfactory bulb hypoplasia was diagnosed in 7 out of 21 patients from main group. Bilateral aplasia was found in 4 patients. Olfactory bulb defects were found in 7 out of 8 nIHH children with no complains of hypo- or anosmia. Only 1 adolescent with hypogonadotropic hypogonadism had normal olfactory bulb size. Height and width of olfactory bulbs were significantly smaller in main group in comparison with controls ($p<0.05$ via Mann–Whitney U test). Median of right bulb height was 1.0 mm [0.2;1.2] in patients from the main group vs. 3.0 [2.5;3.2] in control group. Median of right bulb width was 1,0 mm [0.2;1.7] in patients from the main group vs. 2.5 [2.0;3.0] in control group. Median of left olfactory bulb height was 0.8 mm [0.0;1.1] in main group vs. 3.0 [2.7;3.2] in controls. Median of left olfactory bulb width was 0.4 mm [0.0;1.1] in main group vs. 2.5 [2.0;3.0] in comparison with control group. There were no statistically significant differences in olfactory bulb sizes between patients with KS and nIHH ($p>0.05$). Molecular defects were identified in 9 patients from main group: defects in FGFR1 were found in 4 out of 9 patients, CHD7 - 3, KAL1-1, FGF17 - 1. 5 defects were identified as variants of uncertain significance, 2 as likely pathogenic and 2 as pathogenic.

Conclusion: Bilateral olfactory bulb disorder hypoplasia is a reliable sign of hypogonadotropic hypogonadism: every third adolescent with congenital IHH had bilateral olfactory bulbs hypoplasia. All pathogenic variants were identified in FGFR1 and associated with uni/bilateral hypoplasia. Olfactory bulb defects were identified in 87.5% patients with no complaints of smell disorder, including 2 cases of bilateral aplasia.

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Evaluation of body composition and microcirculation in children and adolescents with growth hormone deficiency: effects of replacement therapy

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Aims: The aim of the study is to evaluate body composition and microcirculation in children and adolescents with growth hormone deficiency (GHD) and the effects of replacement therapy. These parameters were also evaluated in children and adolescents with suspected GH deficiency but in whom drug stimulus testing was later found to be normal.

Materials and Methods: We examined 44 patients (25 males and 19 females) aged between 6 and 16 years who underwent pharmacological testing to evaluate the presence of GHD. Of these 44 subjects, 26 were found to have growth hormone (GH) deficiency, while in the remaining 18 the test excluded the presence of deficiency (not-GHD). In each subject we evaluated body mass index (BMI), fat mass, fat free mass and total body water using Bioelectrical impedance analysis (BIA) and endothelial function using PeriFlux.v12. Patients were then re-evaluated after 6 months repeating the same measurements: 6 GHD in therapy and 6 subjects not in therapy (of which 2 GHD and 4 not-GHD).

Results: As far as body composition is concerned, no statistically significant differences were found at the first evaluation (T0) between GHD and not-GHD patients. In the 6 patients with GHD on therapy, at the 6-month re-evaluation (T1) were detected a reduction in fat mass (FM), an increase in lean mass (FFM) and an increase in total body water (TBW). These changes were not found in the 6 patients not on therapy. Post-occlusive hyperemia (PORH) detected at Periflux gave instead as average value at T0 in GHD subjects 210.9 ± 63.4 perfusion units/second, while in not-GHD subjects 287.8 ± 106.6 perfusion unit/second. The difference is statistically significant ($p=0.01$). Using PORH as a parameter of endothelial function, GHD patients seem to have a greater degree of dysfunction than not-GHD patients.

Conclusions: Since obese patients have been shown to have lower GH levels and respond less to drug-stimulus tests, that the dosage of GH therapy should consider lean body mass and that GH therapy modifies body composition we believe it is important to evaluate the body composition of these patients. The greater degree of endothelial dysfunction found in GHD patients compared to non-GHD patients could contribute to an increase in the cardiovascular risk, a further aspect that would underline the importance of replacement therapy and to evaluate the need to continue it even once the definitive height has been reached in adulthood in case of persistence of GHD.

P2-278

Endocrine dysfunction in CHARGE Syndrome – short case series

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Introduction: CHARGE syndrome is a rare constellation of congenital malformations caused by mutations in CHD7 gene. The acronym stands for **c**oloboma, **h**eart defect, choanal **a**tresia, **r**etarded growth and development, **g**enital hypoplasia, **e**ar abnormalities, and/or hearing loss. Endocrine disorders associated with this syndrome include hypogonadotropic hypogonadism, growth failure with or without growth hormone (GH) deficiency and hypothyroidism.

Objectives: We aimed to evaluate endocrine dysfunction in patients with CHARGE syndrome followed at Pediatric Endocrinology outpatient clinic in a tertiary pediatric hospital.

Methods: Clinical features and endocrine laboratory profile were assessed by retrospective chart review.

Results: In our cohort (N=6, four female and two male), median age at the time of the first Endocrinology visit was 4,1 years (min 1,2- max 11,7). Relevant clinical findings are shown on the table. Short stature was the most frequent endocrinological manifestation (n=4), with mean height of -3,59 standard deviation. None of the patients had thyroid dysfunction. One of the two male patients had bilateral cryptorchidism. Two female patients presented hypogonadotropic hypogonadism with pubertal delay, both having started puberty induction at the age of 14.

Conclusions: Late referral to Endocrinology clinic highlights the importance of raising awareness to endocrine dysfunction in CHARGE syndrome. According to the most recent follow-up protocol (Trider et al. 2017), Endocrinology consultation should begin in the neonatal period, allowing for early detection and intervention. Induction of puberty is a topic that must be increasingly addressed, given its importance in growth, emotional stability and bone health of these patients.

Case, Sex	Age at last visit (years)	CHARGE characteristics	Height z-score	IGF-1 (ng/mL)	Peak GH on stimulation test (ng/mL)	Gonadal findings	Hypo-gonadism	Pubertal induction
1, F	18,2	Atresia choanae, HSC, IVC, pulmonary valve stenosis coloboma, deafness	-3,58	201,0 (164-545)	11,2	Normal	Yes	Yes
2, F	14,0	Coloboma, HSC, IAC, pulmonary valve stenosis, deafness	-4,84	214,0 (120-448)	N/A	Normal	Yes	Yes
3, F	9,8	Atresia choanae, coloboma, HSC, deafness	-3,4	26,8 (51-303)	15,5	Normal	N/A	N/A
4, M	12,2	IVC, DAA, deafness	-2,54	70,8 (50-286)	N/A	Normal	N/A	N/A
5, M	10,2	Coloboma, HSC, deafness	-1,23	93,6 (22-208)	N/A	Cryptorchidism	N/A	N/A
6, F	1,7	Atresia choanae, HSC, Coloboma, IAC	-1,76	113,0 (26,1-128)	N/A	Normal	N/A	N/A

DAA–double aortic arch; F–female; HSC–Hypoplasia of the semicircular canals; IAC-interatrial communication; IVC–interventricular communication; M-male; N/A–not applicable

P2-279

The narrative of a patient with leptin receptor deficiency: personalized medicine for a rare genetic obesity disorder

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Leptin receptor deficiency is a rare genetic disorder that affects the body's ability to regulate appetite and weight. For patients and their families, the disorder seriously disrupts daily life, however, little is published about this impact. We here report the experiences of a 10.5-year-old girl with leptin receptor deficiency and her family. The diagnosis of this rare genetic obesity had a deep impact on the life of the child and her family. It led to a better understanding of the cause of the impaired appetite regulation and early-onset obesity with subsequently less judgement by others and improved cooperation of their social network and school on maintaining a healthy lifestyle for this girl. A strict eating regimen and lifestyle measures resulted in the first year after diagnosis in a significantly decreased BMI, followed by BMI stabilization, still categorized as obesity class three. However, the troublesome challenge of how to manage the disruptive behaviour due to hyperphagia remained. Eventually, due to treatment with targeted pharmacotherapy, i.e., melanocortin-4 receptor agonists, her BMI continued to decrease due to resolving hyperphagia. The daily routine of the family and the atmosphere at home positively changed, as it was no longer dominated by the food-focused behaviour of the child and the adherence to the strict eating regimen. This case report demonstrates the importance and impact of a rare genetic obesity disorder diagnosis in a family. Additionally, it highlights the value of genetic testing in patients with a high suspicion of a genetic obesity disorder as it can eventually lead to personalized treatment, such as guidance by specialized healthcare professionals and educated caregivers or targeted pharmacotherapy.

P2-280

Prevalence of Childhood Obesity Among Children Visited Paediatric Outpatient Clinics in Oman - A Single Centre Experience

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Introduction: Childhood obesity is a significant public health concern, affecting over 100 million children worldwide, with an overall prevalence of 13%. A previous Omani study in 2012 suggested the prevalence of childhood obesity in Oman was 12.5%.

Objectives: This study aims to identify the prevalence of childhood obesity among children under the age of 13 yrs, who visited various pediatric outpatient clinics at Sultan Qaboos University Hospital at any time during 2021.

Methods: Cross-sectional retrospective study. Data were collected from the electronic medical records of pediatric patients. BMI SDS was calculated using Growth-XP software.

Results: 3000 patients were included, revealing an obesity prevalence of 9.5% (286 patients). Males had a higher obesity prevalence than females (10.4% vs. 8.5%). Secondary school students (10-13 years) had the highest prevalence (15.5%) among other age groups. The Bone Marrow Transplant Unit (BMT) had the most number of children living with obesity (n=79/286), and this was thought to be due to their underlying conditions and severity of illness led to frequent hospital admissions, steroids use, and lower chances to exercise. Obesity class 3 (BMI SDS >3) was the most prevalent category among other types of obesity in our centre (42.31%).

Only 36.6% of the total obese patients (104/286) were referred to dietitians, and/or pediatricians with an interest in obesity/pediatric endocrinologists. Almost half of class 3 obese patients were not referred to the appropriate obesity service as the focus was mainly on their primary illness.

Conclusion: The prevalence of childhood obesity in our center is lower than the overall reported prevalence of obesity of the whole population in Oman, which means either children live with obesity are either managed in the primary health care level or they are not recognized/diagnosed, hence not referred. BMT obese patients might benefit from dedicated weight loss programs and individualized exercise programs to be part of the treatment plan to reduce the chances of comorbidities secondary to obesity. Healthcare professionals to be made aware of childhood obesity as a disease, therefore identifying patients earlier on and referring them through the right channels as early intervention may reduce the risk of developing complications and that might also reduce the burden of the disease on the patient, and healthcare system.

P2-281

Monogenic Causes of Early-Onset Obesity in Saudi Pediatric Patients: A Retrospective study

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Background: As a global pandemic and a public health concern, obesity impacts physical health adversely. Obesity is defined as abnormal excessive fat accumulation in adipose tissue. Where a portion of which have polygenic and monogenic etiology. Individuals carrying a rare gene variant that has a striking impact on adiposity are considered to be part of Monogenic obesity. In this study, we aimed to identify the presence of monogenic mutations contributing to early-onset obesity in KFSH&RC.

Aims and objectives:

1. Identify the presence of monogenic mutations contributing to early-onset obesity in KFSH&RC.
2. Identify obesity-related complications and age of onset.
3. Effect of medical and surgical therapy on obese children.

Methods: Cross sectional retrospective cohort study was conducted at King Faisal Specialist hospital and research center. Medical charts of pediatric patients with obesity were reviewed. All clinical and molecular genetic data were collected using Excel data sheet.

Results: Among 120 obese children, 58.8% (70)were males and 41.66% (50) were females.mean age at diagnosis was 9.9 years(±4.1 years), mean BMI of 36.4 kg/m2, and mean age of obesity onset was 2.6 years.Of 85 patients who underwent genetic testing, only(51) 60 % had positive results.MC4R accounted for most of the cases in 33% (17 patients),followed by PWS gene in 15.6 % (8 patients), BBS1 in 13.7%(7 patients),TMeM38P in 5.8%(3 patients),PCSK1 in 3.9 %(2 patient),UCP3 3.9%(2 patients). The most common associated complication was OSA (37.3%) followed by HTN (21.3%), and type 2 DM (8%). The mean age of complication onset was 8 years. 9 patients (7.5%) were started on medical treatment (liraglutide or semaglutide) and Mean BMI % change was 5.8% (±3.2). 8 patients (10.6%) underwent sleeve gastrectomy surgery. Mean BMI % changes was 17.8% (± 9.5) and most of them had Rebound weight gain after the first year of surgery.

Conclusion: Obesity is becoming an increasing global public health issue in Children. Saudi Arabia carries a high number of reported cases of melanocortin receptor mutation. Therefore, pediatric endocrinology assessment for monogenic forms of obesity should be considered in the presence of rapid weight gain from infancy, early-onset severe obesity and hyperphagia. Therefore, Early diagnosis and timely appropriate management are important in childhood obesity to prevent serious health problems. Also it's important to do a genetic test to detect the genetic cause of obesity as there is a new modality of therapy specific for certain gene.

P2-282

Impact of COVID-19 pandemic on vitamin D status in a Portuguese pediatric population: a comparation of pre-pandemic and pandemic periods

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Introduction: Vitamin D (VitD) is a prohormone that is synthesized in the skin after sun exposure. Mandatory lockdown during the COVID-19 Pandemic may have altered the sun exposure time of children.

Aim: to evaluate vitD levels in a sample of children and adolescents, and compare between pre-pandemic and pandemic periods.

Methoths: Children and adolescents, from a Portuguese tertiary hospital, who had 25(OH)D level blood sampling between March 2019 and March 2021 were included. Children with less than 12 months were excluded given the routine VitD supplementation in this age group. When more than one test/child was performed, only the first blood sample was considered. The sample was divided in two groups: before and during pandemic.

Results: From a total 1455 of 25(OH)D blood samples, 1001 were eligible for analysis (69%): 51% male gender, 80% caucasian, median 11.2 years of age (IQR 8.1) and median SDS BMI 0.85 (IQR 2.28). The median VitD level was normal (58nmol/L, IQR 27), with 6% having VitD deficiency (< 30nmol/L) and 32% insufficiency (30-50nmol/L). The characteristic seasonal variability was observed, with maximal levels in summer (M_d=68nmol/L) and minimal in winter (M_d=49nmol/L). The 25(OH)D value correlated negatively with age (r=-0.26, p<0.001) and with SDS-IMC (r=-0.19, p<0.001). When comparing the pre-pandemic (n=665) and Pandemic groups (n=336), a statistically significant increase in the average level of 25(OH)D (54nmol/L vs. 63nmol/L, p<0.001), in all seasons except for summer (68 vs. 66 nmol/L). We also found a statistically significant reduction in SDS-BMI between the two groups (1.04 vs. 0.62, p=0.017). The cases of deficiency reduced from 8% to 2% and insufficiency from 35% to 22%. In the pandemic period, there was a reduction in obesity (27% vs. 19%). VitD supplementation was prescribed in 32%, and was statistically correlated with 25(OH)D value (44 vs. 65nmol/L, p<0.001), season (lower in summer, p<0.001), age group (more frequent in adolescents, p=0.007). It was not related to gender, ethnicity or SDS-IMC.

Discussion: According to the literature reviewed by the authors, this is the first study to identify an improvement in Vitamin D status during the COVID-19 Pandemic. Contrary also to what has been described, we found a reduction in BMI in our sample. Although this is a retrospective study, we may presume that the improvement in Vit D levels may be related to the reduction in BMI and healthier lifestyles, with more outdoor activities.

P2-283

Evaluation of body composition in Brazilian children and adolescents with X-linked hypophosphatemic rickets

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Introduction: X-linked hypophosphatemic rickets (XLH) is characterized by a mineralization disorder in the growth plate and cortical and trabecular bones, resulting in bone deformities with anthropometric changes and potential alterations in body composition.

Objective: To evaluate the body composition of 12 children and adolescents with XLH compared to healthy controls by anthropometric and densitometry data.

Methods: The cross-sectional analysis used anthropometric and densitometric data from the confirmed XLH patients in regular conventional treatment and their respective sex, age, and pubertal stage-matched controls. In these groups, body composition parameters analyzed by dual-energy X-ray absorptiometry (DXA) included bone mineral content (BMC) and total body less head bone mineral density (subtotal BMD), lean mass (LM), fat mass (FM), and percentage of body fat (%). Also, the fat mass and lean mass indexes (FMI and LMI, respectively) were calculated as the FM (kg) and LTM (kg) divided by the height in meters squared and compared between groups. Also, the subtotal-BMD Z score adjusted for the height Z score (subtotal-BMD–HAZ) was calculated.

Results: 66.8% (8) of the sample were female, 66.8% (8) were pubertal, and the median age was 11 [6;18] years. Despite the shorter stature of XLH patients compared to controls ($p<0.01$), there was no significant difference between the groups in body mass index ($p=0.29$). XLH patients had lower BMC compared to controls ($p<0.05$), but subtotal-BMD–HAZ tended to be more significant in the XLH group ($p=0.10$). Meanwhile, fat mass and lean mass were significantly lower in XLH patients ($p<0.05$ and $p<0.01$, respectively), but the percentage of body fat was equivalent between the groups ($p=0.64$). Also, there was no significant difference between the groups regarding FMI and LMI ($p=0.96$ and $p=0.60$, respectively).

Conclusion: Although individuals with XLH had lower fat mass (FM) and lean mass (LM) compared to controls, it is crucial to consider the influence of their shorter stature on these measurements, and adjusting the body composition evaluation for height would yield more accurate data. While XLH is associated with impaired skeletal development, the potential redistribution of body composition in XLH should be examined in the context of hormonal factors and treatment effects on muscle and fat accrual.

P2-284

A new approach to estimate bone mineral density in pediatric subjects: Radiofrequency ecographic multi spettrometry (REMS). A comparison with DEXA

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Introduction: Limitations of the available imaging technique led the introduction of a new quantitative approach ultrasound-based for assessment of bone tissue in pediatric subjects. This new methodology use data from unfiltered radio frequency signals, collected during ultrasonographic acquisition of bone district of interest to estimate the bone mineral density. Advantages of this new technique include absence of radiation exposure, low cost of management and high portability.

Purpose: Radiofrequency Echographic Multi Spectrometry (REMS) is considered a valid methodology to assess osteoporosis and osteopenia in adults. The goal of the study was to research a possible correlation between the Bone Mineral Density (BMD) values obtained with Dual-Energy X-ray Absorptiometry (DEXA) and BMD derived values measured with REMS in a pediatric population.

Methods: A sample of 20 subjects in pediatric age (5-17 years old) underwent spinal and proximal femur DEXA. The same sample on the same visit received echographic scan of both spine al proximal femur. BMD derived from DEXA examination have been there after compared with BMD_{OS} indirectly calculated from Osteoporosis Score (OS) obtained by echographic examination of both body districts.

Results: The BMD values referred from the two methods were compared by Pearson correlation index calculation and a Bland-Altman plot building. The agreement was good for spinal BMD values ($r = 0.72$; $p < 0.003$), but only poor for femoral corresponding ones. The corresponding value of the coefficient of determination ($r^2 = 0.53$) confirms the effective force of the existing relationship between the values of BMD_{OS} and DEXA derived. Otherwise, at the femoral level the correlation between the BMD_{OS} and the densitometric values seems poor ($r = 0.57$) as well as supported by a much lower statistical significance ($p < 0.03$)

Discussion and Conclusions: The results obtained at lumbar spine level highlight the new method potential for future clinical application in pediatric contest, whereas the ones obtained at proximal femur level suggest a less strong correlation. To better understand the potential use of REMS in pediatric population new studies with bigger samples are needed.

P2-285

Combined treatment with leuprolide acetate and burosumab in X-linked hypophosphatemic rickets and precocious puberty: a therapeutic response

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Introduction: Generally, patients with X-linked hypophosphatemic rickets (XLH) experience normal puberty. However, they can be affected by metabolic and environmental factors that may predispose them to central precocious puberty (CPP) and impair their predicted final height, similar to the general population.

Case Report: A female patient was diagnosed with XLH at three and received regular treatment with calcitriol and sodium-potassium phosphate until age six. During this time, she experienced increased growth velocity and decreased height Z-score (from -2.65 SD to -1.8 SD). At the age of six and eight months, she was diagnosed with idiopathic CPP, presenting thelarche, a growth spurt, and an advancement of two years in bone age, which resulted in a reduction in the prediction of her final height Z-score (to -3.23 SD). Subsequently, she started pubertal blockade with leuprorelin acetate. Simultaneously, she switched from conventional XLH treatment to burosumab. The combined use of these medications led to stabilizing bone age, normalizing growth velocity, and improvement in the prediction of final height (Z -2.15 SD) without any side effects or detrimental impact on bone health during treatment.

Discussion: Gonadotropin-releasing hormone analogs (GnRHa) usually cause an immediate decrease in bone mineral density, which usually recovers after discontinuation. In the reported case, aGnRH did not influence her bone formation markers or harm her bone health.

Conclusion: In the described XLH patient with central precocious puberty, combining GnRHa and burosumab was a safe strategy for stabilizing pubertal advancement and bone age and minimizing anthropometric loss.

P2-286

Wilson disease diagnosed incidentally by targeted gene panel sequencing with severe obesity

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Wilson disease (WD) is a relatively common genetic hepatic disease in pediatric area and is characterized by excessive copper accumulation, predominantly in the liver and brain. It is an autosomal recessive disease caused by an *ATP7B* mutation that causes brain degeneration and is potentially fatal if diagnosed late or untreated. In the early phase of WD, its initial presentation may include mild hepatic involvement that may not be noticable. In obese patients, WD could be overlooked as a cause of liver disease due to severe obesity but should not be excluded from differential diagnosis. We report a case of WD with severe obesity and fatty liver diagnosed in the early phase by targeted gene panel sequencing and review the common endocrine problems associated with WD. Early detection of WD by an pediatric endocrinologist would be most important for good prognosis.

P2-287

Central diabetes insipidus in paediatric cerebral tumors: clinical and radiological features

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Introduction: Paediatric brain tumours in the sellar-suprasellar region (SSR) are often associated with central diabetes insipidus (CDI), either at diagnosis caused by the tumour itself or during follow-up as consequence of treatments.

Aims: To define the timing of CDI onset and radiological features on brain MRI in our cohort.

Methods: We retrospectively analysed paediatric patients with CDI and craniopharyngioma (CP) or germ cell tumours (GCT) diagnosed at King's College and Royal Marsden Hospitals between January 1996 and December 2022. We evaluated brain MRI at tumour diagnosis and at the onset of CDI, recording clinical, endocrinological and histopathological data,treatments, and prognosis. MRI features evaluated were tumour size (volume and diameters) and epicentre; posterior pituitary bright spot and pituitary stalk thickness.

Results: 72 patients with CDI were included: 46 CP (M: F=25:21) and 26 GCT (M: F=18:8). CPs were suprasellar (63%), sellar (4%) or both (33%). GCTs were suprasellar (65%), pineal (24%) or bifocal (11%). In CP the mean age at CDI diagnosis was 10.3 years. 7(15.2%) patients had CDI at tumour diagnosis, 37 (80.5%) developed CDI soon after neurosurgery and 2(4.3%) after 2 and 4 months respectively from surgery. In CGT the mean age at CDI diagnosis was 11.9 years; 5(19.3%) had CDI before tumor diagnosis with a latency of 24.4 months (range 4-48), 18(69%) at tumour diagnosis, while 3(11.5%) during follow-up (24 months, range 4-60), due to tumour recurrence. Bright spot absence was reported at diagnosis or at follow up (as surgery consequence) in all patients with CDI. Fourteen GCT patients showed pituitary stalk thickening at diagnosis: between 3-4.5 mm (19.2%), between 4.5-6 mm (19.2%) and >6 mm (23.1%). In the remaining patients with GCT (38.5%) the pituitary stalk was normal (< 3mm). Headache and visual abnormalities were the most frequent clinical symptoms at diagnosis of CP (39/46, 84.8%), with hydrocephalus (16/46, 35%) and displacement of optic chiasm (29/46, 63%) at the initial MRI. GCT patients presented with endocrinological manifestations (10/26), headache and vomiting (10/26), visual

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impairment (5/26) and behavioral changes with fatigue (1/26). The main endocrinological disorders were CDI (18/26, 69%), central adrenal insufficiency (16/26, 61.5%), and central hypothyroidism (17/26, 65%).

Conclusion: A good understanding of clinical characteristics and imaging features in CDI in children with brain tumors helps achieving an early differential diagnosis and accurate therapeutic strategies. Specialist follow-up is required.

P2-288

Validation of utility of a single LH measurement 40 minutes after depot Leuprolide acetate 3.75 mg and 11.25 mg in assessing gonadotropic activity in girls with CPP: Comparison with a standard GnRH stimulation test at diagnosis and during treatment

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Context: Intravenous Gonadotropin-Releasing-Hormone (GnRH) stimulation test has a central role in evaluating gonadotropic activation in the diagnosis and monitorization of the treatment in patients with central precocious puberty (CPP). However, this test is invasive, laborious, costly and availability of GnRH preparation is limited in some countries.

Objective: To evaluate the utility of the LH level measured 40-minutes after intramuscular depot-Leuprolide acetate(dLA) injection, in assessing gonadotropic activation.

Methods: In a prospective study, 92 girls with CPP were randomized to receive ıntramuscular dLA 3.75 mg/4 weeks (Group-1, n=47) or 11.25 mg/12 weeks (Group-2, n=45). A standard GnRH stimulation test was performed before- and at 6 months of treatment to assess gonadotropin suppression. Basal and 40-minute post-dLA gonadotropins and estradiol were measured at the beginning and at the 6th month of treatment

Results: There was no difference in clinical, and hormonal characteristics of Group-1 and Group-2 at the onset of treatment. At the beginning of treatment, mean peak LH in the GnRH test (16,2±16,3 vs 13,5±9,8 mIU/mL) and 40-minute post-dLA injection LH (16,8±18,2 vs 13,2±13,4 mIU/mL) were similar for Group-1 and Group-2, respectively. At 6 months, peak LH levels were similarly suppressed to 2,1±1,6 vs 2,2±0,9 mIU/mL in the GnRH test, and 2,9±1,9 vs 2,9±1,2 mIU/mL in 40-minute post-dLA injection for Group-1 and Group-2, respectively. Mean GnRH-stimulated LH levels and 40-minute post-dLA LH levels did not differ between the groups during treatment. Peak LH at GnRH test and 40-minute post-dLA injection LH were strongly correlated at the beginning (r:0.68, p<0.001) and at the 6 months (r:0.74, p<0.001) of treatment. 89% of the patients whose peak LH >5 mIU/mL on GnRH test at diagnosis, also had a 40-minute post-dLA LH >5 mIU/mL. At the 6 months of treatment, 7 patients in Group-1 and 10 patients in Group-2 had peak LH >3 mIU/mL in GnRH test (suboptimal suppression). In 88% of these patients, 40-minute post-dLA LH was also >3 mIU/mL confirming suboptimal suppression.

Conclusion: Long-acting GnRH analogues used in the treatment of CPP stimulate LH for a short time as strongly as intravenous GnRH. A single LH measurement 40 minutes after the first dose of depot dLA and at 6 months of treatment provides ample information about the gonadotropic activity comparable to a standard intravenous GnRH test before and during treatment.

P2-289

The grey area in treatment of progressive short stature in patient with heterozygous NPR2 mutation

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Introduction: Skeletal dysplasias associated with short stature are caused by inherited cartilage/bone development defects and are often associated with disproportionate short stature. We will present a case of heterozygous NPR2 variants in a patient with ISS.

Case Report: A 8 years 3 months aged girl with normal perinatal and neonatal periods came for short stature evaluation. The clinical exam showed: 115.5 cm (-2.45 SD), normal weight, phenotype with discrete facial dysmorphism, flat nasal bridge, slightly prominent forehead, hypertelorism, brachydactyly, short limbs; Tanner B1G1P2; delayed bone age of 1.5 year. Family history: father 169 cm, mother 142 cm with similar phenotype (MPH=149 cm, SD -2.20), sister with normal height.

Laboratory investigations: Dyslipidemia, euthyroidism, inhibited prepubertal pituitary-gonadal axis, normal prolactin, cortisol and growth hormone and IGF1 score -0.64 SD. The genetician recommended gene panel for bone dysplasia; Results reveal heterozygous nonsense c.2221C>T mutations in exon 15 of NPR2 gene with pathogenic clinical significance (class 5).

Management and treatment: GH stimulation tests were performed with a normal response.

Stimulation tests	**1**	**2**	**3**	**4**
Clonidine	0.363 ng/ml	11.5 ng/ml	16.3 ng/ml	14.6 ng/ml
Insulin	2.72 ng/ml	2.92 ng/ml	5.37 ng/ml	3.2 ng/ml

Even if GH therapy is off-label, few patients have a response to it; larger studies are necessary to establish the efficacy of the treatment on final height in patients with NPR2 heterozygosity. We considered the introduction of Vosorotide treatment which is in clinical trials and is awaiting approval but patients refused This is the first medication that directly targets the pathway in chondrocytes affected by these specific mutations.

	T0	**T1**
Height SDS	-2.45	-2.19
Growth velocity	-	4.6 cm/year
Bone age/Chronological age	6.10/8.3	8.10/9.4

Discussion: There are few scientific studies which mention treatment with rhGH

Conclusion: Identification of rare monogenic causes is critical for a variety of reasons. First, identification of a molecular etiology can end the diagnostic work up and provide the family an answer to why their child isn't growing normally. Second, the genetic diagnosis may alert the clinician to other medical comorbidities. Thirdly, determination of a molecular etiology is invaluable for genetic counseling. Finally, genetic etiology may have implications for therapy.

P2-290

Ovarian steroid cell tumor in a very young girl: clinical and genetic aspects

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Introduction: Precocious pubarche (PP) is characterized by the early development of pubic hair and clitoral enlargement in girls. While commonly attributed to adrenal-related causes, such as congenital adrenal hyperplasia or adrenal tumors, ovarian sources are infrequent etiologies. In this report, we present a clinical case of a young girl with PP due to a rare source.

Case Report: A 1.7-year-old girl presented with the rapid onset of pubic hair and clitoral enlargement, accompanied by acne, increased stature (3 cm), and weight gain (1.5 kg) during one month. Medical history, including gestational and birth records, was unremarkable. Physical examination revealed mild clitoral enlargement (B1P2), and laboratory investigations showed elevated levels of 17 OH Progesterone: 421 ng/dL, (< 100), Androstenedione: 75 ng/dL, (< 50), DHEA-S: 25 µg/dL, (< 19), and Testosterone:7 43 ng/dL, (< 40). Additionally, elevated levels of IGF-1: 415 ng/mL, (44-356) and IGFBP-3: 5330 ng/mL, (700-3500) were observed. Abdominal and pelvic ultrasonography yielded normal results, while other hormonal exams, including LH, FSH, Estradiol, ACTH, and Cortisol, were within normal ranges. An ACTH test at 1.9 years old did not reveal adrenal hormone elevation but confirmed persistently elevated testosterone levels (781 ng/dL). At 2 years old, the patient exhibited further physical changes, including hoarse voice, increased acne, and muscle hypertrophy in the upper and lower limbs, reflecting the clinical progression of hyperandrogenism. Despite normal DHEA-S levels, abdominal and pelvic MRI identified a 2.8 cm mass in the left ovarian region. The patient underwent a laparoscopic procedure, during which the tumor was successfully removed. Histopathologic evaluation confirmed the diagnosis of ovarian steroid cell tumor, not otherwise specified (OSCT-NOS). One-month post-surgery revealed a significant decline in testosterone levels (9 ng/dL) and resolution of hyperandrogenic features. Genetic testing revealed two heterozygous variants: TP53 (pathogenic, associated with Li-Fraumeni Syndrome) and BRCA-1 (probably pathogenic, associated with breast and ovarian cancer). The TP53 variant likely contributes to the clinical presentation, while the likely pathogenic BRCA1 variant may have influenced the early onset of this specific tumor type. Notably, the patient's father carries the heterozygous BRCA-1 variant, while the mother does not.

Conclusion: This case report highlights an exceptionally early presentation of a rare ovarian steroid cell tumor in a very young girl with precocious pubarche. The report emphasizes the diagnostic challenges encountered and elucidates the association

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P2-291

Early Endocrinopathy in Childhood Cancer Survivors in a Specialized Center in Riyadh

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Introduction: Childhood cancer survivors (CCSs) has increased risk of endocrine complications, of which, abnormal growth and hypothyroidism are the commonest. The risk of developing endocrinopathy will vary according to different host factors including type of tumour and factors related to treatment modalities including chemotherapy, radiotherapy, surgery and bone marrow transplantation. we aim to assess the prevalence and associated risk factors of early development of endocrinopathies, namely; abnormal growth and hypothyroidism among CCSs throughout a 5-year follow-up period after exposure to therapy.

Methods: A chart review retrospective cohort study (2015 – 2021) to assess the prevalence and risk of development of abnormal growth and hypothyroidism in CCS during the first 5-year follow-up period after exposure to therapy. We used the health medical informatics system records of all CCSs to scrutinize our data that was analyzed using SPSS V23.

Results: The study recruited 220 children (1-5 (41%), 5-12 (27%) and above 12 years (33%), Males=113, 51%) The main variables were height velocity and BMI (growth) and tumor type (hematological (52.3%) and solid tumors) and hypothyroidism. Hypothyroidism developed in (n=30/220, 14%), height velocity less than 4 cm (n=98/220, 45.8%) and overweight/obesity developed in 32% (n=69/220) of CCSs. The study showed that children above 12 years had increased risk of developing hypothyroidism (P-value=0.004). No gender significant difference although more boys were affected. The height velocity < than 4 cm /year was significantly affected in the first 3 years (P- value=0.013, <0.001, 0.009 in each year, respectively). The modality of intervention associated with highest prevalence of hypothyroidism was the bone marrow transplantation (BMTx) (33%, P-value <0.001). The risk associated with the development of height velocity < 4 cm/year was also the highest in children older than 12 years. They were more affected in the first year in both the hematological and solid tumors, and also post corticosteroids and radiotherapy (P-values =0.017, 0.024, 0.039, 0.006, respectively). Height velocity was affected late in post BMTx, in the second- and third-years post treatment (P values= 0.006 and 0.034, respectively). The risk factors associated with development of overweight (n=16, 7.2%) and obesity (n=30/220, 13.6%) was significant post chemotherapy in third- and fourth-years post intervention (P-value=0.41).

Conclusion: The risk of developing early endocrinopathy was more apparent in the first 3 years post therapy and older age group was the more vulnerable in our cohort. Bone marrow transplantation was the most intervention associated with endocrine complications.

P2-292

Accuracy of opportunistic height measurements in a tertiary pediatric hospital in Riyadh

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Background: Short stature is the commonest problem encountered in endocrine clinics. Accuracy in opportunistic measurements is helpful in guiding subsequent management regarding medication doses including growth hormone treatment. Our study aimed to assess the prevalence and factors affecting inaccurate height measurements in different non-Endo clinic visits in our tertiary institute.

Methods: A retrospective cohort study at King Abdullah Specialist Children Hospital, Riyadh, Saudi Arabia (2017-2018). Data included children's height measurements by healthcare practitioners in different outpatient clinics (endocrine, general pediatric, GI peds, peds surgery) and during ER visits and inpatient admissions. Data was analyzed using SPSS V23.

Results: Data scrutinized from the electronic health records of 305 patients. The median height of the patients at the time of endocrine clinic visit (Endo visit) was 128 (110-145) cm compared non-endocrine (No Endo) clinic visits that was 130 (111-147) cm. The height measurement was recorded in (n=154, 51%) children before the endocrine clinic visit (Pre-Endo visit) with equal gender distribution. Overall, the inaccuracies in height measurements were common in all of the non-Endo clinics (Prevalence = 82%). They were more existing in the Post Endo visits (n=148 /303, 49%) compared to Pre Endo clinics (n=154 /303,51%) with the largest number of inaccurate measurements were in more than 30 days gap between the Endo and non-Endo visits (P=0.001). In addition, the timing of clinic visit before or after the Endo visit also had an effect (p= 0.001). The height measurements were not statistically different between Endo and Non-Endo visits in relation to the "type" of the clinic (specialty clinic) (p=0.03). However, Surgery clinics were reporting the lowest accuracy of height measurement (n= 32, 43.2%) of the children's height that was measured more than the actual height among other patients' treatment areas including: Medicine and General pediatric clinics as well as the ER visits.

Conclusion: Inaccuracy in height measurements is common in non-Endo services in our tertiary center. This could be affected by recent or upcoming Endo visits resulting in higher or less than actual measurements. More efforts need to be taken to address this issue and increase the awareness of the problem among the HCP.

P2-293

Unveiling the Complexities of Growth Failure: A Captivating Case of Short Stature with Coexisting Chronic Conditions

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Background: Short stature is a common presentation in pediatric endocrinology and its etiologies encompass non-endocrine factors, endocrine disorders, and normal variations. Growth failure can serve as an alarmingly subtle indicator of underlying severe diseases, sometimes obfuscating multiple causative factors. Understanding the complexities involved in evaluating growth failure in the presence of chronic conditions is crucial for efficient management. This case highlights the diagnostic challenges encountered in a patient presenting with short stature alongside coexisting chronic illnesses.

Case Presentation: A 16-year-old Romanian male previously diagnosed with spherocytosis at eight months of age, presented to our clinic with a primary complaint of short stature. However, additional findings such as hepatosplenomegaly, jaundice, alopecia, severely dehydrated skin, hoarse voice, bradylalia, and bradycardia were also observed. Anthropometric measurements revealed a stature of 154 cm (-3.04 standard deviations) and a weight of 56.6 kg (-0.57 standard deviations). The ultrasound examination unveiled a small thyroid volume, with heterogeneous echostructure and echogenic septations. Cardiac echography indicated a left ventricular ejection fraction of 40-45% and minimal pericardial fluid. The testicular echography unveiled a substantial presence of bilateral fluid accumulations, suggestive of hydrocele, within a testicular volume of 15 cm3 characterized by a homogeneous echostructure. Additionally, penoscrotal concealment was observed, attributed to the influence of scrotal fluid. Laboratory tests confirmed severe hypothyroidism (TSH>60 uUI/ml, FT4=0.16 ng/dl) and severe hemolytic anemia (Hb=6.9 g/L) requiring multiple transfusions. The wrist X-ray revealed a bone age delay of 4 years and 9 months. Notably, the symptoms of hypothyroidism were concealed by the patient's chronic illness, highlighting the complexity of evaluating growth failure in patients with coexisting chronic conditions. The patient was treated with levothyroxine, beginning at 100 mcg (1.76 mcg/kg) and gradually increasing to 140 mcg (2.74 mcg/kg) over a six-month period. Following treatment, the patient's height increased by 3.5 cm, reaching 157.5 cm (-2.7 SD), with a growth velocity of 8 cm per year. Subsequent evaluations revealed improvements in mental status, bradylalia, bradycardia, skin, and hair.

Conclusion: The intricacies of evaluating growth failure in the presence of chronic conditions necessitate comprehensive investigations for timely diagnoses. This captivating case emphasizes the vital role of early detection and prompt intervention, as it can substantially influence the prognosis of patients with short stature and coexisting chronic illnesses. An improved understanding of these complexities will aid in optimizing patient outcomes and shaping future management strategies.

P2-294

Case report: Untreated Congenital Hypothyroidism associated with hypertrophic pyloric stenosis

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Congenital hypothyroidism (CH) occurs in approximately 1:2,000 to 1:4,000 newborns, in Algeria newborn screening programs do not exist, untreated CH remains a significant health and societal challenge. We report the case of a girl of 12 years old reffered for a failure to thrive, speech deficit and persistant vomiting, On clinical examination her height was –3 SDs with a very delayed bone age and a BMI of 35kg/m2 associated with severe musculoskeletal deformities and cognitive deficits. TSH > 100 mIU/L and free T4 very low with athyreosis on thyroid Ultrasound, Upper Abdominal ultrasonography confirmed hypertrophic pyloric stenosis (elevated pyloric muscle thickness). treatment with levothyroxine was started with improvement in BMI (weight loss). Vomiting and ultrasonography signs of hypertrophic pyloric stenosis disapeared after 3 months of treatment. Cognitive and speech deficits is persistant after 18 months of treatment. In conclusion untreated CH presents with a spectrum of clinical signs, persistant vomiting may indicate an association with hypertrophic pyloric stenosis with good improvment after levothyroxine treatment. We equally have to consider the severity of growth stunting and severe mental retardation in CH when diagnosis is missed or treatment delayed.

P2-295

Metabolic and growth outcome of two-years growth hormone treatment in children born small for gestational age: a retrospective study

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Children born small for gestational age (SGA) not showing catch-up growth in the first two years of life may show decreased growth rate and adult height, as well as worse metabolic profile, compared to general population. In these patients, growth hormone (GH) treatment is recommended, showing positive effects on both growth rate and metabolic profile, with good tolerability.

The aim of the current study was to evaluate the auxological and metabolic effects and the safety of GH treatment in SGA children. The study included 34 SGA children (15 F, 19 M; SGA for length and weight: 6 F, 9 M; SGA for length: 2 F, 1 M; SGA for weight: 6 F, 9 M; mean age: 8.72 ± 2.48 yrs; prepubertal: 19 M, 10 F; pubertal: 5 F) treated with GH (starting dosage: 32.24 ± 2.88 mcg/kg/die) for at least 24 months. Growth and metabolic parameters, including glycemic and lipid profile, transaminases, and urycemia, were collected every six months.

Compared to baseline, SGA children showed a significant improvement in height, weight, and growth rate after two years of treatment with GH ($p < 0.001$), already evident after six months of treatment ($p <0.001$). Noteworthy, patients showed a constant, significant improvement in height throughout the treatment, as a significantly increase was observed both after one year of treatment compared to baseline ($p < 0.001$) and after two years of treatment compared to first year of treatment ($p = 0.03$). Conversely, although significantly higher than baseline at each visit ($p < 0.001$), after the six-months peak growth rate significantly decreased over time until 18 months of treatments ($p < 0.001$ T6 vs T12; $p = 0.015$ T12 vs T18), remaining thereby stable. Considering metabolic parameters, compared to baseline, a recurring increase in glycemia ($p \leq 0.042$ vs T12 and T18) and urycemia ($p \leq 0.01$ vs T12, T18, and T24) and decrease in AST ($p \leq 0.021$ vs T12, T18, and T24) and an occasional decrease in LDL cholesterol ($p = 0.03$ vs T24) were observed. Considering safety profile, treatment was well tolerated, as the most frequently reported adverse event was poor compliance (11.8%); no hyperglycemia or hyperstransaminasemia occurred throughout the treatment, whereas one patient (2.9%) experience hypercholesterolemia.

In conclusion, GH treatment in SGA children is an effective, safe treatment for short stature, improving both height and growth rate, especially during the first year of treatment, although the metabolic profile of treated patients should be carefully monitored during time.

P2-296

Cryptorchidism, and hormones in patients with androgen insensitivity syndrome and 5alpha-reductase type 2 deficiency

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Background: Data on the effect of cryptorchidism on hormones of androgen insensitivity syndrome (AIS) and 5alpha-reductase type 2 deficiency (5α-RD2) are still limited.

Methods: We retrospectively evaluated 47 patients with AIS and 79 with 5α-RD2 to investigate the effect of cryptorchidism on hormone levels.

Results: Anti-Müllerian hormone (AMH) levels in the AIS group were lower than those in the 5α-RD2 group ($P = 0.002$) and controls (P = 0.048), whereas inhibin B (INHB) levels in the AIS group were higher than those in the 5α-RD2 group (P = 0.0005) and controls (P < 0.0001). In patients with AIS, basal follicle-stimulating hormone (FSH) (P = 0.002) and peak FSH (P = 0.01) levels were higher in the cryptorchidism group than in the non-cryptorchidism group; AMH levels in the cryptorchidism group were lower than that in the non-cryptorchidism group (P = 0.002) and controls (P < 0.0001), and INHB levels in the cryptorchidism (P = 0.005) and non-cryptorchidism groups (P = 0.0002) were higher than those in the controls. In patients with 5α-RD2, peak FSH levels (P = 0.017) were higher in the cryptorchidism group than in the non-cryptorchidism group; the basal dihydrotestosterone (DHT) in bilateral cryptorchidism was lower than that in unilateral cryptorchidism (P = 0.0418); AMH levels in the cryptorchidism group were lower than that in the non-cryptorchidism group (P = 0.0008) and controls (P = 0.0005); AMH levels in the bilateral cryptorchidism group were lower than those in the non-cryptorchidism group (P = 0.006) and controls (P = 0.011); and AMH in the unilateral cryptorchidism group was lower than that in the non-cryptorchidism group (P = 0.009) and controls (P = 0.003).

Conclusions: Cryptorchidism showed a high incidence in patients with AIS or 5α-RD2 and influenced AIS and 5α-RD2 hormone levels. AMH levels in the AIS group were lower than those in the 5α-RD2 group and controls, whereas INHB levels in the AIS group were higher than those in the 5α-RD2 group and controls. AMH levels in the cryptorchidism group were lower than those in the non-cryptorchidism and control groups both in patients with 5α-RD2 and AIS. These findings provide deeper insight into cryptorchidism and hormonal assessment.

P2-297

Triglyceride glucose index, Triglyceride to high-density lipoprotein cholesterol ratio and pediatric NAFLD fibrosis index is the most valuable combination of criteria to detect fatty liver disease in overweight/obese boys

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Introduction: The prevalence of obesity constantly increases worldwide and definitely increases the risk of premature death in early adulthood. Metabolic dysfunction-associated fatty liver disease (MAFLD) – a new term for fatty liver disease accompanied by other components of metabolic syndrome (MetS) connected with increase cardiovascular risk either in adult or children. Whereas there is no yet treatment with proven efficacy for the metabolic clamp such as arterial hypertension (AH), insulin resistance, dyslipidemia, diabetes type 2, and MAFLD, it is imperative to find a way to decrease cardiometabolic complications. Early prevention strategies beginning in childhood are the most logical step to reduce premature cardiovascular morbidity and mortality in youth. Therefore, the current study is aimed to determine the most sensitive and specific predictive markers of the MAFLD with high cardiometabolic risk in overweight/obese adolescent boys.

Methods: This study involved 180 adolescent overweight or obese boys [median age was 16.0 (15.0-16.1) years] randomly chosen in rural and urban patients in Ternopil (Western Ukraine). A control group of 30 healthy children with proportional body weight comparable in gender and age to the main group was presented. A list of anthropometrical markers with biochemical values of carbohydrate and lipid metabolism with hepatic enzymes was determined. In the general cohort, 81.5 % were obese, 83.8 % have abdominal obesity, 63.0% - AH, 4.6 % - prediabetes, 26.4 % have hypertriglyceridemia, and 34.7 % have a pathologically low level of HDL-c. In addition, in 38.6% of overweight and obese subjects, ALAT was increased above >25 U/L. All overweight/obese boys were divided into two groups: 72.2 % of boys with MetS by IDF criteria, 27.8 % metabolically healthy obese (MHO) boys without AH, hyperglycemia and dyslipidemia. Boys who have only one criterion (AH, dyslipidemia or hyperglycemia) were exclude from the study.

Results: Based on multiple logistic regression analysis which included all anthropometric, biochemical values and calculated indexes in boys, it was detected that the maximum likelihood in the prediction of MetS makes Triglyceride glucose index, Triglyceride to high-density lipoprotein cholesterol ratio and pediatric NAFLD fibrosis index (PNFI) (R2 =0.721, p<0.000). Tracing the Receiver operating characteristics curve, the model is confirmed as a good predictor of MAFLD (AUC=0.887, Odds ratio=26,124 perc. correct=86.07%) in overweight and obese boys.

Conclusions: Triglyceride glucose index, Triglyceride to high-density lipoprotein cholesterol ratio and pediatric NAFLD fibrosis index is a valuable combination of criteria to detect MAFLD in overweight/obese boys.

P2-298

Insulin-like Growth Factor-1 as a Screening Tool for Central Precocious Puberty

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Gonadotropin-releasing hormone (GnRH) stimulation test is the gold standard test for diagnosing central precocious puberty (CPP), which needs time and effort to perform. Recently, many studies confirmed that Insulin-like growth factor-1 (IGF-1) is involved in the initiation and progression of puberty. With this inspection, we assumed that the IGF-1 level might be correlated with the pubertal stage in central precocious puberty. This study aimed to investigate the value of IGF-1 levels in screening central precocious puberty.

The medical records of 359 patients with a chief complaint of premature breast development who visited the pediatric endocrinology clinic in Myongji Hospital from January 2017 to October 2022 were reviewed. Two hundred thirty-three girls with central precocious puberty (CPP) and 126 girls with premature thelarche (PT) diagnosed were enrolled. Each subject had IGF-1 and GnRH stimulation test results.

The anthropometric data between CPP and PT showed no statistical differences except for weight and the existence of lipomastia. The hormonal indicators including peak luteinizing hormone

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(peak LH), peak follicular stimulating hormone (peak FSH), and estradiol were statistically different between the two groups (P < 0.001). IGF-1 levels were significantly higher in the CPP group than in the PT group. The IGF-1 levels were positively correlated with peak LH, the diagnostic indicator of CPP. The area under the curve (AUC) of IGF-1 was 0.709. The sensitivity of IGF-1 in the diagnosis of CPP is 57.3% and the specificity is 77.6%. There was a strong positive correlation between the diagnosis of CPP and the IGF-1 levels (r = 0.709, p < 0.001; True positive [TP] =133, True negative [TN] = 99; False positive [FP] = 28, False negative [FN] = 99). Tanner staging is more developed in central precocious puberty than in early puberty (p < 0.001). Bone age alone is not suggestive of central precocious puberty compared with early puberty (p = 0.657).

IGF-1 levels were correlated with the diagnostic indicator osis of central precocious puberty CPP. IGF-1 would be a useful tool for screening CPP.

P2-299

Comparative of serum estradiol levels in girls with different types of precocious puberty by liquid chromatography tandem-mass spectrometry and chemiluminescence immunoassay method

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Objectives: To compare the levels of estradiol (E2) in girls measured by liquid chromatography tandem-mass spectrometry (LC-MS/MS) and chemiluminescence immunoassay (CLIA), and to evaluate the correlations between E2 levels measured by the two methods and bone age, uterine length, and uterine volume. To explore the difference, consistency, and accuracy of LC-MS/MS and CLIA in determining E2 in girls with idiopathic central precocious puberty (ICPP), premature thelarche (PT), and normal puberty, and to guide clinical diagnosis and treatment.

Methods: From July 2022 to December 2022, 133 newly diagnosed girls aged 7-9 were selected from the Department of Endocrine Genetics and Metabolism, Children's Hospital Affiliated to Soochow University. There were 80 girls in the ICPP group (44 in the Tanner II stage in the ICPP group, 36 in the Tanner III location in the ICPP group), and 53 in the PT group. A total of 40 healthy girls aged 9-10 years in the Tanner III group of ordinary puberty,The age, gonadotropin-releasing hormone (GnRH) stimulate test, bone age, and uterus and ovary ultrasound results were collected, and CLIA and LC-MS/MS methods detected essential serum E2. The serum basal E2 levels of girls in the PT group, ICPP group Tanner II, ICPP group Tanner III and standard pubertal Tanner III group were compared by the CLIA method and LC-MS/MS method. SPSS 26.0 software was used for statistical analysis of E2 data.

Results and Conclusions:

1. The E2 level detected by LC-MS/MS method differs from that seen by the CLIA method. LC-MS/MS method has higher sensitivity and lower E2 class.,The sample size required for detection is smaller, and LC-MS/MS method can quantitatively detect E2 in a lower concentration range.
2. The stability of the LC-MS/MS method for detecting E2 is higher than that of the CLIA method and has higher specificity.
3. The consistency between E2 detected by LC-MS/MS and the CLIA method could not be better. The detection method and its reference range should be fully understood when evaluating the E2 level in the clinic.
4. The LC-MS/MS method's accuracy for detecting E2 is better than that of the CLIA method, especially in PT girls with low E2 levels. The accuracy of the two methods for detecting E2 was similar in the ICPP group of Tanner III girls with high E2 levels.

P2-300

Short stature and IGF-1 resistance - unexpected association of Wolf-Hirschhorn Syndrome

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Introduction: Wolf-Hirschhorn syndrome (WHS) is a rare congenital disorder characterised by a "Greek-warrior-helmet" nasal appearance, growth delay, intellectual disability, and seizures. Limited studies exist on the growth evolution of WHS children, particularly regarding growth hormone (GH) therapy. We report a case of a 3-year-old boy with WHS and severe short stature.

Case Report: A 3-year-old male child, second born from non-consanguineous parents (mid-parental height 56.36 percentile, Z-score=0.16 SDS), presented to our clinic for short stature. Medical history revealed WHS and 15q13.2-13.3duplication. He was under Topiramate and Nitrazepam treatment for seizures. Physical examination revealed a short stature of 79 cm (-3,7 SDS) and 7,9 kg (-5.67 SDS) on the CDC 2- to 20-year growth charts and 0 SDS on WHS charts. Hormonal investigations revealed the following: GH 2.57 ng/ml (RR 0-6.3 ng/ml), IGF-1 175 ng/ml (RR 13.9-104), IGF-BP3=4.91 (0.8-3.9). Other hormone profiles (TSH, FT4, and basal cortisol) were within normal ranges. Regarding the GH/IGF-1 axis results, IGF-1 insensitivity syndrome was suspected. He would be eligible for GH treatment as he was born small for gestational age. However, he does not meet all our national therapy protocol criteria because of the increased IGF-1 values association. At the most recent follow-up visit conducted after a five-month interval from the initial evaluation, he was stable on CDC and WHS growth charts (-3.67 SDS vs 0 SDS). Hormonal labs were consistent with the suspected diagnosis: IGF-1 levels at 168.8 ng/mL (RR 18.9-116 ng/ml), IGF-BP3 levels at 4.03 mcg/ml (RR 0.8-3.9) and basal GH levels at 0.237 ng/mL (RR 0.094-6.29). Furthermore, an X-ray of the hand indicated a delayed bone age of approximately 2-2.3 years.

Conclusion: GH therapy in patients with WHS leads to significant height increases during the prepubertal period but shows limited improvement in final height. Considering the limited success of GH treatment in improving the final height, treatment decision in WHS patients is challenging. In this patient, the challenge is further complicated because of the IGF-1 insensitivity association. Future research should explore the risk-benefit ratio of GH treatment in WHS patients, especially those with IGF-1 insensitivity, aiming to optimise treatment outcomes and reassess eligibility criteria. Additionally, investigating the association between WHS, 15q13.2-13.3 duplication, and IGF-1 insensitivity syndrome is essential for improving management strategies.

P2-301

Progression in height and bone age during the first year of long-term growth hormone therapy in pre adolescent GHD children

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Keywords: growth hormone defificiency growth hormone, height bone age

Objective: To evaluate the height and bone age (BA) of prepubertal growth hormone deficiency (GHD) children in the first year after long-term growth hormone treatment.

Methods: According to the degree of bone age lag before treatment 36 prepubertal GHD children were divided into two groups Group 1: bone age lagged behind chronological age ≥1; Group 2: bone age lagged behind chronological age <1. The data of their height, weight, secondary sexual characteristics, serum IGF-1 and bone age during the treatment with long-acting growth hormone were analyzed retrospectively.

Results: Two groups of children with GHD were treated with growth hormone for one year, Δ HtSDS was 0.93±0.27 and 0.95±0.37, respectively, with no significant difference; and ΔBA was 1.58±0.67 and 1.02±0.39, respectively, with statistical significance.

Conclusion: In the first year of long-term growth hormone treatment, there was significant height improvement and acceleration of bone age progression in prepubertal GHD children. The degree of bone age backwardness before treatment does not affect the improvement of height of pre pubertal GHD children, but may affect the progress of bone age.

P2-302

ESPE School Sharing Knowledge for Saving Patients' Lives: Empowering Pediatric Endocrinologists in Armenia

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Background: Practicing as a Pediatric Endocrinologist in Armenia means living in a middle- to low-income country with semi-closed borders associated with war and conflicts. There are therefore fewer opportunities to attend educational events or training at highly rated hospitals worldwide to improve knowledge and skills on pediatric endocrinology.

In April 2023 the Endocrine Society of Pediatric Endocrinologists (ESPE) held the ESPE Caucasus & Central Asia School (C&CAS) in Armenia in order to support and increase the expertise and knowledge in the field of pediatric endocrinology. The School brought together international experts and local physicians to exchange best practices and clinical insights in pediatric endocrinology. The educational program covered a wide range of topics including thyroid disorders, diabetes management, growth disorders, and other hormonal disturbances.

Objective: The current abstract highlights the impact of the ESPE C&CA School on pediatric endocrinologists' professional improvement in Armenia.

Results: To evaluate the significance of the ESPE C&CA School we sent a questionnaire to all participants from Armenia (12 participants out of 22). Of the participants, 75% found the school very useful, and 25% found it useful. Three of the participants have experience with one of the previous ESPE schools. Participants were asked "If the ESPE C&CAS had not been held in Armenia would you have participated?" The majority 66.7% (N=8) answered "no", 25% (N=3) answered "yes", and 8.3% (N=1) answered "difficult to answer". This shows the importance of organizing the ESPE School not only in the heart of Europe, but also in countries with less opportunity for doctors to attend and to share the knowledge and expertise.

Conclusion: The improvement and harmonization of knowledge and professional skills in pediatric endocrinology is important for all developing countries, but is crucial in countries such as Armenia, taking into account their income, healthcare organization and geographics. Armed with the latest evidence-based guidelines and therapeutic approaches, Armenian participants returned to their respective practices with newfound confidence and expertise. In addition, the ESPE School promoted networking and collaboration, which helped the Armenian pediatric endocrinology community build a strong support system and what the most important - saving life for the patients. This network continues to serve as a valuable resource for ongoing learning, knowledge sharing, and professional development.

P2-303

The link between birthweight, obesity and insulin resistance

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Background: Childhood obesity has emerged as a global pandemic, posing significant health challenges and necessitating urgent action to address its widespread prevalence and associated metabolic consequences. Understanding the link between childhood obesity, being born large for gestational age (LGA), and insulin resistance (IR) in children is crucial for developing targeted interventions and sustainable preventive measures against long-term health risks associated with cardiovascular disease, and metabolic syndrome (MetS).

Objective: A retrospective observational study was conducted at “Louis Ţurcanu” Children’s Clinical and Emergency Hospital in Timişoara - Departments of Endocrinology, Diabetes, and Metabolic Diseases. The study involved a cohort of 278 patients aged 2 to 18 years, who were diagnosed with obesity, admitted over a 1-year period (March 25. 2022, to April 25. 2023). The aim was to determine the prevalence of LGA among obese children and to compare the metabolic profile of LGA obese children to their appropriate for gestational age (AGA) counterparts.

Methods and Results: Obesity was diagnosed as body mass index (BMI) values exceeding the 95th percentile, using age-specific BMI reference guidelines outlined in the 2000 Centers for Disease Control and Prevention Child Growth Charts. Fasting glucose and insulin levels were determined and used to quantify the homeostasis model assessment for IR index (HOMA – IR). According to age, patients were divided into 3 groups: pre-pubertal group: < 8 years (6.83%), pubertal group: 8 -14 years (58.63%), and adolescent group: > 14 years (34.53%). The 3 main groups were further divided into six subgroups, based on their birth weight (AGA or LGA).

Overall, the prevalence of LGA among obese children was 21.22%. IR had a prevalence of 79.49% in the studied population, with the highest percentage observed in the pubertal group at 51.43%, followed by the adolescent group at 28.05% and the pre-pubertal group at 20.52%. In relation to birth weight, the highest percentage of IR in LGA children was noted in the adolescent group (17.94%) followed by the pubertal group (16.78%).

Conclusions: The relatively high prevalence of LGA among obese children as well as that of IR, that increases around puberty and adolescence, emphasises the need of continuous monitoring of LGA-born obese children, for an early detection and management of metabolic and cardiovascular disease.

P2-304

Metabolic syndrome in overweight and obese children

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Introduction: Metabolic syndrome (MetS) is a group of conditions that occur simultaneously, involving excess body fat, arterial hypertension, impaired glucose metabolism and dyslipidemia. Establishing effective preventive measures and therapies requires an understanding of the relationship between childhood obesity and the early development of MetS components.

Objective: The aim of this study was to identify and explore the early components of MetS present in overweight and obese children.

Results: A retrospective observational study was conducted on 86 patients aged 0-18 years old diagnosed with MetS, who were admitted to the Endocrinology Department of “Louis Turcanu” Children’s Clinical and Emergency Hospital in Timisoara, Romania. The study utilized clinical and biological data collected over 5 years and 3 months, from January 2018 to April 2023. We highlighted the connections between age group, overweight, obesity, high blood pressure, impaired glucose metabolism, dyslipidemia and early MetS development. It was shown that the prevalence of MetS was higher in males (66%), rather than in females (34%). By further stratifying the patients based on age, specifically into prepubertal (< 10 years), pubertal (10-15 years), and adolescents (15-18 years), it was observed that the highest prevalence of MetS and its components was, as anticipated, among pubertal children (47 out of the total 86 patients). Based on body mass index (BMI) percentiles for sex and age, children were classified as overweight and obese, and the results showed a strong correlation between the 64 obese patients (74.4%) and 18 overweight patients (20.9%) and additional MetS components. Overall, the study identified a total of 72 cases with hyperglycemia (83,7%) and 46 cases with high blood pressure (53.4%). The most significant abnormalities observed in the lipid profile were high LDL cholesterol values, which were abnormal in 97.6% of the patients, and elevated triglyceride levels, which were found in 76.7% of the cases.

Conclusions: This study provides data to support the hypothesis that children who are overweight or obese are predisposed for acquiring metabolic syndrome early in life. The results emphasize the crucial importance of implementing early preventive and interventional strategies to reduce childhood obesity and decrease the incidence of MetS.

P2-305

Precocious puberty and fluctuating β-HCG levels in a boy leading to diagnoses of klinefelter syndrome and mediastinal germ cell tumor

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Background: GnRH-independent precocious puberty with elevated β-human chorionic gonadotropin (β-HCG) levels can be the presenting sign of secreting germ cell tumor (GCT) in boys. These tumors are very rare, but have a higher incidence rate in Klinefelter syndrome.

Case Presentation: Here we report a case of a 7.3 year-old boy presenting with precocious puberty. In his physical examination, his height was 143.0 cm (SDS 3.32) and weight 38.5 kg (SDS 2.36). He had a testicular volume (TV) of 8-10 ml bilaterally and stage of puberty according to Tanner of A1 and P3. Biochemical findings revealed suppressed gonadotropins, raised testosterone levels, and elevated β-HCG levels of 105 mIU/ml (normal <5 mIU/ml). The LHRH test revealed a suppression of the gonadotropins with only a minimal increase in the LH level during the test (peak LH level 1.08 mIU/ml). ACTH stimulation test showed normal levels of cortisol and 17-OH progesterone (17-OHP). The skeletal age was markedly accelerated (12 years). Imaging scans including chest X ray, whole body CT, brain MRI and testicular US were normal with the exception of a small pineal cyst. Bone scan was normal, with no evidence of fibrous dysplasia.

After two weeks of his initial presentations, the levels of β-HCG returned to normal (1 mIU/ml). The β-HCG levels in the cerebrospinal fluid were also within the normal range, measuring less than 1 mIU/ml. Throughout the follow-up period, the β-HCG levels showed fluctuations ranging from 1 to 105 mIU/ml. A karyotype test was performed and confirmed the presence of Klinefelter syndrome. After continuous monitoring for 10 months, when the β-HCG levels reached 3.6 mIU/ml, a PET-CT scan detected the existence of a hypodense lesion measuring 37X21X24 mm with calcifications and macroscopic fat tissue. Subsequently, the patient underwent tumor resection, and the histopathological examination revealed an intrathymic mature cystic teratoma.

Discussion: In this case, we present a challenging diagnosis of a mediastinal germ cell tumor in a 7.3-year-old boy. This case emphasizes the significance of performing karyotype testing in boys who exhibit precocious puberty and elevated β-HCG levels and highlights the need for continued monitoring and repeated imaging, even in cases where β-HCG levels decrease spontaneously and remain relatively low.

P2-306

Infancy onset hypocalcemia due to maternal vitamin D deficiency

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Hypocalcemia is a common metabolic problem and a recognized cause of seizures in neonates and infancy. Breastfed infants born to mothers who are vitamin D and or calcium deficient are at risk of developing vitamin D deficiency and hypocalcemia.

Case Report: We present two infants (two weeks old boy and a 9-month-old girl) with hypocalcemia caused by vitamin D deficiency admitted to our pediatric emergency department for seizures and tetany. Both were born at term with normal weight, exclusively breastfed since birth and not receiving vitamin D supplements. Both mothers were having average nutritional diet and no or irregular vitamin D supplements.

Symptomatology started a few days before the admission. The seizures were not associated with fever, lethargy, or feeding abnormalities, and the clinical examination did not reveal any dysmorphic facies.

Laboratory investigations: revealed low ionized calcium and total calcium corrected for serum albumin indicating true hypocalcemia, modestly low magnesium with no evidence of significant hypomagnesemia causing impaired PTH secretion, phosphorus, and alkaline phosphatase in the normal range, and an elevated PTH in response to hypocalcemia.

Table 1. Investigations related to hypocalcemia.

	Case 1	**Case 2**	
Age	**2 weeks**	**9 months**	
Serum			Normal values
Calcium(mg/dl)	7.5	4.7	8.6-10.2
Ionized calcium(mmol/l)	1.04	0.68	1.12-1.35
Magnesium(mmol/l)	0.60	0.62	0.65-1.05
Phosphorus(mmol/l)	3	1.70	1.2.9
PTH(pg/ml)	49.80	76.40	9.2-44.6

Further investigations showed a low 25(OH)D in both infants, confirming vitamin D deficiency.

24-hour urine examen showed calcium and the urinary calcium to creatinine ratio within normal limits, low urinary phosphorus and magnesium.

Thyroid ultrasound detected thyroid and parathyroid glands with normal structure and dimensions. Thyroid function was also normal.

Testing in both mothers found low levels of vitamin D and the cause for vitamin D deficiency was attributed to maternal vitamin D deficiency.

Table 2. Vitamin D biochemical parameters in infant-mother

	Case 1		**Case 2**	
	Infant	**Mother**	**Infant**	**Mother**
25(OH)VIT D (nmol/l) (75-175nmol/l)	34.70	20.20	<20.20	31.70

Management and treatment: Calcium gluconate infusion and vitamin D were initiated with favourable evolution.

Discussion: Vitamin D deficiency is an important predisposing factor for symptomatic hypocalcemia in young infants and maternal vitamin D deficiency is a risk factor for its deficiency during infancy. There is a need to assess the vitamin D status of all pregnant and lactating women and to consider routine vitamin D supplementation for breastfed infants and pregnant women.

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P2-307

Burosumab Therapy response in a family with X-Linked Hypophosphatemic Rickets

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Introduction: X-linked hypophosphatemia (XLH), due to PHEX mutation, is the most common genetic form of rickets in children. This rare disease is characterized by decreased tubular reabsorption and increased renal loss of phosphorus due to increased FGF-23 levels. In children, XLH is often manifested by short stature, rickets and bowel limbs deformity. Conventional treatment with oral phosphorus salts and calcitriol is not always well tolerated which has a progressive and profound impact on patients throughout life. Burosumab is a monoclonal antibody designed to restore renal phosphate reabsorption at proximal tubule and to stimulate endogenous calcitriol production. We report two sisters with XLH on Burosumab treatment with satisfactory results.

Case Report: a 3 years old girl was referred due to presumptive diagnosis of Laron syndrome. Family background: mother with extremely short stature (-7 SD), falling teeth, bone deformity in the lower limbs and healthy 6 months-old sister. She had frontal bossing, short stature (-3,3SD), genu varus and bone pain. Laboratory test: Normal calcium, Phosphorus: 2,5 mg/dl (RV: 3,3-5,5), Alkaline phosphatase (AP): 2550 UI (RV: 150-400), Normal 25 OH D values and TPR: 73 %; Severe Rickets Score (SRS) total: 8 and FGF23: >1991 pg/ml (RV:0-134). Her mother and sister were studied and showed similar features. As clinical biochemical and radiological findings were compatible with XLH, PHEX mutation was confirmed. She started conventional treatment but she had a fracture of the right femur. We decided to start Burosumab treatment and we observed significant improvement with decrease of AP values, pain scale reduced from 8 to 2 with improvement of the SRS to 4 and increased in growth velocity (height form -3.3 DS to -2 DS during first 6 months)

Case 2: Her sister was diagnosed at 6 months of age and despite starting conventional treatment early she presented bad evolution, because of this she started burosumab treatment at 3 years old and after 6 months improved her clinical symptoms, laboratory test and quality of life.

Conclusion: Burosumab treatment was a key to control the excess of FGF-23 and improvement of clinical and biochemical manifestations of XLH. Is an alternative therapy to conventional therapy in growing children with XLH and bad evolution. The greatest achievement was to improve the quality of life of two sisters but the most important thing was the improvement and attenuated evolution in the 2nd girl because of early therapy.

P2-308

The use of growth hormone in children and its effect on the thyroid function at Benghazi children hospital

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Objectives: to describe the effect of GH therapy on thyroid function and the frequency of hypothyroidism during GH therapy.

Patients and methods: This is retrospective case series observational study of 120 children (62 male and 58 female) treated with rGH at Endocrine clinic in Benghazi children hospital (2002 – 2017), categorized according to indication of therapy to main four groups namely: Growth Hormone Deficiency (GHD), Idiopathic Short Stature (ISS), Small for Gestational Age (SGA), and Turner Syndrome. Study variables of all cases were evaluated as follows: age, sex, indication of GH, age at starting therapy, duration of treatment, height at initiation of GH therapy ,height velocity in 1st year of therapy, height velocity in 2nd year of therapy, investigations extracted before starting of therapy: CBC ,Blood sugar, RFT, LFT, TFT (T3, T4, TSH) and MRI.

Results: Total of 120 children were treated with rGH at Endocrine clinic (2002 – 2017). Children with organic brain lesions, systemic diseases, or syndromes that result in growth disorders (apart from TS) were excluded. Their median age at initiation of GH therapy was 11 years and duration ranged from 10mo to 12yrs with median of 3.5yrs. The most common indications for rGH therapy were Growth Hormone Deficiency (GHD) 48 (40 %), Idiopathic Short Stature (ISS) 36 (30.0 %), Small for Gestational Age (SGA) 22 (18.4 %) and Turner syndrome (TS) 14 (11.6%). Younger age at initiation of rGH therapy was associated with significant response to the treatment .

This study shows that shifts in thyroid hormone levels are common during the first year of GH therapy in children who are initially euthyroid. Hypothyroidism however, is uncommon. most of children showed a decline in T4 values within normal range and no significant changes in TSH and T3 level. Only two euthyroid children ~ 1.9% developed central hypothyroidism during rhGH were diagnosed as GHD before treatment and their T4 level was near the lower end of the normal reference range.

Conclusion: All indications showed significant 1-year treatment response to therapy. There is gender deference in receiving rGH where GH indicated in male more than female. Younger age at initiation of rGH therapy was independently associated with significant response to therapy suggesting the importance of identifying children with short stature and prompt initiation of GH therapy.

Shifts in thyroid hormone levels are common during the first year of GH therapy in children who are initially euthyroid and post GH is hypothyroidism

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P2-309

The making of the EndoWatch: A new device for Early Monitoring of Hypothalamic imbalances

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Title: The making of the EndoWatch: A new device for Early Monitoring of Hypothalamic imbalances.

Hulsmann S, Petras S, Fraboulet P, Yuan Lu, van Santen HM (on behalf of the EndoWatch team)

Keywords: Paediatric and adolescent cancer survivors, Brain tumour, Quality of Life ,Wearable, Hypothalamic Obesity

Main goals: Aim for better quality of life

Introduction: Children and adults with a suprasellar (hypothalamic) brain tumour often have excellent survival, but poor outcome due to hypothalamic dysfunction (HD). The hypothalamus is the key-regulator of our body. It not only regulates the anterior pituitary gland, but also regulates core body temperature, circadian rhythm, sodium and energy balance. Patients with HD experience chronic fatigue, recurrent headaches and inactivity due to hypothalamic imbalances. Patients develop (morbid) obesity, due to excessive hunger (hyperphagia) and low energy expenditure. Emotional dysregulation can be present. There is currently no treatment for HD. Patients and families urge us for a solution. Care-givers are overloaded and try to act as the patient's "external hypothalamus" to early detect and prevent imbalances and help to resist hyperphagia and improve activity. Supportive care can decrease the burden for the patient and its family, but is intensive and expensive. Current medical practice is insufficiently making use of the development of new advanced techniques.

Aim: To develop a smart wearable that acts as "external hypothalamus" for brain tumour survivors with HD. This wearable must be available 24/7, monitor body temperature, stress, sleep, daily activity, sodium concentration, give distraction for hyperphagia, and have verbal reminders for the visually impaired. This wearable will improve outcome, self-management, and relieve care-givers.

Methods: The wearable, the Corsano EndoWatch (based on the certified CardioWatch 287-2) will be co-designed by investigators, patients and parents. After development, we will perform a feasibility study, followed by an effectiveness study of the EndoWatch on body mass index (BMI), hypothalamic imbalances and QoL. Simultaneously, a technique for continuous sodium measurements will be developed, as future add-on to the EndoWatch for patients with DI and adipsia.

Results: Funding has been obtained for this 5-year project (Dutch Cancer Society). At ESPE 2023, we hope to share our plans and details for the new external hypothalamus with the endocrine community. As it is still under development, valuable input is appreciated. The new device is expected to be ready for feasibility study in Q2 2024.

P2-310

Exploration of rapidly progressive puberty early prediction in girls

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Objective: To explore the influencing factors of girls with rapidly progressive puberty(RPP), to construct a risk prediction model of RPP in girls,to investigate the value of serum IGFBP-2, Irisin and Ghrelin in prediction of RPP in girls.

Methods: 1.Construction and verification of the prediction model for girls with rapidly progressive puberty

The girls who visited the Department of Endocrinology, Children's Hospital of Soochow University from 2019 to 2021 because of breast development (Tanner stage II) were selected as the study subjects. After follow-up 6 to 12 months without any therapy, Finally, the 211 girls were divided into RPP group (156 cases) and NRPP group (55 cases), The clinical data of the two groups at the first visit were compared. The prediction model was constucted by Lasso-logistic regression, and its diagnostic efficacy was validated and evaluated.

2. The value of serum IGFBP-2,Irisin in prediction of rapidly progressive puberty in girls

Non-obese girls who visited the Department of Endocrinology, Children's Hospital of Soochow University from 2019 to 2021 because of breast development (Tanner stage II) were selected as the study subjects.After follow-up 6 to 12 months without any therapy ,the remaining 60 girls were divided into EP-RPP (30 cases) and EP-NRPP(30 cases). At the same time,30 ICPP girls with Tanner stage II, 30 RPP girls with Tanner stage III were also included. The control group was 30 undeveloped girls aged 8 to 9, The serum concentrations of insulin like growth factor binding protein-2 (IGFBP-2), Irisin and Ghrelin were tested by Enzyme-linked immunosorbent assay, and SPSS25.0 was used for statistical analysis.

Results and Conclusions:

1. The uterine volume, serum IGF-1 level, LH and FSH base value, LH peak value and LH/FSH peak value ratio at the first visit can be used as early warning reference indicators of RPP in girls.
2. The prediction model for RPP girls has better prediction ability than the single predictor and different diagnostic cut-off points can be used for clinical diagnosis or screening.
3. Serum IGFBP-2 and Irisin levels at the first visit may be related to the progression of puberty and can be used as new early warning index of RPP in girls.
4. prediction model of RPP in girls:LN[P/(1-p)]=-1.928+0.649xThe uterine volume+0.005xIGF-1+0.144xFSH base value-0.1xFSH/LH peak value ratio +1.239xLH/FSH peak value ratio.
   when the prediction cut-off point value was 0.85, the specificity and the sensitivity were 87% and 43%.

P2-311

Diagnostic challenges of congenital adrenal hyperplastic (CAH) in a tertiary care hospital of resource limited country

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Background and Objectives: The diagnosis of CAH is a matter of urgent attention as a missed diagnosis can add to mortality due to adrenal insufficiency and inadequate sex of rearing which is psychologically traumatic both for the parents and the child. It is also a matter of grave concern because screening facilities are non-existent in Pakistan along with increase prevalence of intra family marriages thus adding to the increase incidence of this condition. Lack of endocrine facilities and unavailability of confirmatory diagnostic investigations in most of tertiary care hospitals adds to the gravity of situation.

The aim of this study is to determine the challenges faced by pediatricians working in a tertiary care hospital of a developing country in establishing the diagnosis of Congenital adrenal hyperplasia with absence of endocrine facilities and confirmatory investigations.

Material and Method: Cross-sectional study was conducted in the Pediatric Department of tertiary care hospital using consecutive convenient sampling.

Results: 38 patients were enrolled, mean age of presentation was 25 days. Mode of presentation was ambiguous genitalia and electrolyte imbalance.

8/38 patients had persistent vomiting, 6/38 had hyper pigmentation, 4/38 had lethargy.

Electrolyte imbalance was present in 98%. 17 hydroxy progesterone of all the patients was arranged with funds from different sources. 23/38 showed very high levels while 15/38 patients had mild elevation.

Short synacthen test was done of 5/15 and treatment with hydrocortisone and florinef was started of 10/38 to prevent adrenal crises. Treatment of 3/5 was stopped after results of short synacthen test. Karyotyping of 20/38 was done. 12/38 had 46-XX and 8/38 had 46-XY. Ultrasound of pelvic organs of 11/20 showed consistent organs with karyotyping 1/20 had inconsistent organs and 8/20 was inconclusive. 18/20 never agreed for ultrasound. Naming of children with confirmed karyotype was advised to 20/38 while 18/38 were undecisive about naming their child.

Hormone testing of 21/38 for deciding about type of CAH with cortisol, ACTH, renin, aldosterone and DHEA-S was done. Genetic analysis of 2/38 was sent, results are still awaited.

Conclusion: Physicians face diagnostic difficulties in the absence of screening program and confirmatory diagnostic test facilities which are quite expensive and non-existent in government owned hospitals which cater for majority of marginalized population. This leads to delay in initiation of treatment, increase mortality and inadequate sex of rearing.

P2-312

Clinical and Genotypic characteristics of cases of Congenital Adrenal Hyperplasia due to 11- Beta Hydroxylase Deficiency at Alexandria University Children's Hospital

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Introduction: 11-Beta-hydroxylase deficiency (CYP11B1) is the second most common cause of Congenital Adrenal Hyperplasia (CAH). Although the relative frequency of 11-OHD is reported as 3-5% of the cases of CAH, these numbers may have been somewhat underestimated.(1,2)

The resultant clinical picture in 11-OHD is similar to that of 21-OHD, except for the variable presence of hypertension and hypokalemia due to DOC excess.(2,3)

Aim of the Study: The study aims to study the clinical and genotypic characteristics of cases of 11- Beta Hydroxylase Deficiency CAH at Alexandria University Children's Hospital, Alexandria Egypt.

Subjects and Methods: The cases were recruited from Endocrinology Outpatient Clinic at Alexandria University Children's Hospital (AUCH), Alexandria, Egypt. Thorough history taking and clinical examination were taken with special emphasis on family history, degree of virilization by Prader staging, presence of adrenal crisis, hypertension, and Tanner staging of puberty. Laboratory investigations including 17-hydroxyprogesterone (17-OHP), serum cortisol, ACTH, serum testosterone and serum sodium and potassium were done. Molecular Genetic Testing of gene mutations by Whole exon sequencing was done for all cases.

Results: We studied 13 cases of 11 B- CAH, 9 females and 4 males. They aged from 6 months to 15 years. 30 % had adrenal crisis and 23 % had Hypertension. 5 cases presented with Precious Puberty. One patient had Associated Pituitary Adenoma. 3 had siblings with same condition. They all have mutation in CYP11B1 with different genomic positions.

Conclusions: A precise diagnosis of cases of 11 B- CAH is essential for proper replacement therapy and genetic counseling. Molecular Genetic testing is important for phenotype- genotype correlation of cases of 11 B- CAH.

References

1. White PC. Congenital adrenal hyperplasia owing to 11beta-hydroxylase deficiency. Adv Exp Med Biol 2011;707:7-8.
2. Alsanea M N, Al-Agha A, Shazly. Classical 11β-Hydroxylase Deficiency Caused by a Novel Homozygous Mutation: A Case Study and Literature Review. Cureus 2022: 14(1): e21537.
3. Menabò, S., Polat, S., Baldazzi, L. et al. Congenital adrenal hyperplasia due to 11-beta-hydroxylase deficiency: functional consequences of four CYP11B1 mutations. Eur J Hum Genet 2014 ;22, 610–16.

P2-313

Oral Benfotiamine 300 mg Versus Intramuscular Thiamine in Diabetic Patients with Peripheral Neuropathy

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Keywords: Benfotiamine, Bioavailability, Thiamine, Diabetic Peripheral Neuropathy Abbreviations: Adverse Event (AE), Advanced Glycation End products (AGE), Analysis of Variance (ANOVA), Alanine Transaminase (ALT), Body Mass Index (BMI), Case Report Form (CRF), Diabetic Neuropathic Symptom score (DNSS), Diacylglycerol (DAG), Dipeptidyl Peptidase 4 Inhibitor (DPP-4 I), Good Clinical Practice (GCP), Informed Consent Form (ICF), Intent to Treat (ITT), Institutional Review Board (IRB), Ministry of Health (MOH), National Institute of Diabetes and endocrinology (NIDE), Nuclear Factor kappaB (NF-κB), Per Protocol (PP), Protein Kinase C (PKC), Research and health Development (RHD), Serious Adverse Event (SAE), Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), Transient Ischemic Stroke (TIA)Mo

Aim: This is a prospective, pilot, open-label, interventional, comparative, randomized study, enrolled 60 patients with type 2 diabetes mellitus (T2DM) to assess the effect of different doses of oral vitamin B containing Benfotiamine 300 mg versus intramuscular B vitamins containing watersoluble Thiamine HCl.

Methods: Patients ≥ 18 years with T2DM with Peripheral Neuropathy, divided into 3 groups; A & B (Benfotiamine 300 mg) and group C (Thiamine HCl), which were sub-divided to include patients with HbA1c less or more than 8 %. Patients were evaluated at baseline, after 2.5 hours, six days, and two weeks.

Results: Blood vitamin B1 increased from baseline to after 2.5 hours (T2) by 57%, 79% and 33% in group A, B and C respectively, with statistically significant difference in each group (p value < 0.001). Vitamin B1 continued to increase after six days (T6) in patients of groups A & B by 98% and 165% respectively, while dropped in patients of group C from 33% at T2 to 6% at T6, with p-value ≤ 0.001 between the three groups. Diabetic Neuropathic Symptom Score (DNS) decreased in mean value in all groups after 14 days of treatment by 64.4%, 53.7% and 48.6% in group A, B and C respectively, indicating improvement of peripheral neuropathy.

Safety: There was no AE or SAE reported during the study.

Conclusion: Oral Benfotiamine 300 mg is safe and more effective than intramuscular Thiamine HCl, in increasing vitamin B1 blood level in patients with diabetic peripheral neuropathy, which in turn relieves peripheral neuropathy. Clinical Trial Registration Number: NA

P2-314

Evaluation of the usefulness of antymüllerian hormone and inhibin B as markers of ovarian reserve in girls with hyper- and hypogonadotropic hypogonadism

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Hypogonadism is represented by a hypo- and hypergonadotropic variant. Antymüllerian hormone (AMH) and inhibin B are used to assess ovarian reserve, but in pediatric practice their role has not been studied. The main interest is to conduct the study of ovarian reserve in hypogonadism among girls.

Objective of the Research: To compare the content of inhibin B, AMH and estradiol in girls with hyper- and hypogonadotropic hypogonadism

Materials and Methods: 25 girls 15.06 ± 1.2 years with delayed puberty are included to study.

Inclusion Criteria: absence of secondary sexual characteristics at the age ≥13 years or absence of menarche at the age ≥ 15 years or absence of menarche for 3 years or more from the onset of estrogen-dependent signs of puberty.

Noninclusion Criteria: age ≥18 years, abnormal external genitalia.

The stage of sexual development was assessed on the Tanner scale, LH, FSH, estradiol, inhibin B, AMH, in blood serum, blood karyotyping or FISH analysis on the sex chromosomes, molecular genetic study by parallel sequencing (Ion Torrent platform), custom Ampliseq DSD, hypogonadism, hypopituitarism panels; GnRH analogue test results (triptorelin 0.1 mg).

The patients are divided into two groups. The first group – hypergonadotropic hypogonadism (n=16) age 14.78 ± 0.69 years, which consists of: Turner syndrome (n=6), and 10 patients karyotype 46, XX. The second group – hypogonadotropic hypogonadism (n=9), average age 15.06 ± 1.22 years, $p = 0.102$; congenital hypogonadotropic hypogonadism (n=8), 7 of them are isolated (in 3 cases, GNRHR gene mutation), 1 as part of hypopituitarism, PROP1 gene mutation and 1 acquired hypogonadism after removal of craniopharyngioma.

Results: The serum estradiol content in the two groups did not differ significantly (Me=9 pmol/l [0.28 ; 50] vs 25.87 pmol/l [9 ; 48.22], $p > 0.05$). The inhibin B level (Me=2.25 pg/ml [1.2 ; 9] vs 14.2 pg/ml [10 ; 24], $p=0.003$) and AMH (Me=0.1 ng/ml [0.1 ; 0.18] Me=2.92 ng/ml [1.22 ; 8.18], $p=0.002$) in blood serum in patients with hypergonadotropic hypogonadism, it was significantly lower than in girls with hypogonadotropic hypogonadism.

Conclusion: Comparison of groups with hypo- and hypergonadotropic hypogonadism revealed no difference in the content of estradiol in the blood serum, however, the content of inhibin B and AMH in hypergonadotropic hypogonadism was significantly lower compared with the hypogonadotropic variant of the disease. The obtained results rocket the assessment possibilities of the ovarian reserve in girls with hypogonadism.

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P2-315

A case report of a novel mutation in AR gene in two sisters with 46-XY Karyotype

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Introduction: Phenotype gender is the outcome of a long and coordinated set of fetal events that are controlled by genetic factors, hormonal factors and environmental factor.

In the case of the 46XY fetus, SRY gene on chromosome Y determines the gender and cause bipotential gonad change to testes. And other factors such as sertolli cell by secreting anti-Mullerian hormone which leads to regression of the structures rooted in the paramesonephric ducts (tubes, womb, and vagina) and leydig cell that are found within the testicle tissues generate fetal testosterone that converts mesonephric ducts into the penetrating duct, seminal vesicles, and epididymis.

Three common reasons that lead to the formation of female phenotype in an individual with 46XY karyotype are complete androgenic insensitivity syndrome (CAIS), Congenital adrenal hyperplasia (CAH), and complete dysgenesis of sexual glands.

Here, we report two sisters with 46, XY DSD harboring a new mutation in the AR gene.

Case Presentation: A 10 years old girl with female external genital organs (clitoris, major and minor labia, distinct vaginal and urethra orifices) was referred to the health clinic complaining about urine infection symptoms. Complete urine analysis and culture showed no urine infection. For further examination, abdominopelvic sonography was performed and showed that the womb and ovaries were not in their anatomical position. Two hypoechoic oval-shaped regions were observed in the right and left inguinal channels with dimensions of 26 × 10 × 9 mm and 24 × 4 × 8 mm. Both regions appeared as testicles. Magnetic resonance imaging was the same. Cytogenetic tests indicated that the patient was genetically male with a 46XY chromosome structure. After that her 5 years old sister was examined and was exactly the same.

Sanger sequencing showed a novel hemizygous variant (c.2484T>A; p. phe828Leu) in AR (NM_000044.4) gene. They inherited this variant from their heterozygous mother. Their father did not harbor this variation.

Conclusion: Up to now, more than 497 mutation s in the AR gene have been registered in the HGMD database.

In this study, a novel pathogenic variant in AR gene has been introduced. This finding helps in the genotype-phenotype correlation of AIS patients with this variation.

P2-316

Family case of constitutional delay of puberty

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Introduction: One of the strategies of searching the genetic causes of CDGP is analysing the genes responsible for hypogonadotropic hypogonadism (HH).

Objective: To investigate the role of the HS6ST1 gene in development CDGP.

Materials and Methods: Two patients - height and BMI SDS, bone age, genitometric parameters, basal hormones, GnRH analogue test, hCG test, olfactometry, brain-MRI. Four patients (two sisters, brother, mother) - molecular genetic study, parallel sequencing (IonTorent platform), custom Ampliseq_HH panel: FGF8, NELF, SEMA3A, KISS1, KAl2, KAL1, TACR3, WDR11, GREAT, GNRH1, TAC3, KAL4, NR0B1, LHB, PROKR2, GNRHR, KISS1R, CHD7, HS6ST1, INSL3, IL17RD, SPRY4, FGF17, DUSP6, FLRT3, DNMT3L, POLR3A, POLR3B, RBM28, MKRN3.

Results:

Patient 1: male, 13.9 years (proband), Tanner P1G1, height -1.86sd, BMI -2.1sd, bone age 12.5 years, LH 0.1 mIU/ml, FSH 1.22 mIU/ml, total testosterone < 0.1 ng/ml, inhibin B 56.6 pg/ml, AMH 119.5 ng/ml, prolactin 3.93 ng/ml, TSH 1.81 mIU/ml, T4 15.27 pmol/l, IGF1 195.4 ng/ml, GnRH analogue test - LH 10.59 mIU/ml; hCG test testosterone 6.5 nmol/l. Olfactometry - mixed hyposmia. Brain-MRI - pituitary hypoplasia.Age 16.3 years, Tanner P2G2, height -2.4sd, cycle of testosterone esters 100 mg/month for 3 months.Age 20.1 years, height 174 cm, Tanner P5G5, testosterone 17.68 nmol/l, inhibin B 274.3 pg/ml.

Patient 2: female, 13.3 years (sister of the proband), Tanner P1B2, height -1.97sd, BMI -1.72sd, bone age 11 years, LH 4.34 mIU/ml, FSH 4.28 mIU/ml, estradiol 11.2 pg/ml, TSH 2.39 μIU/ml, T4 1.31 ng/dl, IGF-1 188.2 ng/ml, AMH 5.49 ng/ml, the volume of the uterus 1.0 ml, ovary - 3.8 ml/2.2 ml, GnRH analogue test LH/FSH max. 7.72/13.16 mIU/ml. Age at menarche 15.5 once, then wasn't any menstruations during 6 months.

Patient 3: female (sister of the proband): menarche from 15.5 years, regular.

Father and mother have under timely sexual development.

The heterozygous substitution c.652C>T:p.P218S with unknown pathogenicity in the HS6ST1 gene (MIM#:604846, reference sequence (NM_004807) was found in a brother and two sisters and was not in the mother.

Conclusions: Three members of the family showed CDGP of varying severity and the same heterozygous substitution in the HS6ST1 gene with unknown pathogenicity. Clarification of the genetic causes of HH and CDGP will improve the diagnosis of the causes of delayed sexual development. The study of genes associated with HH is one of the strategies for determining the genetic causes of CDGP.

P2-317

"MRKH Type 2 with Menstruation: Unraveling an Unusual Case"

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Introduction: Mayer-Rokitansky-Kuster-Hauser Syndrome (MRKH) is a congenital disorder characterized by agenesis or aplasia of the uterus and upper portion of the vagina in females with a normal karyotype (46,XX). Its incidence is approximately 1 in 4,000 to 5,000 live female births. The etiology of MRKH syndrome is highly complex and remains unclear, although genetics is believed to play a significant role in its pathogenesis.

Case Report: A 14-year-old girl presents with a complaint of abdominal pain that has been ongoing for the past month. The pain is continuous and subsides with the use of analgesic medication. She also reports a lump in the lower right abdomen. She has not yet experienced menstruation. The patient developed secondary sexual characteristics, including breast development and pubic hair at the same time as her peers. Tanner stage M3P3. Pelvic and abdominal ultrasound was performed, which revealed hematometrocolpos predominantly in the vagina, grade I-II hydronephrosis in both kidneys with a duplex collecting system in the right kidney. Abdominal CT scan showed a hypodense mass in the uterine cavity and bilateral adnexa, hematometra and hematosalpinges, a double uterine cavity structure with septa (suggestive of didelphys uterus), vaginal agenesis, bilateral pelvocaliectasis with a double collecting system in the renal pelvis and right ureter, hepatosplenomegaly, ascites. Hormonal assessment shows normal range of LH, FSH and estradiol. The patient was given symptomatic pain management therapy and underwent a double approach vaginoplasty.

Discussion: In cases of MRKH, patients typically present with primary amenorrhea. There are two types of MRKH: type 1, characterized by the absence of the proximal two-thirds of the vagina and uterus, and type 2, which is accompanied by anomalies in other organs such as the heart, kidneys, and skeletal system. We present a patient that almost match with MRKH, type 2. There are: vaginal agenesis and didelphys uterus was found along with renal and skeletal abnormalities. This is a rare case and raises a question: If the patient has MRKH type 2, why is she experiencing menstruation despite having an abnormal uterus? In the literature search, no similar cases of MRKH type 2 like our patient. Mutations in WNT4 were detected in patients with Müllerian aplasia and virilization/hyperandrogenism. Currently, we are investigating the WTF4 gene, which may play a role in this phenomenon. Right now the patient is in recovery after the surgery and waiting for the next follow-up appointment at the clinic.

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