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Challenges in the Management of Short Stature

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Key Words
Short stature · Growth · Normal height · Practical algorithm · Therapeutic options

Abstract
Human growth, from fetal life to adolescence, is dynamic and a good marker of health. Growth is a complex process influenced by genetic, hormonal, nutritional and environmental factors, both pre- and postnatally. To date, no international agreement regarding normal height has been established. Auxological parameters are fundamental to investigate potential short stature (SS), either with a known diagnosis, e.g. disproportionate or proportionate, prenatal and/or postnatal onset, or an unknown diagnosis, i.e. idiopathic SS. The incidence/prevalence of SS is difficult to establish. The measurement of choice in children aged <2 years is length, while in those >2 years of age it is height. A number of monogenic diseases that lead to proportionate SS due to either isolated growth hormone deficiency, multiple pituitary hormone deficiency, growth hormone insensitivity, primary acid-labile subunit deficiency, primary IGF-1 deficiency, IGF-1 resistance, primary IGF-2 deficiency or primary protease deficiency have been discovered in the last 30 years. In addition, the Nosology and Classification of Genetic Skeletal Disorders revised in 2015 includes 436 conditions, with a number of genes of 364. A practical algorithm for the evaluation of SS as well as therapeutic options are discussed.

Introduction

Human growth is regulated by genetic, hormonal, nutritional and environmental factors that interact to culminate in a complex process of cell replication in all tissues [1]. Human growth is characterized by dramatic fetal growth (when growth is most rapid), deceleration of growth immediately after birth, and prolonged growth during childhood followed by prepubertal deceleration before the pubertal growth spurt.

Short stature (SS) in childhood is a frequent reason for referral to pediatric endocrinologists [2, 3]. Normal height is determined according to age, sex and ethnic group as well as the family context. In clinical practice, the projected adult height of a subject is compared with his/

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her 'target height' (TH) or 'genetic height'. However, growth is a dynamic process such that normal height at one specific moment does not exclude the possibility of SS occurring later in development; hence, growth velocity (GV; change in height/year) is employed. However, we are still unable to establish a cut-off that clearly discriminates between 'normal' or 'pathological' height, contributing to the lack of an international consensus that defines the concept of SS/undergrowth. The criteria most commonly used in clinical practice are: (1) Height below –2 SDS for age, sex and ethnic group. (2) Normal height, i.e. between ±2 SDS for the general population, but >2 SDS below the growth curve corresponding to the patient's TH. (3) Projected adult height (prediction of adult height) >2 SDS below the TH. (4) Persistent low GV. There is no international consensus regarding the definition of diminished GV, although a GV below –1 SDS (~25th percentile) for age and sex maintained for >2–3 years is considered 'potentially' pathological.

Do We Know the Incidence/Prevalence of SS?

It is difficult to establish the prevalence of subjects with SS at one specific moment, but it is estimated to be around 3–5%. The prevalence of growth hormone deficiency (GHD) is around 1 in 4,000.

How Should Growth Be Measured?

In the newborn length, weight and head circumference according to gestational age are the most important parameters. The length of newborns and infants is measured using an infantometer. In children older than 2 years, height, weight and head circumference are used. Waist circumference and skin fold measurements can also be employed. A child's height is measured with the child standing erect against a stadiometer. At each time point, height should be measured twice, with the difference between the two measurements being within 4 mm. To obtain an accurate height and weight the scales must be correctly calibrated.

Do We Have Standardized Growth Charts?

The techniques to evaluate growth are well standardized [1]. The WHO international charts (2006) represent standard growth for healthy children and are currently recommended for children <2 years if national charts are not available. For children older that 2 years, local growth charts should be employed, in particular those including longitudinal studies where SDS GV can be analyzed. Local charts should also be used for weight, particularly in Western countries where overweight and obesity are more common, especially in adolescents. Cross-sectional studies are of interest to rapidly establish the median and extreme weights per chronological age and sex.

Etiology and Classification

SS can be classified into two main groups: known and unknown etiology. Amongst known etiologies SS can be classified as proportionate and disproportionate, both of which can be either congenital or acquired. Among children with proportionate SS, we should distinguish between prenatal and postnatal origin. In children classified as having SS of unknown etiology and diagnosed with idiopathic SS (ISS), 'normal variants of SS' [familial SS (FSS)] and constitutional delay of growth and puberty (CDGP) are also frequently included (table 1).

I. Osteochondrodysplasias

The 9th Edition of the Nosology and Classification of Genetic Skeletal Disorders, revised in 2015 [4], provides an overview of 436 conditions included in 42 groups defined by clinical, radiographic, biochemical and molecular criteria. The number of genes has increased to 364. The most common conditions seen by pediatric endocrinologists are included here as it is beyond the scope of this review to go into further detail.

Achondroplasia. Achondroplasia is the most common nonlethal skeletal dysplasia (ACH, MIM 100800), with a prevalence between 1/16,000 and 1/26,000 live births [5]. It is due to mutations in the fibroblast growth factor receptor 3 (*FGFR3*, MIM 134934) gene (approximately 98% show a G to A point mutation at nucleotide 1138) and inheritance is autosomal dominant with essentially complete penetrance. Its main characteristics include a large head with prominent forehead, small midface or midface hypoplasia, flattened nasal bridge, nonproportional dwarfism, spinal kyphosis or lordosis, shortening of the proximal limbs (rhizomelic), short fingers and toes and varus or valgus deformities. The 'trident hand' (the 3rd metacarpal is short, the 4th deviated to the ulnar side and the thumb is radially displaced) is characteristic.

Hypochondroplasia. Hypochondroplasia (HCH, MIM 146000) is a milder form of achondroplasia due to mutations in the *FGFR3* gene [4]. Patients exhibit relatively short extremities with moderate narrowing of the interpedicular distances, increased dorsal concavity of the vertebral bodies, short and broad femoral necks, disproportionate long fibula, short plump tibia and moderately short plump humerus.

Table 1. Classification of SS according to [4]

I	**SS of known etiology**
A	*Disproportionate*
1	Congenital: skeletal dysplasias[1]
	Overall number of disorders: 436
	Number of groups: 42
	Number of genes: 364 (Next Generation Sequencing technologies and whole exam sequencing)
	The Nosology has expanded (new genes and new conditions)
	The Nosology has contracted (limitations in differentiating the phenotype)
	Genetic information will increase in the 10th edition
2	Acquired: secondary to malformations, radiotherapy, tumors and other diseases
B	*Proportionate of prenatal origin (newborn SGA)*
	Due to fetal factors
	Chromosomopathies (Turner, Down, Prader-Willi, etc.)
	Syndromic (Silver-Russell, Cornelia de Lange, Noonan, etc.)
	Primordial dwarfism (MOPD I, II, III)
	Due to uterine of placental features
	Due to maternal features
	Malnutrition
	Drugs
	Cardiac pathology
	Congenital infections (TORCH)
C	*Proportionate of postnatal origin*
	Malnutrition
	Chronic infectious diseases
	Organic diseases
	Gastrointestinal (celiac disease, Crohn's disease, cystic fibrosis, short intestine, etc.)
	Hepatic (biliary atresia, chronic hepatitis, liver transplantation, etc.)
	Renal (glomerular, interstitial, tubular)
	Cardiac (cianosant congenital cardiopathies)
	Pulmonary (FQ, asthma, bronchopulmonary dysplasia, obstructive apnea, pulmonary sequestration, etc.)
	Metabolic (poorly controlled diabetes mellitus)
	Hematological (chronic severe anemia, hemochromatosis)
	Oncological (leukemias, lymphomas, tumors of the central nervous system, bone marrow transplantation, etc.)
	Central nervous system (idiopathic cerebral palsy, myelomeningocele, mental retardation, etc.)
	Rheumatological (chronic juvenile arthritis, systemic lupus erythematosus, etc.)
	Endocrine diseases
	Growth hormone/IGF-1 deficiency or insensitivity
	Hypothyroidism
	Hypercortisolism
	Precocious puberty
	Pseudohypoparathyroidism
	Inherited rickets (hypocalcemic and hypophosphatemic)
	Diabetes mellitus with poor control
	Diabetes insipidus without treatment
	Psychosocial
II	**SS of unknown etiology: ISS**
	Normal variants of SS
	FSS
	CDGP
	Association of FSS and CDGP
	Other causes yet to be known

Multiple Epiphyseal Dysplasias. This autosomal dominant osteochondrodysplasia is a clinically and genetically heterogeneous disorder characterized by mild SS and early-onset osteoarthritis [6]. The phenotypic spectrum includes edgy (not rounded) carpal bones, femoral capital epiphyses and greater trochanters that are smaller than usual but regular in shape, the acetabular roof showing the beginning of degenerative changes, irregularities of the epiphyseal contours in the knee, wedging of the metaphyses and small patella. At least five genes have been implicated in the different types of multiple epiphyseal dysplasias: *COMP*, *COL9A1*, *COL9A2*, *COL9A3* and *MATN3*.

Léri-Weill Dyschondrosteosis. Léri-Weill dyschondrosteosis (LWD, MIM 127300) is characterized by mesomelic limb shortening and the characteristic Madelung deformity. Most Léri-Weill dyschondrosteosis cases are caused by heterozygous mutations in *SHOX* or its regulatory regions located in *PAR1* [7–9]. Heterozygous *SHOX* mutations are also observed in a small proportion (2–5%) of patients with ISS (MIM 300582).

Langer Mesomelic Dysplasia. Langer mesomelic dysplasia (LMD, MIM 249700) is associated with defects in both copies of *SHOX* and characterized by severe disproportionate SS and mesomelic and rhizomelic limb shortening [10].

Acromesomelic Dysplasia Type Maroteaux. Acromesomelic dysplasia type Maroteaux (AMDM, MIM 602875) is caused by biallelic loss of function mutations in the natriuretic peptide receptor B/guanylate cyclase B gene *(NPR2)*, while heterozygous mutations in *NPR2* cause FSS [11, 12]. Patients with acromesomelic dysplasia type Maroteaux exhibit severe disproportionate SS, shortening of the extremities, bowing of the forearm and shortening of metacarpals and phalanges.

II. Proportionate Short Stature

Prenatal Origin. This includes patients with SS due to fetal (chromosomopathies, different syndromes and what is now called 'primordial dwarfism'), uterine or placental features or maternal pathology (malnutrition, drugs, alcohol, tobacco, cardiac pathology or congenital infection). Silver-Russell, Seckel, Cornelia de Lange, Noonan and Prader-Willi are amongst the most common syndromes. A newborn is considered small for gestational age (SGA) when birth weight and/or length are at least 2 SDS below the mean for gestational age (≤–2 SDS) [13]. In developed countries, 4–7% of newborns are SGA. When the newborn shows a combined diminution of length and weight at birth, the risk of SS is higher than if only weight is affected. Characteristically, 80–90% of SGA subjects experience partial or complete catch-up growth during the first or second year of extrauterine life, reaching a height in the normal range (±2 SDS). The other 10–20% remain short after 2 years of life, 50% of whom will have a low adult height. Fetal factors (chromosomopathies, congenital abnormalities and different syndromes) cause one third of SGA newborns, with the rest being due to maternal (malnutrition, infections, toxins) and placental-uterine (uterine malformations, single umbilical artery) factors. In 40% no abnormalities are found.

Postnatal Origin: GHD. Of the causes of proportionate SS due to endocrinopathies (~5%), here we concentrate on the genetic alterations of the growth hormone-IGF axis. GHD represents 1–2% of SS (prevalence 1 in 4,000). GHD can be isolated or combined with other pituitary deficiencies (multiple pituitary hormone deficiency) and can be congenital or acquired (tumors, traumatisms, histiocytosis, infections, radiotherapy). In most cases GHD is idiopathic, with an organic cause identified in only 20%. Among idiopathic cases, abnormalities in MRI (pituitary hypoplasia, lack of pituitary stalk, ectopic posterior pituitary) are frequent. The most common characteristic of GHD is the failure to grow, including a dramatic reduction in GV and delayed bone age. Spontaneous growth hormone secretion and/or growth hormone response to different stimuli are reduced, as are serum IGF-1 and IGFBP-3 levels. The congenital forms are severe and growth failure is precocious [14–17]. Growth failure can be present in the first months of life with a characteristic phenotype: doll face, high-pitched voice, increased periabdominal fat, acromicria and decreased muscle mass. Congenital GHD can be associated with perinatal complications (hypoglycemia, small penis, neonatal jaundice). When GHD is acquired, SS manifests later and may be the only clinical manifestation. The genes implicated are *GH1* and *GHRHR*. Mutations in *POU1F1* [18], *PROP1* [19], *LHX3* [20], *LHX4* [21], *HESX1* [22], *SOX2* [23], *SOX3* [24], *OXT2* [25], *GLI2* [26] and *RNPC3* [27] are associated with multiple pituitary hormone deficiency.

Postnatal Origin: Growth Hormone Insensitivity. Growth hormone insensitivity is caused by mutations in the growth hormone receptor (GHR), with Laron syndrome first described in 1966 [28]. Numerous mutations have been reported in the external, internal and transmembrane domain [29] of the GHR in populations with consanguinity [30]. The first GHR mutations producing 'partial growth hormone resistance' were reported in 1995 [31]. Mutations in *STAT5b* have also been described [32].

Postnatal Origin: Primary Acid-Labile Subunit Deficiency. The IGF acid-labile subunit (IGFALS) is a circulating glycoprotein produced in the liver under growth hormone stimulation. This subunit stabilizes the IGF-IGFBP-3 complex. Mutations in IGFALS lead to SS [33–35].

Postnatal Origin: Primary IGF-1 Deficiency. IGF-1 mediates most of the growth-promoting effects of growth hormone after birth. While growth hormone is not implicated in prenatal growth, IGF-1 is. Woods et al. [36] described the first patient with a homozygous partial deletion of the *IGF-1* gene who presented with severe pre- and postnatal growth failure, sensorineural deafness and mental retardation.

Postnatal Origin: IGF-1 Resistance. Mutations in the *IGF-1R* gene underlie some cases of pre- and postnatal growth failure [37]. These patients are phenotypically distinct from the patients with the *IGF-1* gene mutation described by Woods et al. [36]. *IGF-1R* gene variants, including heterozygous *IGF-1R* mutations or haploinsufficiency of this gene, should be investigated in subjects with FSS [38].

Postnatal Origin: Primary IGF-2 Deficiency. The first *IGF-2* variant (c.191C→A, p.Ser64Ter) was recently described in four family members with growth restriction [39]. Their severe growth failure suggests that IGF-2 affects postnatal growth in addition to prenatal growth. The dysmorphic features of the affected subjects are consistent with deficient IGF-2 levels as a cause of Silver-Russell syndrome [39].

Postnatal Origin: Primary Protease Deficiency. We recently reported the first patients with a mutation in *PAPP-A2* producing a new syndrome with SS [40]. Hence, we propose a new classification for the molecular basis of proportionate SS and look forward to a future international consensus (table 2).

Postnatal Origin: Other Endocrinopathies. Hypothyroidism represents <1% of patients with SS. Due to the universal application of neonatal screening, this figure has declined in recent years. Patients with *chronic hypercortisolism* exhibit SS together with generalized obesity. Hypercortisolism is due to ACTH hypersecretion (Cushing's disease), to adrenal production of cortisol (Cushing's syndrome) or to long-term exogenous administration of glucocorticoids. *Excess sex steroids* (precocious puberty either gonadotropin-dependent or -independent) produces abnormal acceleration of GV and bone age with transitory overgrowth, but short adult height. *Pseudohypoparathyroidisms* represent a heterogeneous group of diseases due to parathyroid hormone resistance.

Table 2. Known molecular basis of proportionate SS

A	*Isolated GHD* IA *(GH1)*-AR- IB *(GH1, GHRHR)*-AR- II *(GH1)*-AD- III *(BTK, SOX3)*-X-linked- Ghrelin receptor *(GHSR)* -*Semidominant*- *RNPC3 (minor spliceosome)* -AR- Unknown
B	*Multiple pituitary hormone deficiency* *POU1F1*-AR, AD- *PROP1*-AR- *LHX3*-AR- *LHX4*-AD- *HESX1*-AR- *OTX2*-AD- *SOX2*-AR- *SOX3*-X-linked- *GLI2*-AD- *GLI3*-AD- *FGF8*-AD- *FGFR1*-AD- *IGSF1*-X-linked- *RIEG*-AD-
C	*Growth hormone insensitivity* *GHR* (Laron/partial) -AR- *STAT5b*-AR- *Bioinactive GH*-AR-
D	*Primary acid-labile subunit deficiency* *IGFALS*-AR-
E	*Primary IGF-1 deficiency* *IGF-1*-AR-
F	*IGF-1 resistance* *IGF-1*-AR-
G	*Primary IGF-2 deficiency* *IGF-2*-paternally inherited-
H	*Primary protease deficiency* *PAPP-A2*-AR-

These patients show hypocalcemia, hyperphosphatemia and high parathyroid hormone levels, with no increase in 1-25$(OH)_2$ or hyperphosphaturia. In addition, some patients exhibit SS, obesity, a round face, moderate mental retardation and bone abnormalities (Albright hereditary osteodystrophy).

III. Idiopathic Short Stature

An international consensus to define ISS [41] established that 'ISS is defined auxologically by a height below

–2 SD score (SDS) with no findings of disease as evident by a complete evaluation by a pediatric endocrinologist including stimulated GH levels. Magnetic resonance imaging is not necessary in patients with ISS. ISS may be a risk factor for psychosocial problems, but true psychopathology is rare.' In the United States and seven other countries, the regulatory authorities approved growth hormone treatment (at doses up to 0.053 mg/kg/day) for children shorter than –2.25 SDS, whereas in other countries lower cut-offs are proposed. 'Specifically, children with ISS have normal birth weight and are GH sufficient. ISS describes a heterogeneous group of children consisting of many presently unidentified causes of SS. It is estimated that approximately 60–80% of all short children at or below –2 SDS fit the definition of ISS.' This definition of ISS includes short children labeled with CDGP and FSS. Hence, 'children with dysmorphic phenotypes or SGA should be excluded from the ISS diagnostic category as they are children with clearly identified causes of SS.' Wit et al. also established a definition for ISS [42] and discussed the management of ISS [43].

It is not clear whether FSS and CDGP will be classified as ISS in the future. Time will tell whether we can be more precise in the diagnosis of FSS (healthy short subjects with normal maturation and relatives with SS), CDGP (healthy subjects with slow maturation and 2–3 years of bone age delay who exhibit SS when they are children and start puberty with a delay, obtaining adult height at an age greater than the population mean). In both situations, the adult height is in accordance with the familial context.

The concept of ISS is controversial, artificial, arbitrary and heterogeneous, including normal and pathological patients, but having one thing in common: our ignorance to obtain an etiopathogenic diagnosis. Around 80% of the children who visit a pediatric endocrinologist could be included in the concept of ISS. Most of them (80–85%) will be what we have called normal variants. Research and new methodologies will allow new diagnosis of patients labeled as ISS, creating new classifications of a known pathology.

Evaluation for Diagnosis of Short Stature

The initial evaluation of every child with SS should include patient history, family history, a complete physical exam, bone maturation (bone age), pedigree and, if possible, the analysis of his/her pattern of growth with data from the parents. With these data, we should be able to conclude whether the patient has SS, if it is proportionate or disproportionate and if it is of prenatal and/or postnatal origin. Subsequent complementary studies should be done to try to make a specific diagnosis and to determine a possible therapy.

A practical algorithm for the evaluation of SS is included in figure 1.

(1) If SS is disproportionate, a skeletal survey should be done. Molecular studies for the most common skeletal dysplasias are indicated *(FGFR3, SHOX, NPR2, COMP, COL9A1, COL9A2, COL9A3, MATN3)*.

(2) If SS is proportionate and of prenatal origin, chromosomopathies and syndromes should be analyzed. A karyotype is indicated to discard chromosomopathies. If there is suspicion of a specific syndrome with a known molecular defect, molecular studies should be done. If there is no orientation to a specific diagnosis, genome-wide association studies or exome studies might be indicated.

(3) If SS is proportionate, of postnatal origin and not very severe (between –2 and –3 SDS), in most cases the diagnosis will be a normal variant of SS or ISS. If SS is more severe (>–3 SDS), it is necessary to explore other diagnoses, including GHD, celiac disease, Crohn's disease, renal failure, renal tubular disorders and hypothyroidism, among others.

(4) There are significant controversies in the diagnosis and management of GHD [44]. Hence, early reassessment of the diagnosis in patients who respond poorly to treatment is recommended [45].

(5) If there is no specific diagnosis and the SS is severe or has a familial component, the possibility of performing an exome study should be considered [46].

Therapeutic Approach to Short Stature

(1) In many cases, SS does not require treatment and a conversation with the parents and child would be the most important medical action. To wait and see the patient every 6 months is the correct action.

(2) If there is a specific diagnosis of organic pathology (celiac disease, Crohn's disease, cardiopathy, cystic fibrosis, hypothyroidism, hypercortisolism), we should treat it.

(3) The therapies available to improve growth are limited: hrGH, hrIGF-1, GnRH analogs, aromatase inhibitors (anastrozole and letrozole) and bone lengthening surgery.

(4) hrGH therapy has been approved by the European Medicines Agency in patients with GHD, SGA, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency and *SHOX* gene abnormalities. The Food and Drug Administration has approved it for all of the above plus Noonan syndrome and ISS. Time will tell whether

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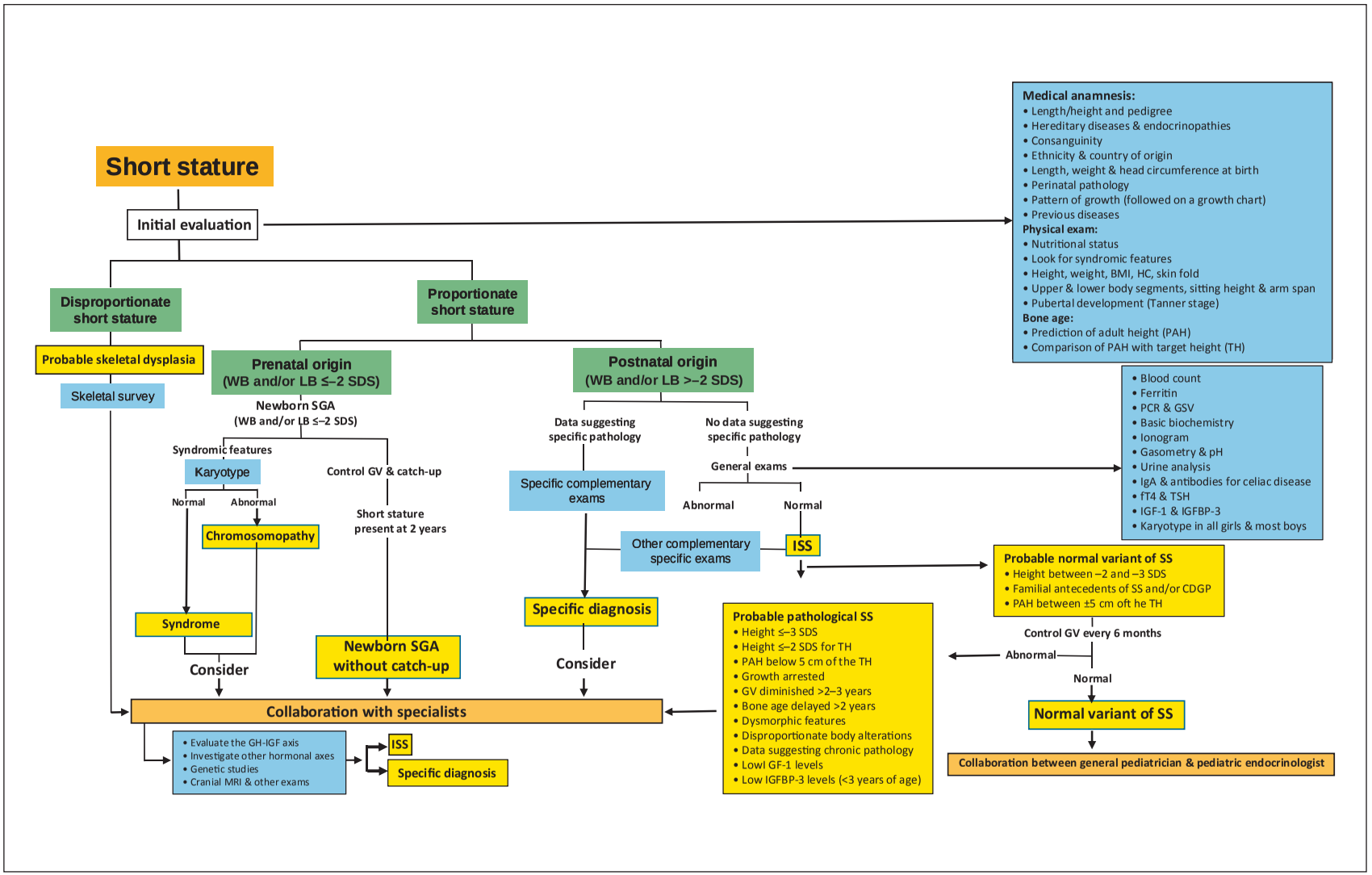

Fig. 1. Algorithm for the diagnosis of SS. WB = Weight at birth; LB = length at birth; HC = head circumference.

all of these indications continue to be accepted: (a) SGA patients show a very heterogeneous response and we need to know why. (b) Although hypotonia improves in some patients with Prader-Willi syndrome, most of them show dramatically increased height and weight. However, some authors report improvement in body composition. (c) The response in patients with chronic renal insufficiency is quite modest, with some not responding at all. (d) Growth hormone is not indicated in most patients with *SHOX* abnormalities, as their height is >–2.5 SDS. Not all patients with *SHOX* alterations and height <–2.5 SDS respond well and some develop pain in the wrists. (e) Pediatric endocrinologists are concerned about the high serum IGF-1 levels in patients with Turner syndrome under growth hormone therapy. Hence, potential side effects should be analyzed in the future. (f) Should we treat Noonan patients with mutations in the proto-oncogene *PTPN11*? Again, we will only know in the future. (g) Should we treat patients with ISS [47]? The door would be open to almost any child with SS, but is this correct?

Long-term hrGH therapy appears to be effective and safe in patients with GHD. The future will delineate the indications of its use, including new diseases and other skeletal dysplasias.

(1) hrIGF-1 therapy is approved for patients with severe primary IGF-1 deficiency. The number of patients is low. Long-term therapy with IGF-1 improves the adult height of patients with severe IGF-1 deficiency, although most patients do not experience sufficient catch-up growth to obtain a height in the normal range [48]. Hence, long-term IGF-1 therapy appears to be effective and relatively safe as a replacement therapy in children with SS due to severe IGF-1 deficiency. The same conclusions are presented in a recent paper reporting the European experience [49]. Backeljauw et al. [50] reported the first study to test the efficacy and safety of coadministration of hrGH and hrIGF-1 (45/150 μg/kg) in children with SS. Linear growth was significantly accelerated compared to hrGH alone, with a safety profile similar to the individual monotherapies. However, the results support the use of a combination of growth hormone and IGF-1 in selective cases and not universally [51].

(2) GnRH analogs together with hrGH could be effective in increasing adult height in GHD children [52]. A minimum of 2 years of continuous therapy is needed to see a meaningful increase in adult height.

It is still uncertain whether aromatase inhibitors could effectively improve adult height in early pubertal boys with GHD or ISS [52].

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