Idiopathic Short Stature: Diagnostic and Therapeutic Approach

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Case Report

Our clinical case for discussion is about a short statured boy who was 14.6 years old at his first evaluation. He was born after a 39-week gestation as the third child of a nonconsanguineous marriage. His birth weight was 3.250 g (−0.3 SDS), and his birth length was not available. His neuropsychomotor development was normal, his school performance was good, and there were no remarkable findings in his medical history. His father's height was 174 cm (−0.1 SDS) and his mother's height was 154 cm (−1.3 SDS), resulting in a target height of 170.6 cm (−0.6 SDS). His father and mother apparently had normal pubertal development, and his mother's age of menarche was 13 years old. His older brother's height was not available, but he had a previous history of pubertal spurt after 16 years of age. Likewise, his older sister's height was also not available, but she had a previous history of menarche at 14.

At the presentation, the height of the patient was 142.5 cm (−2.6 SDS), his weight was 29.4 kg (−3.9 SDS), his body mass index was 14.5 kg/m^2 (−3.1 SDS), and his sitting height was 73 cm (−0.3 SDS). Physical examination was unremarkable, without dysmorphic features. His pubertal staging was G2P1, as determined by Marshall and Tanner criteria. His bone age was 11 years old, as determined by Greulich and Pyle criteria. At this moment, his adult height prediction was 173.1 cm (−0.2 SDS), as determined by the Bayley–Pinneau method.

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Introduction

Growth is an essential process for the development of a healthy adult, and it is a sensitive marker of child health status. It comprises a dynamic, nonhomogeneous, and complex process of replication and differentiation of cells from several tissues. It is generally assumed that growth is regulated by a multitude of genetic and epigenetic mechanisms, which interact with influences from internal and external environments. With respect to genes, it is assumed that both adult height and growth pattern are largely genetically programmed [1].

Growth intensity differs depending on the stage of life, from intrauterine to adult life. During the prenatal period, growth velocity varies greatly according to gestational age, with a median growth of 1.2–1.5 cm per week. In late gestation, growth velocity takes on a process of deceleration that persists until pubertal onset. In the first and second years of life, children's growth velocity is, in average, 25 and 12 cm/year, respectively. After that, it decelerates gradually to an average of 4–6 cm/year until the pubertal spurt starts. During puberty, there is an acceleration of growth, and children can reach an average height velocity (HV) of 12 cm/year. Pubertal spurt onset time is dependent on the age children start puberty. Girls start a rhythm of growth acceleration in the early pubertal development, while boys start this same process in the late pubertal development [2, 3].

Growth disorders are associated with different diseases, which encompass different systems and mechanisms. Therefore, short stature is one of the most common concerns presented to pediatric endocrinologists and other child-caring physicians. Despite the complexity of the matter, some diagnoses can be obtained by a careful analysis of medical history and a comprehensive physical examination [3, 4].

In this chapter, we present referral criteria for children with short stature, diagnostic procedures to detect the causes of this condition, involved differential diagnosis, and possi-

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ble therapeutic approaches. Idiopathic short stature diagnosis and approach will be specifically emphasized.

Short Stature Diagnosis

Criteria for Investigation of Short Stature

Height has an almost perfect Gaussian distribution in large-scale growth studies. Therefore, the first key point in the diagnostic approach of children with short stature is the application of referral criteria for diagnostic workup. With this application we can distinguish if they are simply within the shortest part of the "normal" distribution or if they effectively are with a disorder restricting growth [1, 3].

In the initial evaluation of growth, there are basically three parameters that can be assessed. First, height can be compared with age and sex references and expressed as standard deviation score (SDS) or centile position. Height SDS is a measure of the deviation of the individual height from the mean and is expressed as the number of standard deviation below or above the mean height of the population for the same age and sex [5]. Therefore, by definition, individuals are defined as short statured when they present a height SDS < −2.0 or a height below the 2.3% percentile for a given age, sex, and population.

Second, height SDS can be compared with the sex-corrected parental height (target height) SDS [5]. The target height is a mathematical calculation, which expresses the genetic potential of height of an individual. It can be calculated by the arithmetic mean of parental height with the addition or subtraction of 6.5 cm for boys and girls, respectively [3]. Children should be referred for a diagnostic workup when he/she is "short for the target height," i.e., when the height SDS minus target height SDS is below −2.0.

Third, a longitudinal analysis of growth can be used, either expressed as height velocity (cm/year or SDS) in comparison to age and sex references or as a height SDS change (deflection or deviation) from the original SDS position (height SDS change is the difference in height SDS between two measurements, preferably 1 year apart from each other) [5]. A growth deflection (or a "crossing" of height percentiles) is defined as a height SDS decrease >1 SD and should also be considered abnormal requiring further evaluation.

Diagnostic Approach

Short stature can be the presenting symptom or the suggestive symptom of numerous conditions and diseases. There are different classifications for its differential diagnosis, but most of them include three main groups: primary short stature (skeletal abnormalities), secondary short stature, and short stature without recognizable cause (Tables 16.1 and 16.2). The latter group includes the diagnosis known as idiopathic short stature (ISS).

Clinical evaluation starts with a detailed medical and family history and a thorough physical examination (Table 16.3). A key point is a detailed description of the child's growth pattern, including the time when the growth deficit was first observed. Birth characteristics must be evaluated (gestation and delivery conditions or complications; gestational age, birth weight, length and head circumference). This information is important to distinguish short children in two groups by the onset of the growth impairment: short stature with prenatal or postnatal onset. Medical history must be investigated, with a focus in neuropsychomotor development, nutritional status, medication use, and cardiac, renal, pulmonary, and gastrointestinal diseases. Evaluation of a child's height must take into account the familial patterns of growth and puberty [3–5].

Physical examination should be complete, including the description of anthropometric measurements, facial and body dysmorphic features, and any other clues for one of the many causes of short stature. In children younger than 2 years of age, supine length, weight, weight-for-length, and head circumference will be measured, and fontanelles as well as dentition should be evaluated. In older children, erect height, weight, body mass index (BMI), head circumference, arm

Table 16.1 Differential diagnosis in short stature

Primary short stature—Skeletal abnormalities
With recognizable skeletal dysplasia (achondroplasia, hypochondroplasia)
Without recognizable skeletal dysplasia (turner syndrome, heterozygous *NPR2* and *SHOX* defects)
Secondary short stature
Malnutrition
Psychosocial deprivation
Chronic diseases
Renal (renal failure, tubular acidosis, nephrotic syndrome)
Intestinal (celiac disease, intestinal inflammatory disease)
Hematological (chronic anemia)
Cardiac
Pulmonary (cystic fibrosis)
Endocrine
Hypothyroidism
Disorders of the GH/IGF-1 axis
Cushing's syndrome
Pseudohypoparathyroidism
Rickets
Short stature without recognizable cause
Intrauterine growth retardation without recognizable cause (small for gestational age with failure of catch-up growth)
Idiopathic short stature
Familial short stature
Constitutional delay of growth and puberty

NPR2 natriuretic peptide receptor 2, *SHOX* short stature homeobox, *GH* growth hormone, *IGF-1* insulin-like growth factor type 1

Table 16.2 Disorders of the GH/IGF-1 axis

GH deficiency
Idiopathic
Acquired (craniopharyngioma, pituitary tumors, autoimmune diseases, granulomatous diseases, central nervous system infections, post-radiotherapy, head trauma)
Genetic
GH secretion (*GH1* and *GHRHR* genes).
Pituitary cell differentiation (*POU1F1* and *PROP1* genes).
Pituitary development (*HESX1*, *GLI2*, *LHX3*, *LHX4*, and *SOX3* genes).
Bioinactive GH
GH1 gene mutation.
GH insensitivity
Primary
Laron syndrome (*GHR* gene defect).
Associated with immunodysfunction (abnormalities of GH signal transduction, e.g., *STAT5B* gene defect).
Secondary or acquired (anti-GH antibodies, malnutrition, liver disorders, diabetes mellitus poorly controlled, uremia)
Ternary complex defects (IGF-1/IGFBP-3/ALS)
Acid-labile subunit deficiency (*IGFALS* gene).
Defects on proteolytic cleavage of IGFBPs (*PAPPA2* gene).
IGF deficiency
IGF1 gene mutation.
IGF2 gene mutation (paternal allele).
Bioinactive IGF-1
IGF1 gene mutation.
IGF-1 insensitivity
IGF1R defects and post-receptor defects.

GH growth hormone, *IGF-1* insulin-like growth factor type 1, *IGFBP-3* insulin-like growth factor binding protein 3, *ALS* acid-label subunit, *IGFs* insulin-like growth factors

span, and sitting height (SH) should be measured [3, 5]. In the latter, the pubertal staging has to be evaluated, as determined by Marshall and Tanner criteria [6, 7]. Evaluation of a child's height must be done in the context of normal standards for sex and age with the international data at hand. Such standards can be either cross-sectional (by calculation of height SDS) or longitudinal (by plotting in growth charts). Serial measurements with a minimum interval of 6 months are necessary to determine the height velocity. Because genetic factors are important determinants of growth and height, all children should be assessed considering siblings and parents. For that purpose, the parental target height is calculated and expressed as mentioned above. When a child's growth pattern clearly deviates from that of parents and siblings, the possibility of an underlying pathology should be considered [2].

Many abnormal growth states are characterized by disproportionate growth, which is strongly suggestive of skeletal dysplasia. Therefore, body proportion measurements should be part of the evaluation of short stature. We recommend the use of sitting height-height ratio (SH-H) for age and sex, which can also be expressed in SDS, according to published standards [8]. This ratio allows for the observation of body proportion changes throughout development.

Table 16.3 Specific diagnostic findings and key points in medical history and physical examination of children with short stature

Findings and key points	Interpretation and application
Medical history	
Birth length, weight, head circumference, gestational age	Classification as SGA or AGA
Previous growth data	Height velocity and growth pattern analysis
Age at start of pubertal signs	Early, normal, or delayed puberty
Previous diseases, surgeries, and medication use	Organic or iatrogenic causes
Medical history of the various systems	Search for chronic and systemic diseases
Feeding and nutrition history	As example, silver–Russell and Prader–Willi syndromes can lead to feeding difficulties
Neuropsychomotor development delay and/or intellectual disability	Syndromes, chromosomal disorders, metabolic disorders
Consanguinity If short stature is diagnosed in other family members, it is indicated to draw the family pedigree	To assess disorders with autosomal dominant or recessive inheritance
Parental height (measured)	To estimate the target height
Parents' age at the start of puberty	To assess likelihood of a familiar pattern of delayed puberty
Physical examination	
Length or height SDS	Severity of growth deficit
Body proportions (sitting height-total height ratio SDS; arm spam)	Altered sitting height-height ratio is suggestive of skeletal dysplasia
Weight-for-height or BMI showing underweight	Weight more affected than height, low weight-for-height and low BMI are suggestive of malnutrition
Weight-for-height or BMI showing overweight or obesity	Hypothyroidism, Cushing's syndrome, GH deficiency, pseudohypoparathyroidism
Head circumference SDS	Microcephaly and macrocephaly are important findings, indicating potential diagnosis
Dysmorphic features	Syndromes
Pubertal stage	Early, normal, or delayed puberty
General physical exam	Search for chronic and systemic diseases

SGA small for gestational age, *AGA* adequate for gestational age, *BMI* body mass index, *GH* growth hormone

Children with short stature and an increased SH-H ratio for age and sex have a disproportional short stature caused by limb abnormalities, while children with short stature and a decreased SH-H ratio for age and sex have a disproportional short stature caused by axial segment abnormalities [8] (Fig. 16.1).

It is assumed by most groups that a radiograph of the left hand and wrist is a useful adjunct. On this radiograph, bone age can be determined by comparison with the normal age and sex-related standards published by Greulich and Pyle [9]. Skeletal maturation can be used to predict adult height.

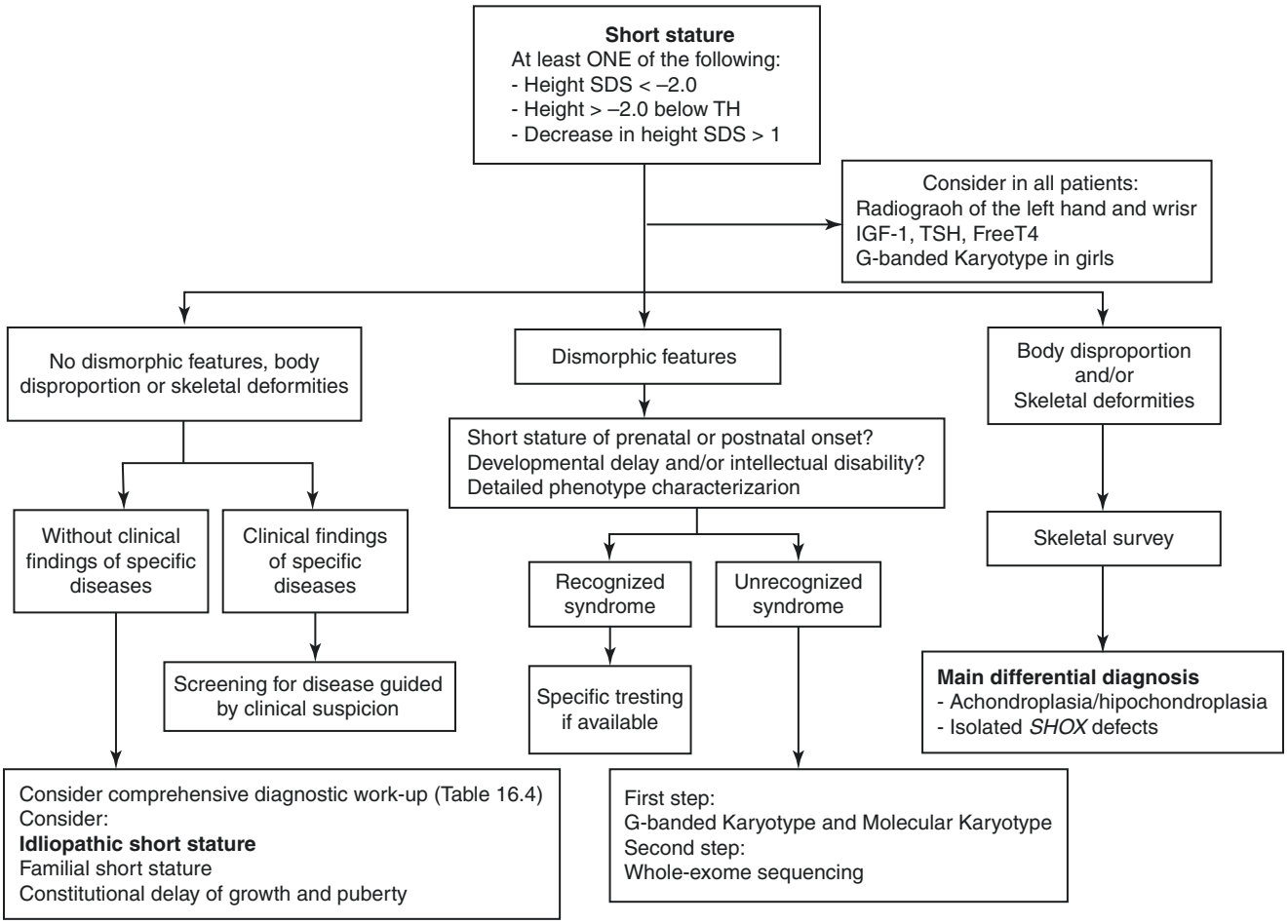

Fig. 16.1 Diagnostic approach in children with short stature. (*SDS* standard deviation score, *TH* target height, *IGF*-1 insulin-like growth factor 1, *TSH* thyroid-stimulating hormone, *SHOX* short stature homeobox)

The most commonly used method for height prediction is the Bayley and Pinneau method [10]. We also consider the measurement of serum concentrations of IGF-1 and TSH/free T4 as initial screening tests for most patients, due to the importance of these hormonal axes to normal growth. Besides the aforementioned, it is generally advised to request initially a karyotype in short girls, even in the absence of typical signs of Turner syndrome [4, 5] (Fig. 16.1 and Table 16.4).

Depending on specific clinical clues at medical history and physical examination, special investigations are required. When skeletal dysplasia is suspected, skeletal survey analysis is indicated for a more precise diagnosis, including the following parts: skull, spine, pelvis, upper limb, and lower limb (Fig. 16.1) [11]. Likewise, when dysmorphic features are suggestive of syndromic causes, diagnostic investigations have to prioritize them. When a specific syndrome is recognized by clinical evaluation, the patient should be specifically tested. On the other hand, if no syndrome is clinically recognizable, patients with short stature associated with dysmorphic features should undergo genetic testing, including molecular karyotyping (single nucleotide polymorphism array or array-comparative genomic hybridization) and whole-genome sequencing [12, 13].

When initial clinical evaluation does not point to a specific diagnosis, including absence of dysmorphisms, body disproportion, or skeletal deformities in physical exam, the diagnostic workup may include tests for a wide group of diseases that can be associated with short stature [5, 14] (Fig. 16.1 and Table 16.4).

One of the most important parameters to be evaluated is the growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis. There are several defects that affect this axis (Table 16.2); among them, growth hormone deficiency (GHD) is the most prevalent. However, the latter is responsible for only 5% of short stature cases.

Laboratorial investigation of GHD is made by direct and/or indirect analysis of the GH secretion. The direct analysis is made by provocative tests (also called stimulation tests), and pharmacological ones are the most appropriate [15]. The most important tests are insulin, clonidine, arginine, and glucagon, which are comparable in terms of sensitivity and

Table 16.4 Most common laboratorial, radiographic, and genetic tests in diagnostic workup of patients with short stature

Exam	Objective (to detect or exclude)
Initial screening tests to be considered in all patients	
Radiograph of the left hand and wrist	Bone age
IGF-1	GH/IGF-1 axis disorders, poor nutritional status
TSH and free T4	Thyroid disorders
Karyotype in female patients	Turner syndrome
Diagnostic workup tests to be considered in patients depending on their clinical evaluation	
Blood cell count, erythrocyte sedimentation rate	Anemia, infections, chronic inflammatory diseases
Albumin, ferritin	Poor nutritional status
AST, ALT, γGT	Chronic liver diseases
Creatinine, sodium, potassium, venous blood gas analysis, urinalysis	Renal disorders, renal tubular acidosis[a]
Calcium, phosphate, alkaline phosphatases	Calcium/phosphate disorders
IgA-anti-endomysium antibodies, IgA-anti-tissue transglutaminase antibodies and total IgA	Celiac disease
GH and IGFBP-3	GH/IGF-1 axis disorders
Skeletal survey analysis (skull, spine, pelvis, upper limb, and lower limb, in two views)	Skeletal dysplasias
Molecular karyotyping (aCGH or SNParray)	Chromosomal copy number variants
Whole-exome sequencing	Pathogenic mutations (monogenic disorders)

IGF-1 insulin-like growth factor type 1, GH growth hormone, TSH thyroid-stimulating hormone, Free T4 free tetraiodothyronine, IGFBP-3 insulin-like growth factor binding protein 3, aCGH array-comparative genomic hybridization, SNParray single nucleotide polymorphism array

[a]Renal tubular acidosis should be excluded in children younger than 4 years old with short stature and difficulty in gaining weight

specificity. The choice of a test to provoke GH secretion is dependent on the center experience and on the test availability. A substantial number of healthy short statured children without GHD may have an inadequate response to one test. Because of this, two provocative tests must be made for GHD diagnosis [15] (Fig. 16.2). A technical topic related to provocative tests is the use, or not, of sexual steroid priming. It is well known that the peak of GH level after a stimulation test is higher if the patient has been recently exposed to sex steroids. Clinical practice guidelines suggest that priming should be used mainly in children with pubertal delay, in order to prevent unnecessary GH treatment of children with constitutional delay of growth and puberty [15].

The indirect analysis of the GH secretion is made by serum concentrations of IGF-1 and insulin-like growth factor binding protein 3 (IGFBP-3). Both of them are directly related to GH action and are used as screening tests to select short statured children for GHD diagnostic tests. The IGF-1 and IGFBP-3 serum levels vary with age, sex, and pubertal staging [16, 17]. When the hormonal diagnostic is established, a hypothalamic–pituitary magnetic resonance imaging (MRI) is requested for anatomical evaluation (Fig. 16.2).

It is noteworthy to highlight that recently several genomic approaches have been transforming the diagnostic investigation of growth disorders in an attempt to identify monogenic etiologies of short stature phenotype [18, 19]. These approaches include mutational analysis of candidate genes, large-scale genome-wide association studies, molecular karyotyping, and whole-exome sequencing. This technological development is revealing novel causes of short stature, involving hormone signaling, paracrine factors, matrix molecules, and intracellular pathways [20]. Consequently, some authors are now proposing a new conceptual framework for understanding growth disorders, with a diagnostic classification centered on epiphyseal growth plate [21].

In this "genomic approach" context, the selection of patients for genetic testing should take into account several factors and key points that increase the likelihood of a monogenic etiology for short stature: the severity of growth failure, the presence of associated clinical features, the familial segregation (family members with similar phenotype), and consanguinity [18, 20]. Besides the etiology definition of growth retardation, the genetic testing approaches may be valuable tools for genetic counseling and future therapies [20].

Case Report Evolution and the Diagnosis of Idiopathic Short Stature (ISS)

Continuing our clinical case discussion, we can conclude that the boy met the referral criteria to initiate diagnostic workup: height SDS −2.6 (<2.5) and height below target height (difference of 2.0 SD). Skeletal maturation analysis showed a significant bone age delay (chronological age of 14.6 years with a bone age of 11 years). Serum concentrations of IGF-1 and IGFBP3 were both < −2.0 SDS. As the patient presented a proportional short stature (SH-H SDS of −0.3), skeletal survey analysis was not performed. Likewise, as he did not present dysmorphic features, karyotype or other diagnostic investigations for specific syndromic causes were not necessary. Additional laboratory analyses, including TSH, free T4, blood cell count, erythrocyte sedimentation rate, creatinine, sodium, potassium, calcium, phosphate, alkaline phosphatase, venous blood gas analysis, ferritin, albumin, AST, ALT, γGT, IgA-anti-endomysium antibody, and urinalysis analysis, were all normal. As such, a clonidine test was performed, but the GH peak after the pharmacological stimulus was 17 μ/L, ruling out GHD.

At this moment, we had excluded the most recognizable diseases associated with short stature, and we formulated a hypothesis of idiopathic short stature (ISS). The term ISS does

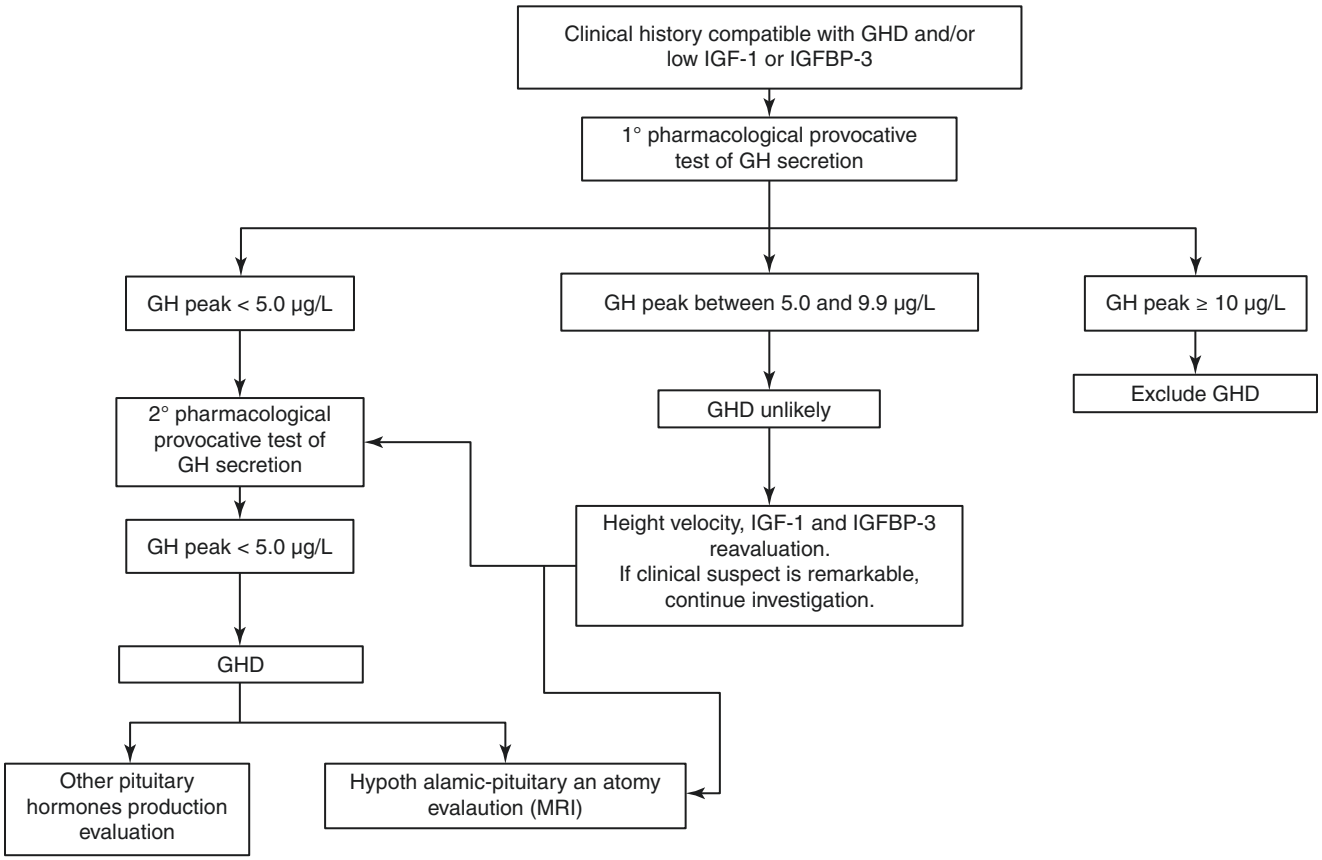

Fig. 16.2 Investigation protocol of children with suspected GHD. (*GH* growth hormone, *GHD* growth hormone deficiency, *IGF*-1 insulin-like growth factor type 1; *IGFBP*-3 insulin-like growth factor binding protein 3, *MRI* magnetic resonance imaging)

not reflect an exactly defined diagnosis. It is usually used for children whose shortness compared to age-matched normal population cannot be attributed to specific diseases [22]. According to the Consensus Statement on the diagnosis of ISS, "it is defined as a condition in which the height of an individual is more than 2 SDS below the corresponding mean for height for a given age, sex and population group, without evidence of systemic, endocrine, nutritional or chromosomal abnormalities; it describes a heterogeneous group of children consisting of many presently unidentified causes of short stature" [4]. It is estimated that 60–80% of all short children presented to pediatric or endocrinological evaluation can be labeled according to this definition. ISS can be subcategorized. The main distinction is between children with a familial history of short stature (familial short stature, FSS) and those children who are short for their parents (nonfamilial short stature, non-FSS) [4]. In FSS, children are short compared with the relevant population but remain within the expected target range for the family. In non-FSS, children are short for the population as well as for the target range. In addition, ISS children can also be subcategorized according to the age of puberty onset, presenting a constitutional delay of growth and puberty (CDGP). The diagnosis of CDGP is based on lack of breast development by the age of 13 in girls and testicular volume <4.0 ml by the age of 14 in boys (Tanner stage 2), absence of other identifiable causes of delayed puberty, delayed bone age, as well as spontaneous and complete achievement of pubertal development during follow-up [1].

In the presenting case, we could classify the patient with a nonfamilial proportional short stature of postnatal onset. And, because he presented a remarkable bone age delay and a delayed puberty, the most appropriate hypothesis was CDGP. The patient was evaluated every 6 months, when the auxological data were repeatedly measured (Fig. 16.3). He started puberty at the age of 15. His bone age was 12 years and at that time height velocity increased from 3.7 to 5.1 cm/year. The peak height velocity was 8.8 cm/year, observed at 16.5 years old and pubertal staging G4P3 (Fig. 16.4). At 17.5 years old, his height was 165.3 cm (−1.4 SDS), his bone age was 14.5 years, his pubertal staging was G5P5, and his adult height prediction was 174.3 cm (0.0 SDS). At 20 years old, he reached his final height (or adult height) in 170 cm (−0.7 SDS) (Figs. 16.3 and 16.4).

The abovementioned case report is a common example in clinical practice. It brings out two important points in the management of patients with ISS. First, ISS is not a diagnos-

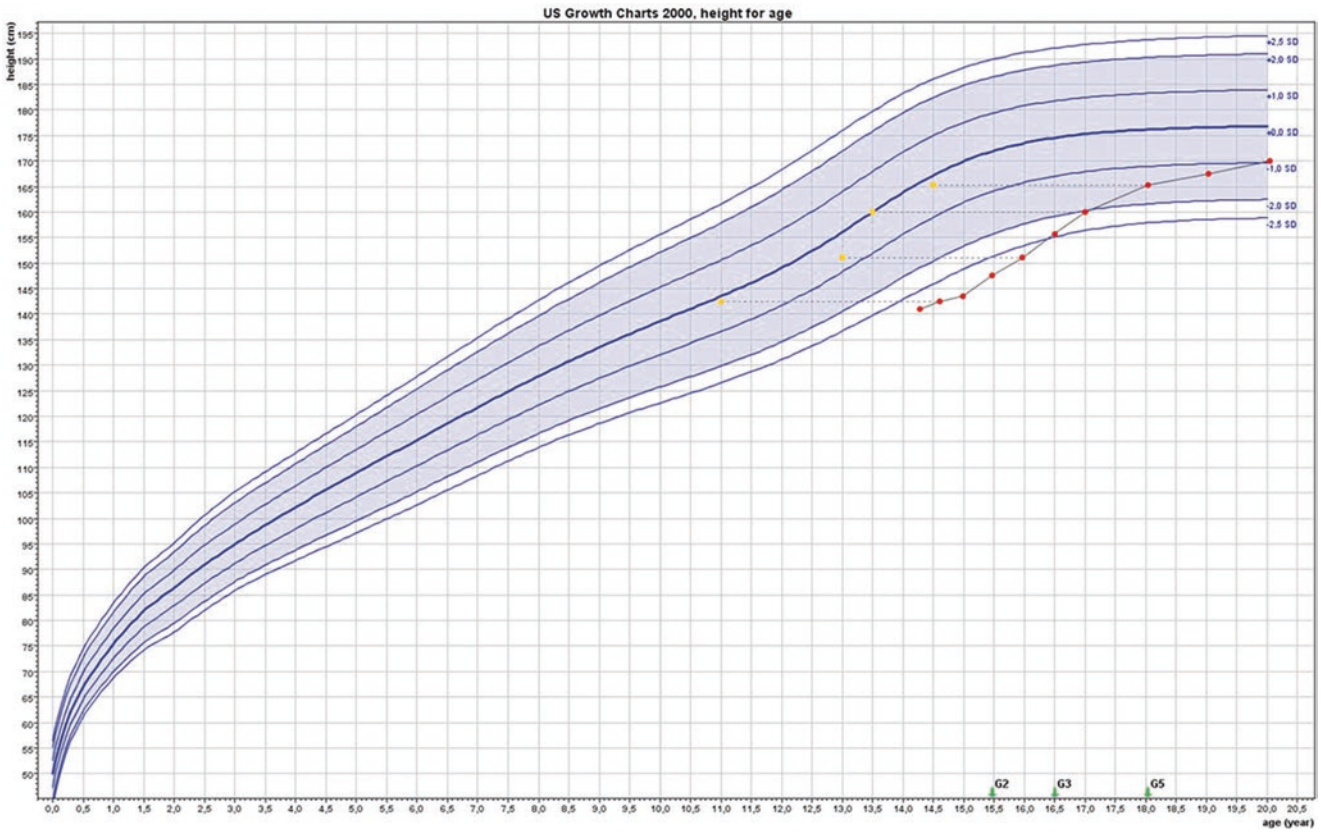

Fig. 16.3 Height for age growth chart of the patient presented. (*Red marks* = height measures in follow-up visits; *yellow marks* = bone age as determined by Greulich and Pyle criteria; G2, G3, and G5 = pubertal stages 2, 3, and 5, respectively, as determined by Marshall and Tanner)

tic entity in terms of etiology or pathogenesis. It is a term used to describe such forms of growth failure that cannot be attributed to any known cause of short stature and are usually considered normal variants of growth [22]. Secondly, the choice whether using growth-promoting therapies or not has to take into account the natural history and the growth pattern of children with ISS.

Several studies have been published about the natural history of ISS. In most of them, it is assumed that FSS and CDGP are different. Children with FSS tend to be younger at presentation of short stature, reach an adult height SDS similar to the initial height SDS, and reach the target height more precisely than the predicted adult height. Conversely, children with CDGP tend to be older at presentation and reach an adult height SDS higher than initial height SDS and more compatible with predicted adult height based on bone age [1, 22].

In an important study evaluating the spontaneous adult height in ISS, Ranke et al. found that 67% of children with FSS reached adult height within the normal range, whereas 81% of children with CDGP reached it as well. As a group, only 5% of children with ISS did not reach an adult height above −2.0 SDS, thus becoming short adults. Moreover, 10% of children with ISS did not reach an adult height within the range of their target height. In clinical observation of the natural history of ISS, there are three main indicators of a poor adult height outcome: younger age at presentation, lower target height, and lower predicted adult height at presentation (as measured by BP method) [22]. Once aware of the spontaneous growth pattern of children with ISS, growth-promoting therapies to improve final height are no longer widely justified.

Present Therapies for Short Stature

When a specific disease is known to be the cause of growth retardation, the treatment of this condition is considered the best therapy for short stature. Current available treatments, used for different causes of short stature, are recombinant human GH (rhGH), recombinant human IGF-1 (rhIGF-1), gonadotropin-releasing hormone analogs (GnRHa), and aromatase inhibitors.

The rhGH is the main hormonal treatment of short stature and is accepted as a safe and effective therapy up to now. Presently, according to the US Food and Drug Administration (FDA), the indications for its use are GHD, small for gestational age (SGA), Turner syndrome, Prader–Willi syn-

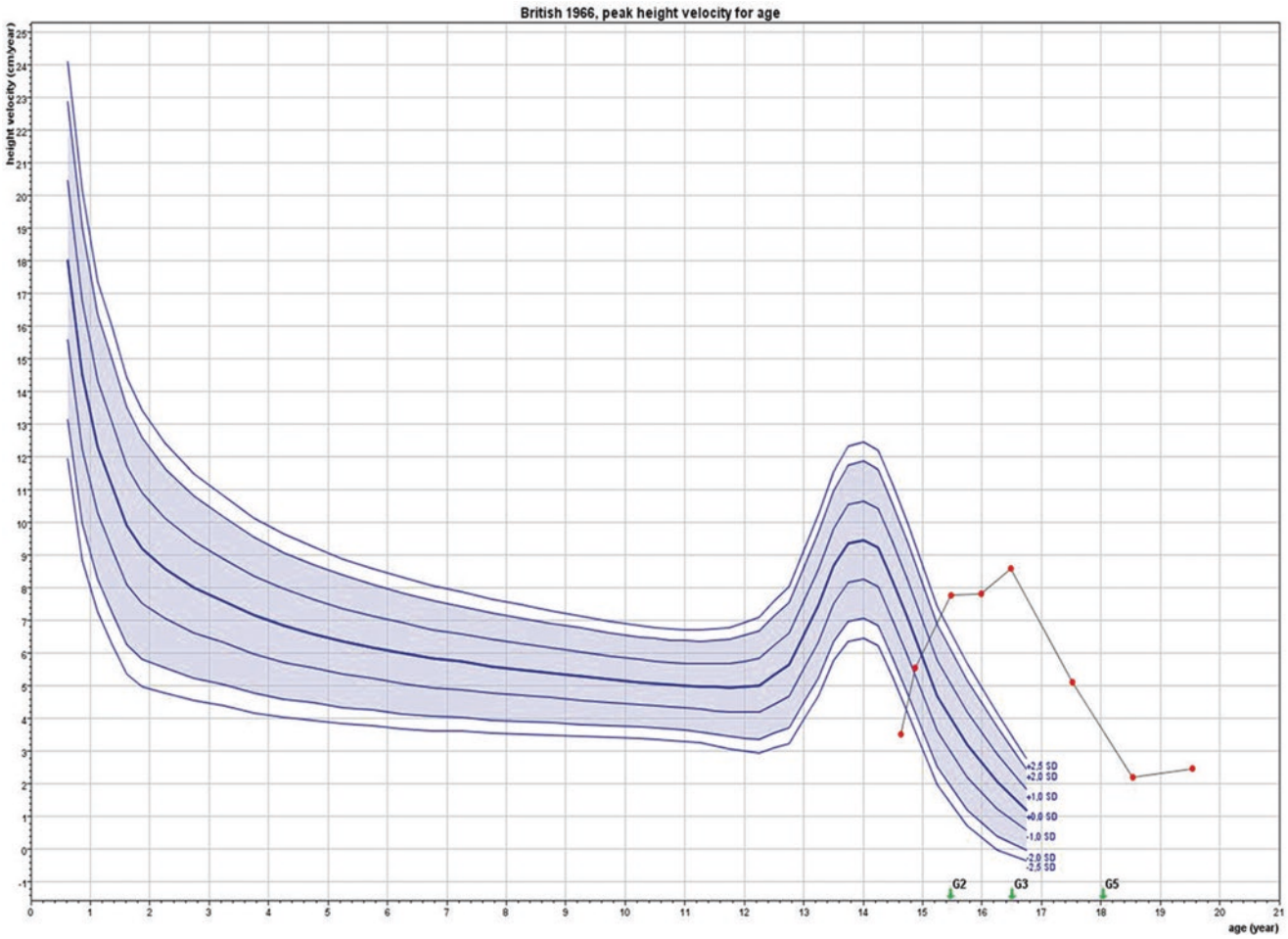

Fig. 16.4 Height velocity for age growth chart of the patient presented. (*Red marks* = height velocity measures in follow-up visits; G2, G3, and G5 = pubertal stages 2, 3, and 5, respectively, as determined by Marshall and Tanner)

drome, chronic kidney disease, *SHOX* gene haploinsufficiency, Noonan syndrome, and ISS. According to the European Medicines Agency (EMA), indications are the same, except for Noonan syndrome and ISS, which are not included. Several studies assessed different variables which can influence final height after rhGH therapy in children with different conditions. Duration of treatment, height at the start of treatment, bone age delay, height at puberty onset, midparental height, and first year of treatment growth velocity were positively correlated, whereas age at the beginning of treatment had a negative correlation [2, 15].

GHD is the most accepted indication for rhGH treatment. In these cases, the reposition of physiological doses of GH (33 μg/kg/day) allows for growth normalization and should be initiated as soon as the diagnosis is established [15]. Children with severe GHD have higher height velocity in initial treatment and greater height gain in overall treatment than other causes of short stature. When initiated early, GH reposition results in adult height close to target height [23].

The use of rhGH to increase adult height in ISS is controversial. Most studies indicate that height velocity increases in short term and that final height gain is modest, with a mean increase of 4 cm [24]. Studies about the natural history of ISS show that most children become normal adults with adequate stature outcome, even without treatment [22]. In addition, in children with ISS, there is a great interindividual variability in the response to GH therapy, and there are no effective tools to predict the individual response. The treatment has a high cost and is not completely free of adverse effects. Most studies do not show sufficient evidence with respect to safety and psychosocial benefits in this condition [25]. For these reasons, in recent clinical practice guidelines, Grimberg et al. suggest that GH treatment for ISS patients should be made on a case-by-case basis after assessment of physical and psychological burdens and discussion of risks and benefits [15] with the family and the patient, if possible [25].

Besides rhGH, alternative growth-promoting therapies have been assessed in ISS as well as in other causes of short

stature. Some studies evaluated the use of GnRHa, with or without concomitant GH in short stature. Those that kept the agonists for 3 or more years showed a modest final height gain in children with GHD, ISS, and SGA [26–28]. However, the consequences of its use in long terms are still unclear.

The use of aromatase inhibitors has also been evaluated in boys with short stature. They are capable of inhibiting the conversion of testosterone in estradiol and thus enhancing height potential by delaying epiphyseal fusion while promoting linear growth [29]. Initial questions about bone health are still not completely elucidated. Despite that, trials in CDGP boys and ISS pubertal boys show promising results with a well-tolerated and safe use [29–31].

Recombinant human IGF-1 is the treatment of choice in children with primary or secondary forms of GH insensitivity, and its use is recommended to increase height in these conditions [15].

Last but not least, we should take into account the importance of ethical aspects on growth promotion and the challenge to resist cosmetic endocrinology. The advent of recombinant human GH brought the narrative of "GH for height," meaning "increasing height gain and attainment in children who are short for reasons other than GHD," mostly in ISS children [25]. This narrative considers a psychosocial belief that "distress in short children is due to their shortness," which is biased, uncertain, and not proved by quality of life studies. In agreement with Allen [25], we believe that our responsibility is putting on the scale the most appropriate choice for these children: indicating them necessary treatments or protecting them from unnecessary ones.

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