

MANAGEMENT OF ENDOCRINE DISEASE

Diagnostic and therapeutic approach of tall stature

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Abstract

Tall stature is defined as a height of more than 2 standard deviations (s.d.) above average for same sex and age. Tall individuals are usually referred to endocrinologists so that hormonal disorders leading to abnormal growth are excluded. However, the majority of these patients have familial tall stature or constitutional advance of growth (generally associated with obesity), both of which are diagnoses of exclusion. It is necessary to have familiarity with a large number of rarer overgrowth syndromes, especially because some of them may have severe complications such as aortic aneurysm, thromboembolism and tumor predisposition and demand-specific follow-up approaches. Additionally, endocrine disorders associated with tall stature have specific treatments and for this reason their recognition is mandatory. With this review, we intend to provide an up-to-date summary of the genetic conditions associated with overgrowth to emphasize a practical diagnostic approach of patients with tall stature and to discuss the limitations of current growth interruption treatment options.

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Introduction

Height is a classic example of human trait that exhibits a normal (Gaussian) distribution within each sex, age and ancestry. Standard deviation score (SDS), or Z-score, is a well-established method used to analyze and represent height according to a specific population (1). Tall stature

is usually defined as a height above 2 standard deviations (s.d.) from mean height for a specific population or also as a height above 2 s.d. from mid-parental height SDS after excluding factors that could have negatively affected the stature of the parents. Statistically, the first definition

Invited Author's profile

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includes 2.3% of the population, but the referrals for tall stature are not as frequent as expected. This could be explained by the fact that most cases are familial and therefore do not concern physicians, parents and patients. Additionally, tall stature has a wider social acceptance than short stature. More extreme cases, with height SDS above 2.5 or 3 (which would comprise approximately 0.6 and 0.1% of the population respectively) are more often referred for clinical investigation, usually due to problems with social adjustment and/or to concerns about the increased possibility of diseases associated with growth disorder. It is interesting to consider that as height SDS is dependent on the origin of the population, a given height s.d. can differ among countries. According to World Health Organization (WHO) data, height s.d. of 2 and 2.5 in adults are equivalent to respectively, 191.1 and 194.8 cm in men and 176.2 and 179.5 cm in women (2). Height s.d. of 2 and 2.5 for different countries are described in [Supplementary Table 1](#) (see section on [supplementary data](#) given at the end of this article).

Factors involved in global regulation of gene expression, cell cycle control and growth plate development have critical roles in linear growth (3, 4). The main endocrine factors that regulate growth are GH/IGF-1 axis and sex steroids, each one of them having more importance in a specific period of life (5). During pregnancy, fetal

growth is influenced by nutritional status, insulin and IGF system. In the first years of life, nutritional status still has an important impact on growth. GH/IGF1 axis has a major role during childhood growth and sex steroids during puberty. There are far more secondary conditions that cause growth impairment than conditions that cause overgrowth. Consequently, genetic influence is expected to be proportionally higher on tall than short stature, both for syndromic and non-syndromic disorders.

Subjects with tall stature are usually referred for evaluation during childhood or adolescence, but some individuals first seek medical assistance in adulthood. Depending on the timing of clinical presentation and patient phenotype, the investigation has particularities. In this review, we will discuss the main differential diagnoses, the clinical approach and a diagnostic work-up of patients with tall stature and revise the current knowledge about growth interruption treatment.

Differential diagnosis

Tall stature results from a generalized overgrowth condition. There are disorders associated with segmental overgrowth (6), but this issue is beyond the scope of this review. The differential diagnosis of tall stature is complex given the diversity of rare

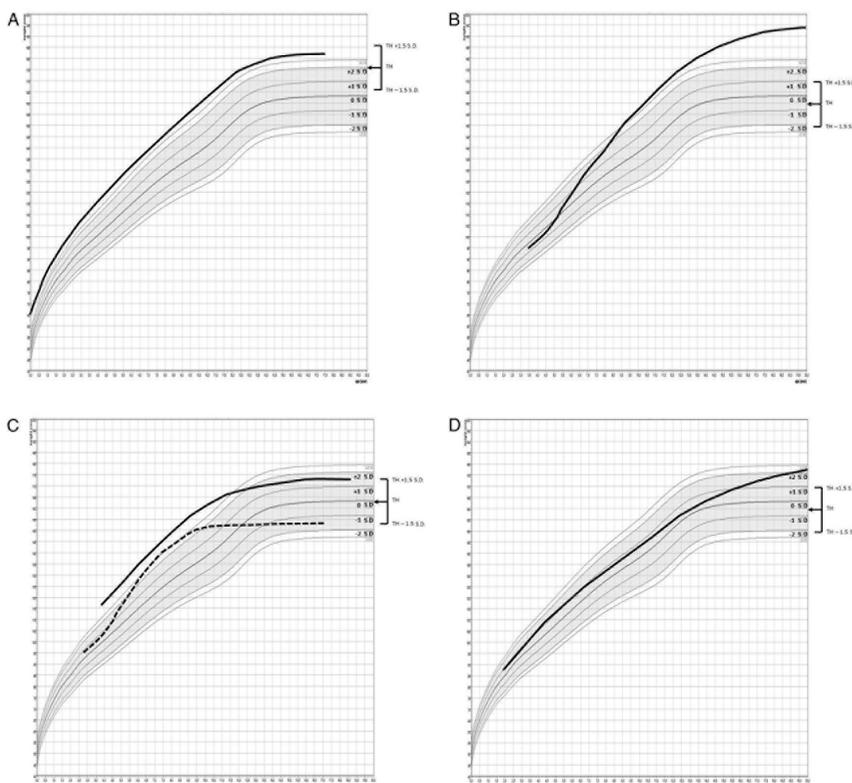


Figure 1

Representative growth chart of the main patterns observed in individuals with overgrowth conditions: (A) a patient that grows above 2 s.d. throughout childhood and reaches an adult height above 2 s.d., but consistent with his/her target height; (B) a patient that crosses through higher percentiles during childhood, reaching an adult height above 2 s.d. and above his/her target height; (C) a patient that has tall stature during childhood, but has an accelerated bone maturation and reaches a normal adult height (solid line) or even a stature below the normal range in adulthood (dashed line) and (D) a patient with normal height during childhood who has a prolonged growth beyond adolescence, resulting in an adult height above 2 s.d.

conditions that can cause height above 2 s.d. and their variable presentations.

There are four main growth patterns observed in children with tall stature. The first one is seen in children who are above 2 s.d. in height and grow remaining in the same percentile (Fig. 1A) (7, 8, 9). The second pattern is seen in children who cross upwards percentiles during childhood and/or puberty (Fig. 1B) (10), reaching an adult height above 2 s.d. Another pattern is observed in children who are above 2 s.d. during childhood but have an accelerated bone maturation and reach an adult height between -2 and 2 s.d. or even a stature below -2 s.d. in adulthood (Fig. 1C) (11, 12, 13). Lastly, there are children with height between -2 and 2 s.d. during childhood, who have a prolonged growth beyond adolescence, resulting in an adult height above 2 s.d. (Fig. 1D) (14). In addition to growth patterns, patients with tall stature can also be sorted according to the presence/absence of syndromic features or according to their size at birth.

Tall stature causes can be classified conforming to these characteristics (Table 1).

As height and pubertal development are human traits with a high heritability (15, 16), it is expected that a significant proportion of tall individuals have genetic variants responsible for the observed phenotype. Consequently, it is essential for physicians who evaluate patients with tall stature to be aware of the genetic conditions associated with overgrowth (see below and Supplementary material).

A monogenetic disorder is usually identified in patients with tall stature associated with a syndromic condition. Various genetic defects and molecular genetic mechanisms are associated with syndromic overgrowth. Chromosome imbalance can cause excessive growth due to the disruption of genes that negatively regulate growth, as observed in some cases of Sotos syndrome (12) (MIM 117550) and Beckwith–Wiedemann syndrome (17) (MIM 130650). In addition, partial trisomy can cause tall stature because of an increase in the copy number of genes that

Table 1 Main conditions to consider in the differential diagnosis of tall stature.

Diagnosis	Large for gestational age	Dysmorphic features	Intellectual disability	Adult height	MIM
Familial tall stature	Yes	No	No	Tall stature	N/A
Obesity	No	No	No	Normal	601665
Precocious sex-steroids exposure	No	No	No	Short stature	*
Precocious puberty					*
Virilizing disorders					
Prolonged growth by delayed fusion of growth cartilage	No	Mild	No	Tall stature	
Hypogonadism					*
Aromatase deficiency					613546
Estrogen resistance (<i>ESR1</i> mutation)					615363
Supernumerary sex chromosome aneuploidies	No	Mild	Variable	Tall stature	N/A
Klinefelter syndrome					N/A
Triple X syndrome					
Homocystinuria	No	Yes	Yes	Tall stature	236200
Beckwith–Wiedemann syndrome	Yes	Yes	No	Normal/upper limit	130650
Marfan syndrome	No	Yes	No	Tall stature	154700
Sotos syndrome	Yes	Yes	Yes	Normal/upper limit	117550
Weaver syndrome	Yes	Yes	Yes	Tall stature	277590
Fragile X-chromosome syndrome	No	Yes	Yes	Normal/short stature	300624
<i>IGF1R</i> duplication	Yes	Yes	Yes	Tall stature	N/A
Growth hormone excess	No	Yes	No	Tall stature	*
Epiphyseal chondrodysplasia, Miura type (CNP / NPR-B)	Yes	Mild	No	Tall stature	615923
CATSHL syndrome (<i>FGFR3</i>)	Yes	Yes	Yes	Tall stature	610474
Bannayan–Riley–Ruvacaba syndrome	Yes	Yes	Yes	Normal	153480
Simpson–Golabi–Behmel syndrome	Yes	Yes	Variable	Tall stature	312870
Lujan–Fryns syndrome	No	Yes	Yes	Normal/upper limit	309520
Congenital contractural arachnodactyly	No	Yes	No	Tall stature	121050
Sclerosteosis	No	Yes	No	Tall stature/upper limit	269500

N/A: non-available.

*Several entries.

positively regulate linear growth: *SHOX* (18), *NPPC* (19) and *IGF1R* (20). Loss-of-function point mutations in estrogen receptor alpha (*ESR1*) or *CYP19A1* cause estrogen resistance (MIM 615363) and aromatase deficiency (MIM 613546) (21) respectively. Both conditions are associated with delayed epiphyseal closure and prolonged growth period, resulting in tall stature. On the other hand, gain-of-function point mutations in growth promoter genes, such as natriuretic peptide receptor type B (*NPR2*), lead to overgrowth by upregulating mechanisms that control growth of epiphyseal cartilage (MIM 615923) (22). Additionally, there are several genetic defects extrinsic to growth plate, such as those associated with pituitary GH-secreting tumors, precocious puberty and hypogonadism, that also contribute to the genetic basis of overgrowth.

However, the majority of individuals with tall stature are healthy and non-syndromic. The height of these tall individuals can be partially explained by the combination of several common variants in a typical polygenic effect. Nevertheless, the ability to predict tall stature using several polymorphisms identified in genome-wide association studies about height is limited (12.25% of tall stature phenotype explained by 182 SNPs) (23). The area under the receiver-operating characteristic (ROC) curve for prediction of tall stature using 182 height-associated SNPs is inferior than the area obtained using the traditional approach of predicting adult height by mid-parental height (0.76 vs 0.84) (23). It is possible that taking into account the genetic interaction between SNPs and/or the addition of other genetic variants and haplotypes can improve our ability to predict non-syndromic tall stature. Alternatively, part of these patients may also have monogenic conditions, representing a milder form in the spectrum of classical disorders (24).

The main conditions associated with overgrowth will be briefly characterized below. Less common causes are described in the Supplementary material.

Familial tall stature

Familial tall stature comprises non-syndromic children who are above 2 s.d. since infancy, growing through the same percentile and reaching a tall adult height (Fig. 1A) (7). There is no abnormal growth velocity and height SDS minus target height SDS is less than 2, without dysmorphic features or pubertal disorders. Therefore, it is a diagnosis of exclusion. It is the most common diagnosis among people with tall stature (25, 26).

Endocrine causes

GH/IGF-1 excess

GH excessive production during adult life leads to acromegaly and, when it happens before epiphyseal closure, clinical presentation is pituitary gigantism (Fig. 1B). Most referrals of tall stature to endocrinologists have the objective of ruling out this diagnosis. Children with gigantism have an abnormally high growth velocity, tall stature, symptoms found in acromegaly, such as hyperhidrosis and acral enlargement and symptoms due to direct tumor effect, like headache and visual impairment (27). Serum IGF-1 is the recommended screening approach, with a lack of suppression of GH to $<1 \mu\text{g/L}$ within 2h after 75g of oral glucose as the confirmation step (28). Patients with gigantism usually have macroadenomas, about 50% of which are invasive. The majority of them develop hypopituitarism, mainly after surgery or radiotherapy, affecting specially the gonadal axis, which may increase even more their adult height if not adequately treated (10). A recent study has shown that 46% had an identifiable genetic condition, in descending order of prevalence: *AIP* gene, Xq26.3 microduplications (X-linked acrogigantism), McCune–Albright syndrome, Carney complex and *MEN1* gene (10).

Precocious exposure to sex steroids

Sex steroids play an important role in pubertal spurt. Estrogen not only enhances growth hormone secretion during puberty but also speeds up chondrocytes senescence in growth plate, leading to its fusion (Fig. 1C, dashed line) (29). Androgens also mediate growth spurt in part through their conversion to estrogen and also through their own action in the growth plate (5). Normal pubertal timing seems to be changing, but it is still defined as above 8 years in girls and 9 years in boys (13). Children with precocious puberty or virilizing disorders, such as congenital adrenal hyperplasia, have an increased growth velocity and height SDS compared to their peers, but at a cost of advanced bone age and short stature in adulthood if not recognized in time for appropriate treatment (13, 30).

Prolonged growth due to delayed fusion of growth plate

It comprises a heterogenous group of diseases, including hypogonadism, aromatase deficiency and estrogen resistance. As the opposite from precocious puberty, those patients do not have a growth spurt due to the absence

of or resistance to sex steroids. Growth rate is slow but, as the epiphyseal plate fusion is delayed, these patients keep growing into adulthood, developing tall stature with eunuchoid proportions (increased arm span and upper-to-lower segment ratio) only later in life (Fig. 1D) (5).

Hypogonadotropic hypogonadism can be isolated or occur concurrently with other pituitary deficiencies. When it is congenital, cryptorchidism and micropenis can raise suspicion after birth. It is important to search for anosmia as a clue for Kallmann syndrome (MIM 308700), and affected relatives can present only with an impaired sense of smell (31). Aromatase deficiency (MIM 613546) is a rare autosomal recessive disorder. Affected males have no major findings but tall stature and insulin resistance, whereas females have genital ambiguity, poor breast development, multicystic ovaries and infertility (21, 32, 33). Both genders show low bone density and biochemically boys have normal testosterone levels, normal to increased FSH levels and undetectable estrogen levels. As the placenta is a tissue partially derived from the embryo, mothers can develop virilization during pregnancy of affected children because of the placental inability to convert androgens synthesized in fetal adrenal glands to estrogen (21, 32, 33). Estrogen resistance (MIM 615363) shares a similar phenotype, except for no maternal virilization during pregnancy or in affected girls (32).

Thyrotoxicosis

Hyperthyroidism is an uncommon condition during childhood. Many signs and symptoms in children are the same as in adults, like weight loss, goiter, tachycardia and ocular involvement (34). Regarding growth, an increased height velocity rate and advanced bone age are observed but, as a large number of affected children are in early-to-mid puberty, the evaluation of the isolated effect of thyroid hormone excess on height is compromised (34, 35, 36). However, in a limited number of prepubertal children, thyrotoxicosis had the same effect on growth. Rarely children are above 2 SDS for height in this condition. When adequately treated, their adult heights are within normal range, usually above 0.54 to 0.63 s.d. from target height SDS (34, 35, 36).

Obesity

Although obesity and tall stature are not related in adults, there is an important association between them during childhood. Several studies have shown that obese children

are taller than their normal-weight-matched controls by a mean of 4–5 cm, and the age when this difference reaches its maximum varies between genders and among studies. Those patients show an accelerated growth with advanced bone age and early puberty in comparison with their pairs, resulting in a decreased growth velocity earlier during adolescence, and no significant difference in adult height between overweight/obese and normal-weight subjects (37, 38). Obesity probably influences growth through hormonal pathways, such as GH/IGF1/ghrelin/insulin and leptin/GnRH, but the exact mechanisms of how these neuroendocrine hormones relate to promote growth are still unknown (39).

Constitutional advance of growth (CAG)

Constitutional advance of growth is the opposite development pattern in relation to constitutional delay of growth, and it can be associated, although not exclusively, with obesity. It has been suggested that CAG could predict late onset of childhood obesity in non-obese children (40). Affected children have an abnormally high growth velocity from birth to age 4 years, when they become tall. From 5 to 9 years of age, growth velocity is maintained at 97th percentile and it drops to 50th percentile after that (7). Puberty is often earlier in those children, suggesting that CAG could be a spectrum of idiopathic precocious puberty (40). It has been shown an increase in IGF-2 levels and a higher IGFs/IGFBPs molar ratio prior to puberty, a possible mechanism of tall stature in children with CAG (41).

Syndromic causes

Supernumerary sex chromosome aneuploidies

Klinefelter syndrome: The most frequent chromosomal aneuploidy in males (1.1–1.7 cases per 1000 births), Klinefelter syndrome is associated with hypergonadotropic hypogonadism, small testes, gynecomastia, tall stature and learning disabilities (42). Beside these characteristics, patients with Klinefelter syndrome have a higher risk of developing breast cancer, metabolic syndrome and type 2 diabetes (42). Diagnosis can be easily achieved by a 47,XXY karyotype or variations. During childhood, patients present with disproportionate tall stature due to longer legs, probably because of a third copy of *SHOX* gene (43). This effect is nonlinear, and it has been demonstrated that males carrying 5 or more copies of sex chromosomes are actually shorter than expected (44). During adolescence, as

a result of delayed bone maturation due to hypogonadism, those patients can grow even taller.

Triple X syndrome: Triple X syndrome has an incidence of 1/1000 female births and remains an underdiagnosed condition due to lack of exuberant physical findings. Affected girls can present with mild ocular hypertelorism, epicanthal folds, pes planus and 5th finger clinodactyly (45, 46, 47). Height is normal until the age of 4, and they become taller because of longer legs, reaching a stature in the upper limit of the normal range or mildly above 2 s.d. (45). Fertility is not an issue, although premature ovarian failure has been reported in some cases. Learning disabilities, especially regarding expressive language, are also present, and many girls are diagnosed during an investigation for developmental delay (47). Diagnosis is achieved by a 47,XXX karyotype with or without mosaicism. As seen in males, females carrying 4 or more copies of sex chromosomes are also shorter than expected (44).

Monogenic forms

Marfan syndrome: Marfan syndrome (MIM 154700) is a cause of disproportionate tall stature often remembered by clinicians, although height is not a criterion for diagnosis. As Marfan syndrome causes aortic root aneurysm that can lead to rupture and death, it is important to be aware of this differential diagnosis. Disease-specific growth charts were developed in the United States and South Korea and both show mean heights above the 95th percentile for general population by the age of 2–3 years (Fig. 1A) (8, 9). It is an autosomal dominant disease caused by a mutation in *FBN1* gene, which encodes fibrillin-1. This protein is found in the extracellular matrix of cartilage and around 25% of affected patients harbor a *de novo* mutation (48). According to the revised Ghent criteria (2010), in cases with a family history of the syndrome, presence of *ectopia lentis* (subluxation of the lenses) or aortic root dilation ($Z \geq 2$ s.d. above 20 years or $Z \geq 3$ below 20 years) or a systemic score ≥ 7 points are sufficient for diagnosis. When there is no family history, the necessary criteria are (a) presence of *ectopia lentis* and a *FBN1* mutation known to cause aortic root dilation or (b) presence of aortic root dilation and *ectopia lentis* or a systemic score ≥ 7 points or a *FBN1* mutation. The systemic score includes phenotypic characteristics such as wrist and thumb signs, scoliosis, *pectus carinatum* and facial features (49) (Supplementary Table 1).

Sotos syndrome: Sotos syndrome (MIM 117550) patients have birth length above 95th percentile and birth

weight often is less affected. Height continues above 2 s.d. until puberty, when there is a tendency toward the mean, which leads to adult height often in the upper limit of normal range (Fig. 1C, solid line). Approximately 75% of patients have an advanced bone age. Macrocephaly is a striking feature present since birth and is accompanied with a broad range of learning disabilities and variable abnormalities in cranial imaging (12). Facial features include frontal bossing, down-slanting palpebral fissures, pointed chin and dolichocephaly; cardiac and renal abnormalities may also occur (50). Sotos syndrome is mainly caused by haploinsufficiency of *NSD1* gene. Most mutations are *de novo*, although there are few reports of autosomal dominant transmission. *NSD1* product is suggested to be a histone methyltransferase that could positively or negatively affect the transcription in different cells (51). There are other syndromes with clinical overlap with Sotos syndrome, commonly referred as ‘Sotos-like’ or Sotos syndrome 2 and 3 (Supplementary material).

Beckwith–Wiedemann syndrome (BWS): BWS (MIM 130650) is an overgrowth syndrome in which there is an increased occurrence of embryonal tumors, such as Wilms tumor and hepatoblastoma, especially until the age of 8 years. The most common features are macroglossia, abdominal wall defects and neonatal hypoglycemia due to islet cell hyperplasia (52, 53). Newborns are macrosomic and children grow parallel or above the 95th percentile until around 8 years, with a fall in growth velocity after that. Therefore, adult height is usually in the upper limit of normal range (Fig. 1C, solid line) (11, 53). The majority of BWS cases are sporadic and associated with abnormal methylation at chromosome 11p15.5 or paternal uniparental disomy of the same region; less commonly, an autosomal dominant form of the syndrome can result from a mutation in *CDKN1C* gene in the maternal allele or from chromosomal deletions/duplications involving this locus (17, 53). In this chromosomal region, the maternal allele expresses *CDKN1C* gene, which encodes p57(KIP2), an important regulator of cell cycle progression (54). In contrast, the paternal allele expresses *IGF2* gene that is positively involved in fetal growth. Case–control studies suggest an increased risk for BWS when conception is achieved by assisted reproductive technologies (55). Several score systems were developed to allow a clinical diagnosis, but no consensus was reached. Diagnosis is established by one of the clinical score systems or by the identification of alterations leading to an abnormal methylation in chromosome 11p15.5 along with clinical findings (53).

Homocystinuria: Homocystinuria caused by the deficiency of cystathionine β -synthase (MIM 236200) has

clinically overlapping features with Marfan syndrome, such as *ectopia lentis*, *pectus carinatum* and scoliosis. Three main differences are an autosomal recessive inheritance, the presence of intellectual disability and thromboembolism, which is the major cause of early mortality in homocystinuria (56). Osteoporosis can also occur in these patients. Diagnosis can be established by the presence of high serum concentrations of homocysteine, total homocysteine and methionine or an increased urinary homocysteine concentration. Furthermore, the diagnosis can also be achieved by the assessment of cystathionine β -synthase enzyme activity in fibroblasts or molecular testing of *CBS*, which encodes cystathionine β -synthase (56).

Fragile X syndrome: Classically, fragile X syndrome (MIM 300624)-affected boys show developmental delay, intellectual disability, abnormal behavior/autism spectrum disorder, prominent forehead and jaw, large ears, macroorchidism, mitral valve prolapse, strabismus and joint laxity (57, 58). Heterozygous girls can also exhibit these features, but in a milder presentation. Most studies related to growth patterns in fragile X syndrome evaluated only boys; growth velocity was higher during prepubertal period, but it decelerated after puberty, resulting in a normal height in adulthood (59, 60). However, other studies have shown growth curves that

were very similar to those seen in healthy children (61). It is a X-linked dominant syndrome caused by an expansion of CGG repeats beyond 200 in 5'UTR of *o* gene, leading to hypermethylation of this region and a diminished or even absent transcript (57).

Evaluation of children and adults with tall stature

Children with tall stature are usually referred to pediatric endocrinologists because of the possibility of GH excess or precocious exposure to sex steroids. Both conditions are associated with an increase in growth velocity, a height SDS that is frequently incompatible with parental height and specific clinical findings (Fig. 1B and C). Additionally, endocrinologists are also requested to evaluate adults with tall stature due to the possible association with hypogonadism (Fig. 1D). Overgrowth syndromes form a heterogeneous disease group with which it is necessary to have familiarity, especially because some of them have important implications for patients' follow-up and genetic counseling (49, 58). However, the two most frequently observed conditions in children referred for tall stature are anticipation of growth associated with obesity and familial tall stature, both of which are diagnoses of exclusion (25, 40). In two large series of tall stature patients, with a total of 638 children evaluated, pathologic causes of

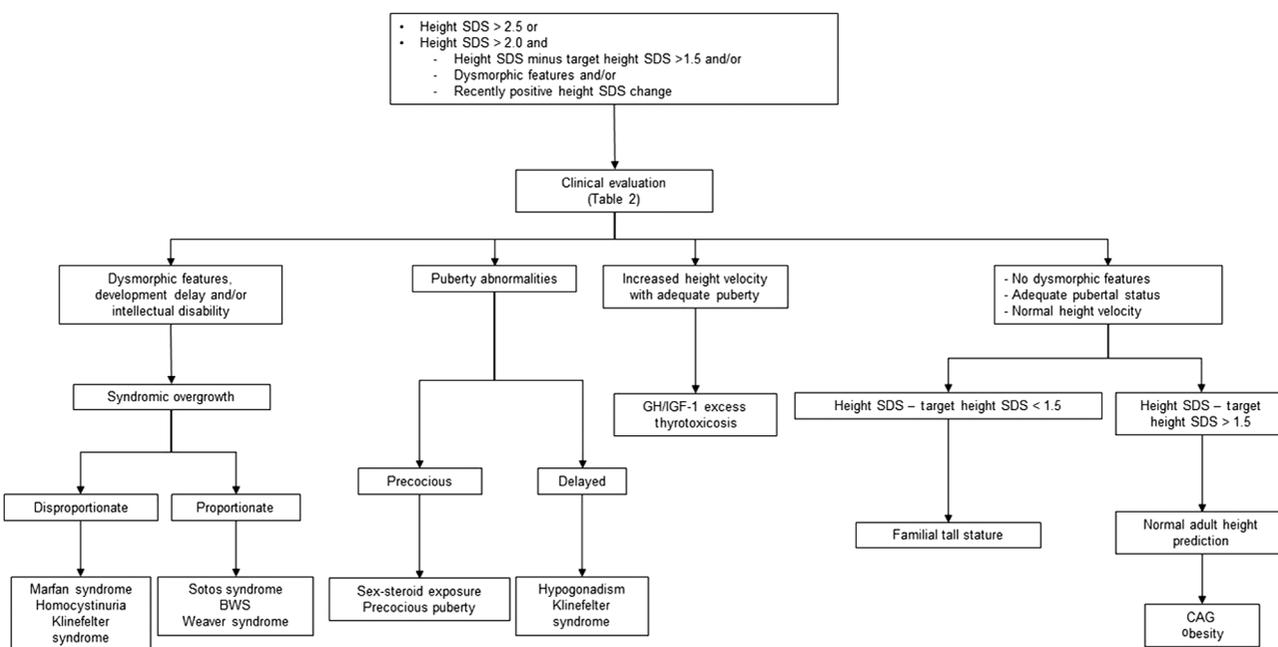


Figure 2

Suggested diagnostic flow chart for evaluation of patients referred for tall stature and the main differential diagnoses. (CAG=constitutional advance of growth; BWS=Beckwith–Wiedemann syndrome).

Table 2 Main clinical findings associated with tall stature and correlated disorders.

Key signs and symptoms	Disorders
Presence of consanguinity Family history suggesting an autosomal dominant inheritance of tall stature	Homocystinuria, sclerosteosis Familial tall stature, Marfan syndrome, epiphyseal chondrodysplasia and Miura type (increase of signal by CNP/NPR-B)
Developmental delay, intellectual disability and behavior problems Hearing loss	Homocystinuria, Sotos, CATSHL, Fragile X-chromosome, Bannayan–Riley–Ruvacaba, Weaver and Lujan-Fryns syndromes Sclerosteosis, CATSHL, Simpson–Golabi–Behmel and Sotos syndromes
Increased birth weight and length SDS for gestational age	Several syndromic tall stature conditions are associated with an increase in birth weight and/or length (Table 1)
Head circumference SDS	Macrocephaly is observed in Sotos, Bannayan-Riley-Ruvalcaba, Weaver, Lujan-Fryns, Simpson-Golabi-Behmel and Fragile-X syndromes Microcephaly is observed in CATSHL syndrome
Increased BMI SDS	Obesity can be associated with tall stature during infancy. Some syndromic overgrowth conditions are also characterized by obesity during infancy or adult age (like Weaver syndrome) Thyrotoxicosis
Sleep difficulties, hyperactivity, decrease in school performance, palpitations and weight loss Stare and lid lag, exophthalmos, goiter, tachycardia and tremor	
Dysmorphic facial features	Several syndromic forms of overgrowth conditions, each one with particular features (see text and supplementary material)
Presence of precocious secondary sexual characteristics	Precocious sex steroids exposure (precocious puberty, virilizing disorders) Several different causes; in males, mainly Klinefelter syndrome
Signs of hypogonadism (small testes, amenorrhea, underdevelopment of breast and body hair)	
Body disproportion (arm span that exceeds the height and/or sitting height: total height SDS < -2)	Klinefelter syndrome
Marfanoid habitus (arm span that exceeds the height, arachnodactyly and hyperlaxity)	Marfan, Sotos, Lujan-Fryns syndrome, Homocystinuria, Epiphyseal chondrodysplasia Miura type
Severe kyphoscoliosis	CATSHL syndrome, Epiphyseal chondrodysplasia Miura type
Campodactyly	CATSHL, Weaver syndrome

overgrowth were identified in approximately 9% of cases (25, 26). In both series, Marfan syndrome was the most frequently identified disease followed by supernumerary sex chromosome aneuploidies, precocious sex steroids exposure, Sotos syndrome and Beckwith–Wiedemann syndrome. A third study assessed 132 children referred for tall stature and a pathologic cause was identified in only 2 (1.5%) patients with precocious puberty (62).

There are no evidence-based recommendations on which patients should be evaluated for pathological causes of tall stature or on which is the best strategy to investigate them. Considering that the number of diseases that may cause tall stature is smaller than the number which may be responsible for short stature, a more conservative approach is reasonable. In general, children or adults who have height SDS > 2.5 should be clinically evaluated. Additionally, we also recommend the investigation of patients with height SDS minus target height SDS > 1.5 (63) and/or with a significant positive height SDS change and/or with dysmorphic features

compatible with known syndromes associated with tall stature (Fig. 2).

Clinical evaluation starts with a detailed medical and family history (Table 2). Birth weight and length should be assessed to classify tall children in two groups by the size at birth: adequate or large for gestational age (Table 1). An increased birth length is observed in several genetic conditions associated with overgrowth. Other key point is to determine if tall stature occurs in isolation or as part of a syndromic condition (Fig. 2). For this propose, medical history should focus on the presence of malformations and on neuropsychomotor development. Physical examination should be complete, including anthropometric measurements, an evaluation of facial and body dysmorphic features and a search for any other clues for one of the main causes of tall stature (Table 2).

Complementary diagnostic tests should be individualized for each patient depending on the clinical findings and taking into account the possible differential diagnoses. An X-ray of the non-dominant hand should

Table 3 Complementary diagnostic tests that can be useful during investigation of a patient with tall stature.

Exam	Objective
X-ray of non-dominant hand	Bone age determination, which is important to predict adult height. Advanced bone age is often observed in patients with Sotos and Beckwith-Wiedemann syndrome, precocious sex steroids exposure, constitutional advance of growth and obesity. Delayed bone age is observed in hypogonadism conditions, aromatase deficiency and estrogen resistance.
Serum IGF-1	Screening for growth hormone excess
Serum TSH, free-T4	Screening for hyperthyroidism
LH, FSH, Testosterone/Estradiol levels	For evaluation of precocious sex steroids exposure or hypogonadism
Serum homocysteine	Screening for homocystinuria mainly in patients with Marfanoid habitus, consanguineous parents and intellectual disability
Karyotype	Assessment of chromosome aberrations (i.e. Klinefelter syndrome, 47 XYY, 47 XXX) or CAIS
Echocardiogram	Assessment of congenital cardiac defects (i.e. Sotos syndrome) and aortic root dilation (i.e. Marfan syndrome)
Ophthalmologic evaluation	Assessment of <i>ectopia lentis</i> (i.e. Marfan syndrome and homocystinuria)
Analysis to the trinucleotide repeat region of <i>FMR1</i>	To confirm or exclude the diagnosis of Fragile X-chromosome syndrome
<i>FBN1</i> sequence	To confirm or exclude the diagnosis of Marfan syndrome in patients with suggestive clinical findings
Submicroscopic copy number variation analysis (SNP or CGH array)	To identify submicroscopic copy number variation, mainly in patients with unexplained developmental delay/intellectual disability, autism spectrum disorders and multiple congenital anomalies
Target high throughput sequence (whole exome or gene panel sequence)	To simultaneously investigate the presence of pathogenic variants in several genes associated with tall stature, especially in patients with high suspicion for genetic causes

SNP, single nucleotide polymorphism; CGH, Comparative genomic hybridization; CAIS, complete androgen insensitivity.

be used to evaluate the skeletal maturity of tall children and adolescents and is useful to predict adult height. It is important to consider that the available methods for adult height prediction are imperfect as Bayley–Pinneau method may overestimate adult height, whereas Tanner–Whitehouse Mark 1 and 2 may overestimate or underestimate it depending on bone age (64, 65). The main complementary diagnostic tests that can be useful during an investigation of a patient with tall stature are shown in Table 3.

As several causes of tall stature have a genetic basis and molecular genetic tests are becoming more available and less expensive, it is expected that these tests will be more frequently used to assist with the diagnosis of tall stature patients. Presently, the diagnosis of genetic conditions associated with tall stature is performed based on clinical, laboratory and imaging findings. When a syndromic diagnosis is made based on the patient phenotype, genetic testing is targeted for a particular gene or genetic defect and mainly serves to confirm the diagnosis (candidate gene approach) (66) (Table 3). Genetic tests become especially important in mild or atypical cases in which the clinical diagnosis is difficult. However, the diversity of genes involved in overgrowth conditions, the

rarity of these diseases and the considerable variability in phenotypes may hamper a diagnosis based only on clinical findings or on a candidate gene approach. In this scenario, a genomic approach offers an advantage in the assessment of several genes at once and has become an important tool to establish a precise diagnosis (67).

Chromosomal microarray is a well-established first-tier diagnostic test in patients with unexplained developmental delay/intellectual disability, autism spectrum disorders and multiple congenital anomalies (68). Single-nucleotide polymorphisms (SNP) or comparative genomic hybridization (CGH) arrays are also useful tools to investigate patients with syndromic overgrowth of unknown cause that have the above characteristics. Whole exome sequencing (WES) derived from targeted massively parallel sequencing allows searching for pathogenic allelic variants throughout all coding and splice-site regions in virtually all known genes. Several novel genes involved in overgrowth conditions were recently identified through WES (Supplementary Table 2) (69, 70, 71). WES was proved to be a useful and powerful tool to establish the diagnosis of complex conditions (72, 73). In the years to come, with increased access to these techniques, it is possible to expect an improvement in the establishment of the diagnosis of overgrowth patients.

Treatment

When families seek medical assistance for their children because of tall stature, their most frequent concern is that their excessive stature may cause difficulties regarding their social life. In general, families tend to worry more about tall girls than tall boys and, when treatment for overgrowth was initially proposed, intervention was recommended for girls even when their predicted height was only 10 cm above average (74). Presently, tall stature has less influence in social acceptance and treatment to cease growth is less frequently sought (74). There are no evidence-based guidelines available on whether to treat or not and on which medication to use. Currently, the decision on whether to intervene or not to cease growth is based on the prediction of adult height. Children with a predicted adult height above 2 SDS can be considered for treatment, although a more conservative cut-off point above 2.5 or 3 SDS is preferred (75, 76, 77).

As predicted adult height is a crucial point for intervention, it is necessary to have reliable methods to assess this parameter. Equations to predict adult height were developed within groups of healthy children with normal stature, except for the Tanner–Whitehouse Mark 2, which included a group of tall girls. There are few studies assessing specifically which prediction method is the most reliable in children with tall stature. Overall, Bayley–Pinneau method usually overestimates adult height, especially when the bone age is less than 9 years, whereas Tanner–Whitehouse Mark 1 and 2 can overestimate adult height when bone age is less than 9 years, but underestimate it when bone age is higher. Generally, the prediction error is around 3 cm in boys and 2 cm in girls (75). Thus, both methods offer a reasonably accurate mean prediction and can be used in clinical practice, although major errors can occur in an individual basis (64, 65, 75, 78).

When indicated, specific treatment could lead to better height outcomes, like somatostatin analogs for GH excess, GnRH analogs for central precocious puberty and sex steroids for hypogonadism. However, in the majority of patients with tall stature, it is not available.

Sex steroids were the most studied and used off-label treatment to cease growth. The rationale is the closure of the epiphyses, caused mainly by estrogen, as seen in precocious puberty and other forms of early exposure to sex steroids. In boys, supraphysiological doses of testosterone result in an initially increased growth velocity, probably due to an increase in GH and IGF-1

levels caused by androgens (75, 79). In girls, high doses of estrogen, mostly synthetics, decrease growth velocity and were used to achieve a mean height reduction between 2.1 and 10 cm (65, 75). A recent retrospective study using 17 β -estradiol has shown an adult height reduction around 1.6 \pm 2.1 cm (26). Studies comparing high and low doses of ethinylestradiol have demonstrated that low doses such as 100 μ g per day are sufficient to reduce adult height in girls (65, 80, 81, 82, 83). The best outcomes were achieved in girls who were treated when their bone age was equal to or below 12 years (65, 81, 82, 83, 84, 85, 86). Tables summarizing different treatment regimens studied in boys and girls are available in the Supplementary material.

Few studies assessed satisfaction with sex steroid treatment retrospectively (76, 78, 87). Although two studies showed only about 7% of dissatisfaction in treated patients, the largest one, comprising around 400 women in each treated and untreated groups, has shown that 99.1% of untreated and 57.9% of treated women were satisfied with this decision. The dissatisfaction in the treated group was mostly not related to the achieved adult height, but was instead caused by the small difference between actual and predicted adult height, by side effects during the treatment or concerns about its long-term consequences and by the lack of participation in the decision process of whether to be treated or not (87).

Currently, sex steroids are no longer widely recommended to cease growth due to their short- and long-term consequences. In the short term, boys treated with androgens may present with myalgia, acne, gynecomastia and weight gain, whereas girls treated with high doses of estrogen may have weight gain, night cramps, galactorrhea, ovarian cysts and predisposition to thrombosis (75, 76). Long-term studies in boys have shown a slight increase in FSH levels, a significant decrease in testosterone levels, although still within normal range and a lower testicular volume, without impairment in fatherhood (76, 88, 89, 90). The long-term side effects in girls are more concerning as it was documented that in adulthood they have more fertility problems. One study showed that around 16.5% of treated women had follicular-phase FSH above 10 IU/L and decreased levels of inhibin B and AMH before 40 years, revealing a diminished follicle reserve (91, 92, 93). Considering these findings along with the failure in demonstrating a better psychological wellbeing in adult women treated during childhood, sex steroids should not be routinely prescribed to halt growth in a healthy child (94).

Other treatment approaches, such as bromocriptine and pirenzepine, have been evaluated but had little effect on adult height (95, 96). Somatostatin analogs have shown to cause a modest height reduction. One promising study with long-acting lanreotide demonstrated a mean height reduction of 3.8 cm; however, this treatment is still considered experimental (97, 98). Pegvisomant, a GH receptor antagonist, has not yet been studied as a growth reduction treatment in patients with tall stature without GH excess. No new clinical therapy has been evaluated since 2009.

Percutaneous epiphysiodesis is a surgical procedure in which the epiphysis of a long bone is attached to its diaphysis to cessate growth. It can be done in distal femur and proximal tibia, promoting mean height reductions of 4 cm in girls and 6–7 cm in boys. It has been shown to be safe in the short term, but should only be considered in children with an extremely tall predicted adult height (above 3 SDS) and should be performed in a center with expertise (99, 100).

Drug strategies tested to interrupt linear growth rely either on GH/IGF-1 axis or on puberty, but not on growth plate only. Future possibilities include drugs not yet tested on humans or used for other diseases. Recently, it has been shown that estrogen promotes growth plate fusion in female mice through estrogen receptor α (ER α) (101), and the same result was demonstrated earlier in ER α knockout male mice (102). Selective estrogen receptor modulators (SERM) have been studied *in vitro* (tamoxifen) (103) and in animal models (raloxifene) (104), and they successfully ceased growth. In another example, retinoids are commonly used to treat cancer and skin problems, such as acne and hyperkeratotic disorders. Several reports in children exposed to retinoids have shown premature epiphyseal closure, mainly in lower limbs, with consequent development of short stature, usually around 4–5 years after a high-dose treatment (105, 106, 107). Those findings were supported by animal models of hypervitaminosis A in rats and of use of retinoids in guinea pigs, showing a direct effect in epiphyseal plate (108). However, children under retinoids treatment can develop hyperostosis, with ligament and tendon calcifications in vertebrae and other bones, limiting movement, among other severe side effects. For these reasons, retinoids have not been evaluated in children with tall stature. However, these examples could be an inspiration for the development of new therapeutic strategies that act on growth plate-exclusive pathways, like a growth plate-specific SERM, a NPR-B antagonist or a FGFR3 agonist.

Conclusion

Tall patients are commonly referred to endocrinologists to rule out GH excess or other hormonal disturbances affecting growth. Although most of these patients have an anticipation of growth or a familial trait with no major consequences, it is important to have in mind the differential diagnoses, especially those associated with medical problems, such as aortic aneurysm, thromboembolism and tumor predisposition. In recent years, our knowledge on the genetic basis of overgrowth conditions has increased considerably. Novel molecular genetic techniques, such as exome sequencing, began to be incorporated into the evaluation of syndromic conditions, including those associated with overgrowth. This is expected to improve the etiological diagnosis and to fasten medical knowledge progress, bringing medicine to a new level. Treatment options to cease growth are still limited and should be discussed thoroughly with patients and families before being used in a healthy child.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-16-1054>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as influencing the impartiality of the research reported.

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