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ADVANCES IN PEDIATRICS

Tall Stature in Children

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Keywords

• Familial • Constitutional • Pathologic • Bone age • Growth hormone • Estrogen • Testosterone • Percutaneous epiphysiodesis

Key points

- Most tall children are healthy and simply have a familial tendency to tallness.
- Bone age determination is useful in the differential diagnosis of the various causes of tall stature and prediction of adult height of an individual.
- Children with constitutional and familial tall stature rarely require therapeutic intervention.
- Hormonal administration of estradiol or testosterone to children should be used with caution and only if the benefits outweigh the risks.

INTRODUCTION

Tall stature in children is arbitrarily defined as a height greater than 2 standard deviations (97.7%) more than the mean height for a population of the same sex, age, and race [1–5]. By definition, 2.3% of children have tall stature [3]. Stature is determined by the complex interaction of genetic, hormonal, nutritional, and

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environmental factors [3,5,6]. The growth hormone (GH)–insulinlike growth factor-1 (IGF-1) axis is only 1 of many regulatory systems that control chrondrogenesis in the growth plate and ultimate adult height [7]. Many other hormones such as thyroid hormone, glucocorticoids, estrogens, and androgens regulate linear growth [7]. In some cases, genetic mutations may lead to tall stature [7]. Familial tall stature is the most common cause of tall stature, followed by constitutional tall stature. Many pathologic conditions, although uncommon, also present with tall stature. Some of these conditions are associated with severe comorbidities. It is, therefore, important to distinguish tall children who are otherwise healthy from those who have underlying pathology [4]. Furthermore, excessively tall stature, especially of girls, can cause serious psychological problems. Tall individuals may also experience backache or other musculoskeletal complaints.

MEASUREMENTS OF GROWTH

The child should stand straight, with the back of the head, back, buttocks, and heels touching a firm vertical structure such as the vertical bar of a stadiometer, with shoes off and interfering hair accessories removed [8]. The horizontal measuring bar of the stadiometer should be lowered to level with the child's head to obtain the measurement [4]. Alternatively, a firm object can be placed at a right angle on the top of the head and against the wall above the head for the measurement to be made. A child younger than 3 years of age should be measured on a firm horizontal platform that contains an attached yardstick, a fixed head plate, and a movable foot plate [8]. The child's feet should be held steady while the measurement is made [4].

The growth charts that have been widely used are those published by the World Health Organization (WHO) as well as those published by the Centers for Disease Control and Prevention and National Center for Health Statistics (CDC/NCHS) [9]. The former are based on a pooled sample from 6 participating countries (Brazil, Ghana, Oman, India, Norway, the United States [California]) where children are raised under optimal environmental conditions (ie, economically advantaged, breastfed infants, and children of nonsmoking mothers), whereas the latter are based on large surveys of multiethnic populations for children living in the United States [9,10]. The WHO standards define a pediatric population that is leaner and taller than the CDC/NCHS standards [9]. The CDC and the American Academy of Pediatrics (AAP) recommend using the WHO growth charts for children younger than 2 years and the CDC/NCHS growth charts for children older than 2 years [11]. Because there are significant differences in growth rates, adult heights, and age of onset of puberty among different ethnic groups, it would be of great advantage to use standards based on ethnicity, whenever possible, for the child being assessed [6,12]. Unfortunately, such standard growth charts are not always available for every ethnic group.

In addition to the height and weight, careful and precise measurement of arm span (distance between tips of the middle fingers with the arms raised and

stretched to a horizontal position) and upper/lower segment ratio is important in the physical examination [1]. The lower body segment can be determined by measuring the distance from the symphysis pubis to the floor with the child standing erect against a wall [1]. The upper body segment value can be obtained by subtracting the lower body segment value from the child's height. The upper/lower segment ratio is then derived by dividing the upper segment value by the lower segment value. For North American children, the upper/lower segment ratio is approximately 1.7 at birth [4]. With growth of the limbs, the ratio declines gradually to 1.25 at around 3 years of age and to 1 at around 14 years of age, with little change thereafter [13]. In adult black individuals, the upper/lower segment ratio is approximately 0.85 to 0.9, as blacks have relatively long limbs. On the other hand, Asian children have shorter limbs and therefore have a higher upper/lower segment ratio [14]. Children with proportional overgrowth such as familial tall stature, constitutional tall stature, exogenous obesity, precocious puberty, Soto syndrome, Weaver syndrome, and fragile X syndrome have a normal upper/lower segment ratio [4,11]. On the other hand, children with Klinefelter syndrome, Marfan syndrome, and homocystinuria have disproportionally long lower extremities and therefore have a decreased upper/lower segment ratio [11].

CAUSES AND CLINICAL MANIFESTATIONS

Familial tall stature

Familial or genetic tall stature is the most common cause of tall stature [1,2,15,16]. These children are usually tall from early infancy, grow along the same percentile and reach a correspondingly tall adult height [3]. These children have a high normal growth rate and otherwise normal findings on physical examination. The height age is greater than bone age, which is compatible with the chronologic age [1,17]. These children have tall parents. Comparing the growth of the patient and the parents on a growth chart reveals that the tall stature is appropriate for that family.

Constitutional tall stature

Constitutional tall stature, also known as constitutional advancement of growth, is the second most common cause of tall stature [4,15,18]. Children with constitutional tall stature have normal length at birth. The growth velocity accelerates in early childhood and the tall stature is usually evident by the age of 2 to 4 years [1,19]. The growth velocity slows down after the child reaches 4 or 5 years. The growth curve is parallel to and above the normal curve, and the child grows along this percentile until puberty [11,19]. The height age corresponds to the slightly advanced bone age and is greater than the chronologic age [11,17]. Pubertal development usually begins in the early range of normal, and final adult height is often in the upper range of normal [11,17]. There is usually a family history of "early bloomers." A recent study suggested that there may be a greater expression of the growth receptor gene in these children [18].

Exogenous obesity

Children with exogenous obesity are usually tall for their age and have an early onset of puberty, especially in girls [5,20]. In these children, bone age is advanced and proportional to height age, and the adolescent growth spurt begins and ends early [3]. These children often attain normal adult height or are only slightly taller than average as adults [5,21]. Presumably, the tall stature and increased growth velocity is mediated by ghrelin, which is a GH secretagog, as well as insulin and IGF-1 [21,22].

Precocious puberty

True precocious puberty (gonadotropin-dependent precocious puberty) results from a premature increase in pituitary secretion of gonadotropins with a consequent increase in gonadal sex hormones, as in normal puberty [23]. The condition is more common in girls than in boys [23]. Pseudoprecocious puberty (gonadotropin-independent precocious puberty) results from autonomous gonadal or adrenal sex hormone secretion, independent of pituitary gonadotrophic secretion, or from iatrogenic administration of sex hormones [23]. In children with precocious puberty, acceleration of linear growth invariably occurs simultaneously with signs of premature sexual development. Rapid growth is accompanied by a rate of osseous maturation that is greater than expected for the chronologic age. The advanced bone age results in early epiphyseal closure [19,23]. Consequently, the ultimate adult height is less than it would have been otherwise [19,20,23].

Pituitary growth hormone excess

GH hypersecretion in children is usually caused by a GH-producing pituitary adenoma [16,20]. Circulating basal GH levels are easily detectable and are often greater than 15 μg/L (normal range, 0–3 μg/L for males and 0 to 8 μg/L for females) [24]. The diagnosis of GH excess is confirmed by dynamic testing with failure to suppress the serum GH level to less than 1 μg/L (with specific cutoffs dependent on laboratory assay) 2 hours after an oral glucose load of 1.75 g/kg (maximum 75 g) [25]. Because of the large intraindividual variability in serum GH levels, serum IGF-1 is the recommended screening test [3]. Before the epiphyses close, an excess of GH produces accelerated linear growth and results in gigantism. Bone age is often advanced, but may be normal or delayed if the disease interferes with pituitary gonadotropin secretion [5]. An excess of GH after the epiphyses fuse results in acromegaly, a disorder characterized by large hands and feet, overgrowth of the mandible and supra-orbital ridges, and coarse facial features [1]. Pituitary tumors are associated with headache, decreased visual acuity, visual field defects (typically bitemporal hemianopsia), and symptoms or signs suggesting increased intracranial pressure. Tumors may also be associated with deficiency of other pituitary hormones, such as thyrotropin, corticotropin, and gonadotropin, as well as prolactin excess [1].

Sotos syndrome (cerebral gigantism)

Children with Sotos syndrome are often large at birth, and their growth is most rapid during the first few years of life [1]. Height continues to be more than 2

standard deviations until puberty [3]. Thereafter, the growth velocity slows down and the growth curve remains parallel to and above the normal curve. Other features include macrocephaly, frontal bossing, prominent forehead, hypertelorism, coarse facial features, prominent ears, pointed chin, high arched palate, malar flushing, down-slanting palpebral fissures, large hands and feet, increased arm span compared with height, clumsiness, intellectual and developmental disability, and tendency to aggressive behavior [3,21,26,27]. The bone age is often advanced and compatible with the height of the patient [3,27]. Puberty usually occurs early with premature epiphyseal fusion and most children achieve normal adult height [5]. Biochemical studies, including serum GH levels, are normal. In most patients, the lateral and third ventricles are mildly dilated. Electroencephalograms (EEGs) are often abnormal. Seizures, scoliosis, cardiac anomalies, and renal anomalies occur in 15% to 30% of patients [3,27]. Most cases are sporadic [5]. Familial cases are usually consistent with an autosomal dominant mode of inheritance [6]. Mutations and deletions of nuclear receptor set domain containing protein 1 (*NSD1*) gene at chromosome 5q35 occur in more than 90% of patients with Sotos syndrome [3,21,27,28]. Most mutations are de novo [3].

Hyperthyroidism

Excessive thyroid hormone in early childhood leads to an acceleration in linear growth and proportional osseous maturation [3]. Presumably, the thyroid hormone works synergistically with IGF-1 to stimulate growth [21]. Craniosynostosis sometimes develops when hyperthyroidism appears early in life. Proper and timely treatment of hyperthyroidism restores euthyroidism and normalizes the growth rate so that the ultimate adult height is unaffected [3].

Marfan syndrome

Marfan syndrome is characterized by tall stature, arachnodactyly, upward subluxation or dislocation of lens, and aortic or mitral regurgitation [21]. The arm span is greater than the height with an arm span to height ratio greater than 1.05 [24]. The upper/lower segment ratio is diminished. Bone age is usually normal. Other clinical features include joint hyperextension, striae distensae, hypotonia, narrow facies, high arched palate, inguinal/femoral hernia, pectus excavatum/carinatum, kyphoscoliosis, megalocornea, and myopia. Retinal detachment, mitral valve prolapse, and aortic aneurysm and rupture are important complications. Marfan syndrome is inherited as an autosomal dominant trait. The condition results from a mutation in the fibrillin-1 (*FBN1*) gene on chromosome 15q [3,29,30].

Homocystinuria

Homocystinuria is an autosomal recessive disorder caused by a deficiency of cystathionine β-synthetase (CBS) with resultant excretion of large amounts of homocysteine in the urine [21]. Patients with this disorder have a phenotypic appearance similar to those with Marfan syndrome [19]. Additional features of homocystinuria include intellectual and developmental disability, malar flush,

downward subluxation or dislocation of lens, an increased incidence of seizures, arterial and venous thrombosis, osteoporosis, and vertebral collapse [3,19]. The condition results from mutation of the gene that encodes CBS.

Klinefelter syndrome

Klinefelter syndrome is due to the presence of more than 1 X chromosome in a male patient. The most common abnormal karyotype is 47 XXY. Affected children are tall and have eunuchoid proportions with a long arm span and legs, a decreased upper/lower segment ratio, possibly because of a third copy of the *SHOX* gene [31]. Tall stature is present before puberty [21,28]. Genital abnormalities, such as hypogonadism, cryptorchidism, a small phallus, and hypospadias are sometimes present [32,33]. Sertoli cell function and spermatogenesis are often defective, with resultant subfertility/infertility. Gynecomastia is common during adolescence [33]. Cognitive impairment, which may be evident in learning disabilities, especially in expressive language, and behavioral difficulties, such as excessive shyness, aggressiveness, and antisocial behavior, are often present [1]. Other features include hypertelorism, hypotonia, and clinodactyly. Bone age may be normal or delayed, depending on the level of testosterone secretion [5]. The condition is associated with hypergonadotropic hypogonadism. Serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels are usually normal in prepubertal children, but are high in adolescents and adults [5]. Serum testosterone levels are usually in the low normal range [5]. Patients with Klinefelter syndrome are at risk for breast cancer, cholelithiasis, type 2 diabetes mellitus, and metabolic syndrome [34,35].

XYY syndrome

The presence of an extra Y chromosome predisposes an individual to tall stature [1]. Patients with 1 (47, XYY) or more (48, XYYY) extra Y chromosomes achieve a greater than average adult height. Other features include severe nodulocystic acne, macrocephaly, large teeth, hypertelorism, clinodactyly, radioulnar synostosis, hypotonia, incoordination, tremor, macroorchidism, subfertility, learning difficulties, delayed speech, autism spectrum disorder, impulsivity, attention deficit hyperactivity disorder, physical aggressiveness, violence, and antisocial behavior [5,36,37].

Trisomy X (47, XXX females)

Patients with trisomy X tend to be tall, most probably because of the extra X chromosome and an extra copy of the *SHOX* gene [21]. The height is usually normal until 4 years of age. Affected children have long legs, which are obvious before puberty [21]. Most of these patients have a normal phenotype and have normal sexual development; fertility is not an issue, although ovarian failure and amenorrhea have been reported in some cases [3]. Some patients have minimal dysmorphic features such as epicanthal folds, up-slanting palpebral fissures, hypertelorism, hypotonia, joint hyperextensibility, pes planus, clinodactyly, and syndactyly [21].

Fragile X syndrome

Fragile X syndrome is characterized by intellectual and developmental disability, large and protruding auricles, and tall stature [3,21]. Other features include hypotonia, long and narrow face, flexible fingers, delayed speech, autism, strabismus, hyperactivity, and mitral valve prolapse [3,6]. Heterozygous females may also exhibit these features, although to a lesser extent [3]. Males with fragile X syndrome have macroorchidism [3,21]. An increase in growth rate often occurs during the preadolescent period. The growth rate slows down after puberty, resulting in a normal height in adulthood [3]. Fragile X syndrome is an X-linked dominant disorder with variable expressivity [6]. The gene that when disrupted results in fragile X syndrome has been mapped to Xq27.3 [21]. The DNA segment shows a peculiar stretch of trinucleotide (cytidine, guanosine, guanosine [CGG]) repeats in the fragile X mental retardation gene 1 (*FMR1*) [3,21]. The hypermethylated CGG-repeat stretch results in constriction of the X chromosome [6]. Fragile X syndrome may also arise in patients with deletions and point mutations of the *FMR1* gene without CGG amplification [21].

Hypogonadal syndromes

Hypogonadal syndromes such as aromatase deficiency, estrogen resistance, androgen insensitivity, and Kallmann syndrome can cause tall stature and eunuchoid body proportions (long legs, lower upper/lower segment ratio) [3,19]. The lack of sex hormones delays osseous maturation and epiphyseal fusion [19]. This allows continued, although slow, growth to a later age and tall stature in adolescence and beyond [19].

Familial glucocorticoid deficiency

Familial glucocorticoid deficiency is an autosomal recessive disorder of adrenal unresponsiveness to adrenocorticotropic hormone (ACTH). Type 1 is caused by mutations in the ACTH melanocortin 2 receptor (*MC2R*) gene, whereas type 2 is caused by mutations in the melanocortin 2 receptor accessory protein (*MCAP*) [38]. The condition is characterized by glucocorticoid deficiency, high ACTH levels, and normal mineralocorticoid levels [38]. Clinically, the condition presents with tall stature with advanced bone age, hypoglycemic episodes, fatigability, weakness, anorexia, vomiting, abdominal pain, weight loss, and generalized hyperpigmentation [38].

Beckwith-Wiedemann syndrome

Beckwith-Wiedemann syndrome is characterized by macrosomia, macroglossia, visceromegaly, abdominal wall defects (omphalocele, umbilical hernia, diastasis recti), and neonatal hypoglycemia [3,17]. Other features include facial nevus flammeus, earlobe malformation, prominent occiput, hemihyperplasia, renal medullary hyperplasia, cardiovascular abnormalities, hypothyroidism, thyroxine-binding globulin deficiency, and increased risk for embryonal tumors, notably Wilms tumor and adrenal cortical carcinoma [3,17,28,39]. Postnatal gigantism is common. Bone age is advanced but is appropriate for height age. Adult height is usually higher than the range predicted by the family [5].

Most cases are associated with maternal hypomethylation of 11p15, paternal uniparental disomy at chromosome 11p15, unbalanced translocations leading to trisomy of the 11p15 locus, and, less commonly, from a mutation in *CDKN1C* gene in the maternal allele [17,26,28]. IGF-2 plays an important role in the expression of this phenotype [5].

McCune-Albright syndrome

McCune-Albright syndrome is characterized by polyostotic fibrous dysplasia of bone, café au lait spots typically with irregular margins giving them a "coast of Maine" appearance, and sexual precocity. There is a high frequency of testicular abnormalities in boys and ovarian abnormalities in girls [6]. The syndrome is caused by an activating mutation in the *GNAS* gene, which encodes the alpha subunit of the stimulatory G-protein complexes involved in G-protein signaling [6,17,40]. The tall stature in McCune-Albright syndrome is due to excess GH, thyroid hormone, or sex hormone, or a combination of these [28]. The adult height can be less than normal owing to early fusion of the epiphyses if the condition remains untreated.

Weaver syndrome

Weaver syndrome is characterized by accelerated linear growth, advanced bone age, camptodactyly, mild intellectual and developmental disability, and characteristic facial features, including micrognathia, hypertelorism, down-slanting palpebral fissures, strabismus, large and dysplastic ears, megacephaly, broad forehead, flat occiput, long and wide philtrum, and depressed nasal bridge [17]. The excessive growth is present at birth or has its onset during infancy [21]. The syndrome is caused by missense and truncating mutations in enhancer of zeste homolog 2 (*EZH2*) or embryonic ectoderm development (*EED*) genes [41]. *EZH2* and *EED* are core components of the polycomb repressive complex 2 (*PRC2*), which possesses histone methyltransferase activity and catalyzes trimethylation of histone 3 at lysine 27 [41].

Proteus syndrome

Proteus syndrome is characterized by overgrowth of various body parts, macrocephaly, frontotemporal exostosis, multiple hyperpigmented warty nevi, and subcutaneous vascular tumors. In most individuals, the overgrowth starts in the first few years of life. The overgrowth can be generalized (whole body), unilateral (hemihyperplasia), or localized (macrodactyly). The syndrome is caused by activating mutations of *AKT1* and *PTEN* genes [6].

Congenital generalized lipodystrophy

Congenital generalized lipodystrophy is an autosomal recessive disorder [5]. Children with congenital generalized lipodystrophy have accelerated linear and muscular growth together with advanced bone age. Affected children have a generalized loss of subcutaneous and visceral fat. Acromegaloid changes, large hands and feet, prominent mandible, acanthosis nigricans, penile/clitoral enlargement, prominent superficial veins, hirsutism, alopecia,

hepatomegaly, and hypertrophic cardiomyopathy can be present [1,5,21]. There is an increased risk for hyperlipidemia, insulin resistance, hyperinsulinism, and nonketotic diabetes mellitus [21].

Simpson-Golabi-Behmel syndrome

Simpson-Golabi-Behmel syndrome is characterized by prenatal and postnatal overgrowth (tall stature, macrocephaly, macroglossia, visceromegaly), distinctive craniofacial features ("coarse" or "bulldog" face, hypertelorism, broad nasal bridge, macrognathia, cleft lip/palate, macrostomia), and multiple congenital abnormalities (cardiovascular malformations, central nervous system malformations, multicystic dysplastic kidneys, congenital diaphragmatic hernia, omphalocele, polydactyly, broad hands and feet with hypoplastic/absent fingernails, vertebral segmentation defects, pectus excavatum) [6,17,21,42]. Other features include neonatal hypoglycemia and hypotonia. Affected individuals are at risk for embryonal tumors, notably Wilms tumor, neuroblastoma, and hepatoblastoma [21]. The bone age is advanced. Simpson-Golabi-Behmel syndrome is an X-linked recessive disorder. The classic form (type I) is caused by mutations in glypican-3 gene (*GPC3*) at Xq28. The extremely rare and lethal form (type II) is caused by mutations in the gene at Xp22 [21,42].

CLINICAL EVALUATION

In most cases, a diagnosis can be established from a careful history and physical examination. Familiarity with the many diseases and syndromes associated with tall stature is important; in some cases, the diagnosis can be established immediately.

The most important historical information in the evaluation of a child with tall stature is the family history of the pattern of growth and the age of onset of puberty in parents and siblings. In familial tall stature, the child's height is consistent with the midparental height [4]. On the other hand, in pathologic tall stature, the child's projected height usually far exceeds the midparental height [4]. The midparental height can be calculated by averaging the parents' heights after first adding 13 cm to the mother's height if the patient is a boy or subtracting 13 cm from the father's height if the patient is a girl [4]. Any familial conditions associated with tall stature should be noted. All previous heights, weights, and head circumferences (if applicable) should be obtained and plotted on a growth chart. The size at birth and the period of growth acceleration should be noted [43]. If the growth records of the parents are available, they should also be plotted for comparison.

A functional inquiry is important and in some cases reveals the underlying cause of tall stature. Any medical, social, or psychological problems associated with tall stature should be noted. Developmental, behavioral, and learning problems are associated with many syndromes.

A careful and precise measurement of the height, weight, head circumference, arm span, and upper/lower segment ratio is necessary. Children with familial tall stature and constitutional tall stature have a normal upper/lower

segment ratio and arm span, whereas those with pathologic conditions such as Marfan syndrome and Klinefelter syndrome have an increased arm span and a decreased upper/lower segment ratio [4]. An obese child with no other abnormal physical findings suggests obesity as the cause of the tall stature. The body mass index, calculated by dividing the weight in kilograms by the height in meters squared (kg/m^2), is a widely accepted measure of adiposity. The stage of puberty should be assessed. A patient with absent or markedly delayed puberty may have hypogonadism, be it primary or secondary [21]. On the other hand, early pubertal changes suggest true precocious puberty or pseudoprecocious puberty.

A complete physical examination should be performed. Any dysmorphic features and abnormal physical findings (eg, heart murmur, organomegaly, pectus excavatum, scoliosis) should be noted. Coarse facial features, large hands and feet, and overgrowth of the mandible suggest GH excess or Sotos syndrome. Individuals with Sotos syndrome have, in addition, frontal bossing, macrocephaly, clumsiness, and intellectual and developmental disability. Superior subluxation of lens suggests Marfan syndrome, whereas inferior subluxation of lens suggests homocystinuria [4]. Macroorchidism is found in patients with fragile X syndrome, whereas signs of hypogonadism are found in patients with Klinefelter syndrome.

DIAGNOSTIC STUDIES

If the history and physical examination point to familial tall stature or constitutional tall stature, no investigation is usually necessary as long as the child is developing normally [16]. Bone age determination can help to confirm the diagnosis and is useful in estimating the probable adult height of the individual. The most commonly used tool to assess bone age is the atlas developed by Greulich and Pyle [44,45]. In this method, the appearance of different epiphyseal centers on the left hand and wrist radiograph is compared with the standards in the atlas [46,47]. If the bone age is delayed or advanced, then the projected height should be recalculated based on the bone age rather than the chronologic age [5]. The table developed by Bayley and Pinneau can be used to predict the adult height based on the child's bone age and chronologic age [5,48]. The Bayley and Pinneau method tends to overestimate the adult height in those with a bone age of 14 years or less, whereas the height predictions are accurate thereafter [49]. On the other hand, the Tanner-Whitehouse mark II method gives a good estimation of final height up to the bone age of 13 years in boys and 12 years in girls but tends to overestimate thereafter [44,45,49].

A significantly advanced bone age is sometimes seen in patients with true precocious puberty, adrenal or gonadal neoplasms, and congenital adrenal hyperplasia. Bone age is mildly or moderately advanced in patients with exogenous obesity, pituitary GH excess, hyperthyroidism, Sotos syndrome, Beckwith-Wiedemann syndrome, Weaver syndrome, and congenital generalized lipodystrophy [1,3,4]. Bone age is mildly advanced in children with constitutional tall stature and consistent with the height age, normal in children with familial tall stature, and delayed in patients with a hypogonadal syndrome.

Serum IGF-1 levels should be obtained to screen for GH excess [20,21]. The definitive test for the diagnosis of excessive GH secretion is the failure of serum GH to decrease to less than 1 μg/L (with specific cutoffs dependent on the laboratory assay) after an oral glucose load (1.75 g/kg; maximum 75 g) [21]. Magnetic resonance imaging (MRI) evaluation of the pituitary should be performed if there is evidence of GH excess.

If there is evidence of precocious puberty, determination of serum FSH, LH, estradiol, testosterone, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), androstenedione, and 17α-hydroxyprogesterone may help to distinguish true (central) precocious puberty from pseudoprecocious puberty [23,43,50].

A karyotype is needed because trisomy X (XXX females) and XYY males may have tall stature as the sole manifestation [19,21]. Chromosome analysis should be performed in the presence of dysmorphic features especially with development delay and when the presentation is atypical and the diagnosis difficult. Fluorescence in situ hybridization can be used to detect small chromosomal abnormalities such as duplications and deletions. This approach is only useful when the clinicians is considering a specific deletion or duplication for a differential diagnosis. For example, *NSD1* and *FBN1* gene sequencing should be considered if Soto syndrome and Marfan syndrome are suspected, respectively [6]. Analysis of *FMR1* and CGG number should be considered if fragile X syndrome is considered [6].

Other laboratory tests and diagnostic imaging studies (Table 1) should be performed if suggested by the history or physical examination.

COMPLICATIONS

Some tall children, especially girls, are teased or ridiculed by their peers [17]. The psychologic stress can be severe enough to cause social withdrawal and depression in later life [51]. Anxiety and depression are more frequent among girls than boys and have an adverse effect on quality of life [24,52]. The incidence of spinal deformities, such as scoliosis or kyphosis, is increased in tall children [17]. Tall children can have difficulties purchasing appropriately sized clothes [43]. Tall girls sometimes have difficulties finding compatible male partners. Other complications can be related to the underlying disease. There is increasing evidence that some tall people are at increased risk for breast cancer, ovarian cancer, prostatic cancer, colon cancer, lung cancer, thyroid cancer, and melanoma; cancer incidence increases with increasing adult height for most cancer sites [53–58]. The exact cause of an increase in cancer risk is not known but might be related to the underlying disease and genes associated with tall stature.

MANAGEMENT

The underlying cause should be treated whenever possible. Children with familial and constitutional tall stature rarely require therapeutic intervention [5,51]. Reassurance is the cornerstone of management for those with normal variant tall stature. Psychologic counseling may be necessary if emotional stress

Table 1
Laboratory tests and diagnostic imaging studies helpful in the evaluation of a child with tall stature

Suspected diagnosis	Suggested tests
Precocious puberty	Serum FSH, LH, estradiol, testosterone, DHEA, DHEAS, androstenedione, 17α-hydroxyprogesterone, human chorionic gonadotropin; gonadotropin response to gonadotropin-releasing hormone; MRI of the sella
Ovarian or adrenal tumor	Serum estradiol, testosterone, DHEAS, androstenedione; abdominal ultrasonography or CT
Congenital adrenal hyperplasia	Serum electrolytes; serum testosterone, DHEAS, androstenedione, testosterone, 17α-hydroxyprogesterone, 11-deoxycortisol; ACTH
Pituitary growth hormone excess	Serum IGF-1-3; GH suppression test; MRI of the sella
Sotos syndrome	Skull radiography, cranial CT, or MRI; electroencephalography; renal ultrasonography; echocardiography
Hyperthyroidism	Serum free thyroxine, triiodothyronine, and thyroid-stimulating hormone
Homocystinuria	Plasma cystine, homocysteine, and methionine; urinary homocysteine
Beckwith-Wiedemann syndrome	Serum glucose, insulin; renal ultrasonography; echocardiography; tumor surveillance justified
Marfan syndrome	Spine radiography; echocardiography
Simpson-Golabi-Behmel syndrome	Spine radiography; renal ultrasound; echocardiography; tumor surveillance justified
Klinefelter syndrome	Serum FSH, LH, testosterone; karyotype; tumor surveillance justified
Hypogonadal syndromes	Serum FSH, LH, estradiol, or testosterone; tumor surveillance justified
Familial glucocorticoid deficiency	Serum cortisol, ACTH

Abbreviations: ACTH, adrenocorticotropic hormone; CT, computerized tomography; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; IGF, insulinlike growth factor; LH, luteinizing hormone; MRI, magnetic resonance imaging.

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is associated with the tall stature. Treatment may be considered for children, especially girls, who have severe psychologic problems because of their height and when the predicted adult height is excessively tall (greater than 4 standard deviations greater than the population mean) [52].

For girls, estrogen treatment can be considered to reduce the final height. Estrogen acts by accelerating epiphyseal fusion. It also has indirect effects on the GH-IGF-1 axis. Satisfactory results can often be obtained by starting treatment before the bone age reaches 12 years [3]. In this regard, high-dose ethinyl estradiol can be given, starting at doses of around 100 to 300 μg per day with titration, if needed, for a maximum dose of 500 μg per day [43,59]. Conjugated estrogens may also be used. Cyclic progesterone (eg, medroxyprogesterone acetate at a dose of 10 mg per day for 7 days), may

be added [6,17]. Therapy is continued until the growth curve has leveled off and epiphyseal fusion is documented radiologically. The usual duration of treatment is approximately 2 years. A recent retrospective observational study of 60 Danish girls with constitutional tall stature treated with oral 17β-estradiol for a duration of 1.7 years showed an adult height reduction of 1.6 ± 2.1 cm [60]. Side effects of estradiol therapy are infrequent and include nausea, migraine headache, weight gain, leg cramps, transient hypertension, increased areolar pigmentation, benign breast disease, galactorrhea, ovarian cysts, hyperlipidemia, glucose intolerance, cholelithiasis, thromboembolism, post-therapeutic menstrual irregularities or amenorrhea, and increased risk of breast cancer [1,6].

Treating excessively tall boys with testosterone has been studied less extensively because boys do not usually complain of tall stature. Intramuscular injection of supraphysiologic amounts of testosterone enanthate at doses of 250 to 500 mg every 2 weeks for approximately 6 to 12 months has been shown to be effective [1,6,43,61]. Testosterone acts by accelerating bone maturation and epiphyseal fusion through aromatization to estrogen, thereby reducing the ultimate adult height. For most patients, therapy is initiated with the first signs of puberty, before the bone age reaches 14 years, until the epiphyses are completely closed [61]. Adverse effects include acne vulgaris, aggressive behavior, weight gain, edema, headache, hypertension, transient decrease in testicular volume, painful erections, myalgia, and increased risk of prostatic cancer [3,6,43,61].

Because of the greater social acceptance of tall stature and recognition of adverse effects associated with treatment, sex steroids should be used with caution and only after a thorough discussion of the potential side effects with the patient and parents.

A preliminary study showed that nocturnal infusion of octreotide, a somatostatin analogue, reduces GH secretion and leads to a significant reduction in height prediction in tall children [62]. A subsequent study, however, showed that long-term treatment with a somatostatin analogue does not reduce the final adult height in a manner sufficient to justify its use in the treatment of children with tall stature [63]. Pirenzepine and bromocriptine have been evaluated in the treatment of tall stature, but had little effect on adult height [64,65].

Percutaneous epiphysiodesis around the knees can be considered to reduce adult height in extremely tall boys and girls [43,66–68]. The procedure involves damaging the growth plates of the distal femur and proximal tibia and fibula with a drill and curettage, thereby preventing further longitudinal bone growth [19,43,67]. In general, the procedure should be performed before bone age 12.5 years in girls and 14 years in boys [19,43]. Complications include wound infection, peroneal nerve injury, joint effusion, and valgus deformity of the knee [67]. Overall, the complication rates are low with no significant decrease in knee function [66,67]. Although invasive, some have reported high patient satisfaction with the procedure [67].

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