Disorders of Growth and Stature

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Education Gap

It is often challenging to identify children with abnormal growth patterns and distinguish normal growth variants from pathologic variants.

Objectives

After completing this article, readers should be able to:

1. Perform growth measurements and interpret growth charts to be able to identify children with short or tall stature.
2. Differentiate among the common origins of short and tall stature and plan an appropriate diagnostic evaluation for a slowly or rapidly growing child.
3. Describe when treatment is indicated for children with short and tall stature.

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ABBREVIATIONS

ACTH	adrenocorticotropic hormone
CDC	Centers for Disease Control and Prevention
CDGP	constitutional delay of growth and puberty
CNS	central nervous system
FSS	familial short stature
GH	growth hormone
GnRH	gonadotropin-releasing hormone
IGF-BP3	IGF-1 binding protein 3
IGF-1	insulin-like growth factor 1
ISS	idiopathic short stature
NPR2	natriuretic peptide receptor B
rhGH	recombinant human GH
SGA	small for gestational age
SHOX	short stature homeobox
TSH	thyroid-stimulating hormone
T4	thyroxine

INTRODUCTION

Growth parameters are routinely measured in general pediatrics, with the goal of identifying children with abnormalities in growth and stature. Short stature is defined as a height less than 2 standard deviations (SDs) below the mean of the "normal" population, while tall stature is defined as a height greater than 2 SDs above the mean of the normal population. Both single growth measurements and the pattern of growth over time (growth velocity) are useful in identifying children with abnormal stature. The growth velocity changes over time, with relatively rapid growth in infancy and early childhood, followed by slower growth (approximately 5 cm per year) in later childhood and then rapid growth again during puberty. There is a range of pubertal peak growth velocities of around 7 to 12 cm per year and 6 to 10.5 cm per year in boys and girls, respectively, representing approximately the 3rd to 97th percentiles. The timing of peak growth velocity varies with the age of puberty onset and frequently reflects familial pubertal and growth patterns. Overall, it is thought that genetics may explain more than 80% of the variation in heights within a population. When children exhibit abnormal growth patterns, it is critical that pediatricians perform a proper diagnostic evaluation, which may ultimately include referral to a pediatric endocrinology subspecialist.

Measurement of Growth

The identification of physiological and pathologic growth patterns relies on accurate measurements of length and height. (1) In children under the age of 2 years, measurement of supine length is preferred. In children older than age 3 years,

standing height measurement is the favored method. For children between ages 2 and 3 years, it is best to measure both supine length and standing height and compare the two measurements. To measure supine length, the child should be on a firm surface, with a fixed headboard and mobile footboard. Measurement of height is ideally performed with a stadiometer, with the child's shoes and headwear removed and the child's head, shoulders, buttocks, and heels touching the wall. The "Frankfurt plane," the anatomic line that connects the outer canthus of the eye and the external auditory meatus, should be perpendicular to the board or the wall for length and height measurements, respectively. Measurements should be obtained to the nearest tenth of a centimeter and, if possible, measured in triplicate and averaged. This is ideally performed by a well-trained and consistent staff member. Head circumference should be measured with a measuring tape around the forehead above the eyebrows, over the ears, and around the most prominent part of the back of the head. Weight measurements should be obtained without shoes and with minimal clothing by using a well-calibrated scale. Height velocity can be computed at a minimum interval of 3 months between measurements; however, 1-year intervals are ideal, given seasonal variations.

Measurements should be plotted on standardized growth charts. The US Centers for Disease Control and Prevention (CDC) growth charts, developed by the National Center for Health Statistics, were initially published in 1977 and have been updated periodically, most recently in 2000. The data collected for the initial 1977 growth charts are mostly from the Fels Longitudinal Growth Study, with the caveat that the Fels cohort was predominantly children of European ancestry who were formula fed and middle class, from a single community. The 2000 update contains information collected from 5 cross-sectional nationally representative surveys (National Health Examination Survey, or NHES, II and III; and National Health and Nutrition Examination Survey, or NHANES, I, II, and III). In response to the limitations of the 1977 growth standards, the World Health Organization formed the Multicentre Growth Reference Study and collected growth information from healthy children in 6 different countries, with a key distinction being the use of breastfed children as the standard model for growth and development. The American Academy of Pediatrics and the CDC both recommend use of the 2006 World Health Organization growth charts for children between birth and age 2 years and the 2000 CDC standard growth charts for children aged 2 to 20 years. (2) By entering growth measurement inputs into both growth charts, medical providers can obtain growth percentiles and z-scores (this process is automated in many electronic health record systems). In addition to standard growth charts, a number of disease-specific growth charts are also available for disorders with atypical growth patterns, such as Turner syndrome, Down syndrome, and Noonan syndrome.

Although length and height measurements among healthy children have a wide distribution, height velocities are relatively uniform. A diagnostic evaluation is therefore warranted if a child is "falling off" the height percentile or crossing two major percentile lines between age 2 years and the onset of puberty.

Midparental Height

An individual's adult height is strongly correlated to his or her familial height. The midparental height calculation can be used to estimate a child's genetic target range height. If parents are available, it is preferable to directly measure parents' height rather than relying on self-reported values, which may be inaccurate. The caveat with estimating midparental "target height" is that inheritance patterns of stature are complex, as partly evidenced by marked height variations among healthy siblings in the same family. Further, it is worth noting that an abnormally short or tall child from parents with similar stature should not necessarily be declined further evaluation, since the child and parent(s) may possess the same genetic mutation. The midparental height is calculated as follows:

$$\text{Girls}: \frac{[\text{Father's height(cm)} - 13\text{ cm} + \text{Mother's height(cm)}]}{2}$$

$$\text{Boys}: \frac{[\text{Father's height(cm)} + \text{Mother's height(cm)} + 13\text{ cm}]}{2}$$

Bone Age

Skeletal maturation occurs in a predictable pattern in healthy children. An assessment of skeletal maturation can be performed with a simple radiograph of the left hand, which can be used to determine bone age. This radiograph is compared to age- and sex-matched published standards to determine a child's bone age, although this should be performed by an individual with experience in interpreting bone age radiographs. The comparison of skeletal age to chronological age is often helpful in the diagnostic evaluation of abnormal stature. By using standard references, a child's bone age and current height can also be used to estimate an adult's height, with the caveat that many other variables (including the tempo of puberty and other comorbid medical conditions) may affect the true adult height. The bone age is usually not reliable in children under the age of 5 years.

CONDITIONS ASSOCIATED WITH SHORT STATURE

Idiopathic or familial short stature and constitutional growth delay are relatively common causes of short stature, while true endocrine disorders are comparatively rare, accounting for as few as 5% of short stature cases. (3) Of note, malnutrition is a major cause of short stature worldwide.

Constitutional Delay of Growth and Puberty

Constitutional delay of growth and puberty (CDGP) is a growth pattern characterized by a normal size at birth and subsequent slowing of height velocity in the first 3 to 5 years of age. Individuals then maintain a prepubertal growth velocity during the expected time of pubertal growth spurt, resulting in a markedly decreased height percentile (can be below the 5th percentile), especially in early adolescence (Fig 1A). The hallmark in diagnosis is a delayed bone age finding. Family history often reveals a parent or other relatives who reportedly underwent puberty late, so-called late bloomers. Individuals with CDGP require close monitoring of growth and pubertal advancement. Psychosocial distress resulting from short stature is common—this is particularly prevalent in boys, whose height discrepancy from peers is marked as peers enter puberty, and can ultimately lead to a decline in school performance. (4) These individuals may benefit from a consultation with a pediatric endocrinologist for possible hormonal therapy to initiate pubertal changes. Individuals with CDGP undergo complete catchup growth (with or without hormonal intervention) and achieve an adult height that is within range for their genetic potential.

Familial Short Stature

Familial short stature (FSS) is considered a normal variant, where a child's height is less than 2 SDs for his age, but the child's height is expected to still reach the calculated mid-parental height. These children have low normal height velocities, a normal laboratory evaluation finding, and a bone age that is in agreement with his or her chronological age. FSS is generally considered a subset of idiopathic short stature (ISS). It is worth noting that a diagnosis of FSS does not preclude underlying monogenic or polygenic alterations, as it is possible that multiple family members may carry genetic variants responsible for short stature.

Small for Gestational Age

Neonates born small for gestational age (SGA) are at risk for numerous future health issues, including short stature. SGA is defined as a birth weight and/or length less than

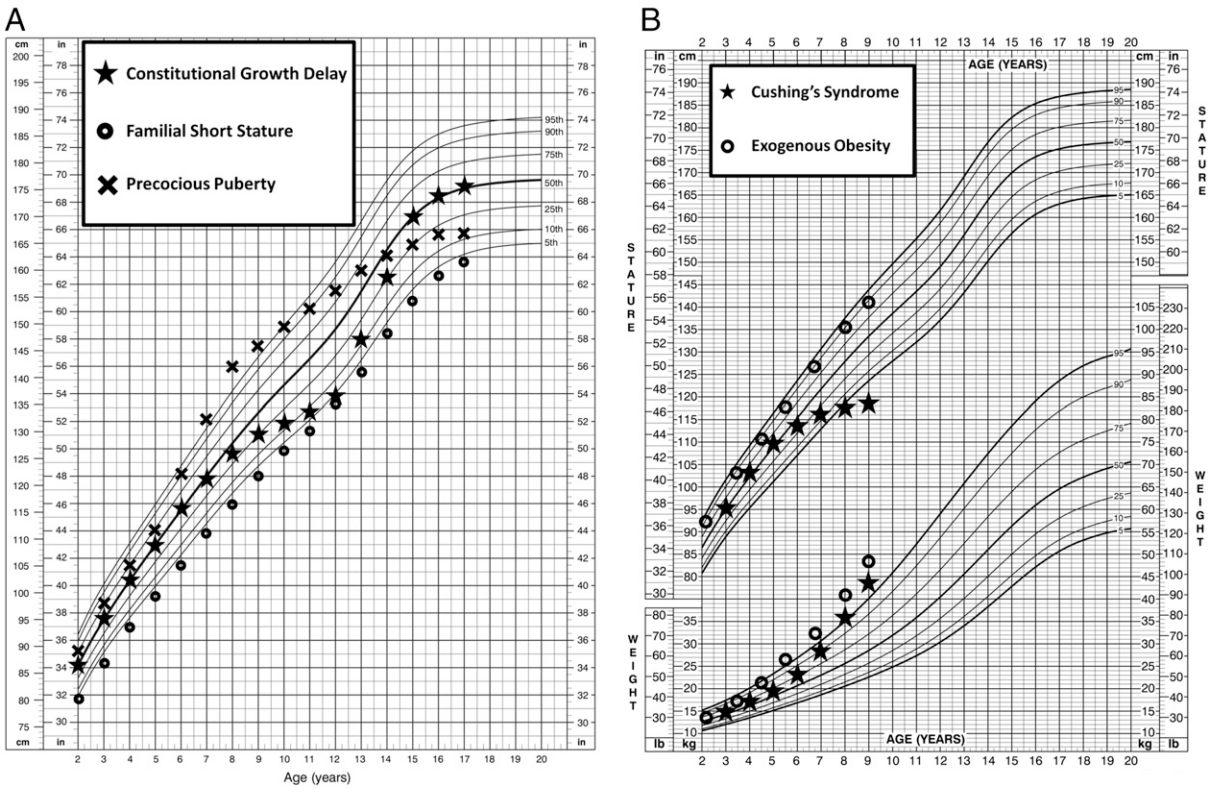

Figure 1. A. Typical linear growth pattern of a child with constitutional growth delay (★), precocious puberty (X), and familial short stature (o). B. Typical linear growth and weight pattern of a child with Cushing syndrome (★) and exogenous obesity (O). Adapted from 2000 CDC growth charts for males ages 2 to 20 years. (2)

2 SDs below the mean (2.3rd percentile or lower). An estimated 15% of children who were born SGA fail to achieve full catchup growth by age 2 years. The mechanism of growth failure in these children is not well understood, and an assessment of the growth hormone (GH) insulin-like growth factor 1 (IGF-1) axis in early life is not predictive of catchup growth. Despite the heterogeneous origins and mechanisms of poor intrauterine and extrauterine growth in this cohort, these children may benefit from therapy with recombinant human GH (rhGH).

Hypothyroidism

Children with acquired hypothyroidism may lack many of the clinical signs and symptoms that are classically present in the adult population, such as fatigue, cold intolerance, and constipation. Thyroid enlargement is often not present or is overlooked at physical examination, and one-third of children with acquired hypothyroidism receive a diagnosis in the absence of clinical symptoms. Clinically significant and progressive growth failure may be the only clinical feature of chronic acquired hypothyroidism in the pediatric population. Failure to diagnose hypothyroidism and initiate thyroid hormone replacement therapy with levothyroxine can markedly compromise adult height. The most common cause of acquired hypothyroidism in children and adults is autoimmune hypothyroidism (Hashimoto thyroiditis), with a prevalence of 1% to 2% and a 4:1 female predominance. Congenital hypothyroidism is typically diagnosed in the neonatal period, as newborn screening programs for congenital hypothyroidism are present in all 50 states and most developed countries. Screening for hypothyroidism should be performed in all children with unexplained growth failure, with or without other clinical symptoms, by measurement of thyroid-stimulating hormone (TSH) and free thyroxine (T4) levels.

Glucocorticoid Excess

Chronic exposure to excess glucocorticoids has a profound effect on linear growth, with growth failure accompanied by concurrent weight gain (Fig 1B). Cushing syndrome in children is most often exogenous as a result of glucocorticoid therapy. Endogenous Cushing syndrome is rare and can be a result of pituitary adrenocorticotropic hormone (ACTH) oversecretion (Cushing disease), a primary adrenal tumor, or, rarely, an ectopic source of ACTH or corticotropin-releasing hormone. Characteristic features of glucocorticoid excess include growth failure, truncal obesity with thin limbs, round facies, dorsocervical fat pad, decreased muscle mass, delayed puberty, striae, easy bruising, glucose intolerance, and osteoporosis, although younger children may not exhibit all of the classic stigmata. If suspected, a 24-hour urine collection for urinary free cortisol, midnight salivary cortisol, or low-dose dexamethasone suppression testing should be performed, and a referral to a pediatric endocrinologist is warranted. In patients who receive glucocorticoid therapy for treatment of a chronic underlying condition, growth should be closely monitored, and the treatment should be titrated to the minimal amount of glucocorticoid exposure required to achieve the desired treatment effect. The current data regarding effects of chronic inhaled corticosteroid on growth are controversial, with investigators in one study citing a mean 1.2-cm decrease in adult height in children treated with low-dose budesonide for a mean of 4.3 years. (5) While there may be a risk of minimally decreased adult height in this population, this risk should be weighed against the benefits of inhaled corticosteroids in preventing severe asthma exacerbations. Further, there remains a lack of definitive data on the effect of chronic inhaled corticosteroids on adult height. (6)

GH Deficiency

GH deficiency should be suspected in children who have a below-average growth rate, are crossing height percentiles, and have a delayed bone age finding. GH deficiency has a reported incidence of about 1 in 3,500 children. The origin of GH deficiency is frequently not determined, with 41% of cases reported as idiopathic. Among known causes, GH deficiency is attributed to intracranial lesions or treatment with radiation in 35% of cases, is congenital in 20% of cases, and occurs in the setting of syndromes with concomitant GH deficiency in 4% of cases. (7) Risk factors for GH deficiency include a history of head trauma, central nervous system (CNS) radiation, or CNS infection. Neonates with congenital GH deficiency are typically a normal size at birth; however, they may have signs suggestive of a combined pituitary hormone deficiency, such as micropenis, midline structural defects, prolonged jaundice, or hypoglycemia. Low GH values in infants at the time of hypoglycemia are diagnostic of this disorder. In children, initial laboratory testing for GH deficiency includes measurement of serum IGF-1 and IGF-1 binding protein 3 (IGF-BP3) levels. GH is secreted in a pulsatile manner; thus, single measurements are nondiagnostic for GH deficiency. If IGF-1 levels are low for age and pubertal status or if there is high clinical suspicion, a GH stimulation test should be performed.

Idiopathic Short Stature

ISS is a heterogeneous diagnosis of exclusion, which is, by definition, stature 2 SDs below the mean for age, gender, and population, with normal size for gestational age at birth; absence of chronic disease, endocrine deficiency, or

chromosomal abnormalities; and normal nutritional status. (8) The bone age is variable and may be consistent with chronological age or slightly delayed or advanced. Referral to a pediatric endocrinologist is warranted to rule out other pathologic conditions and to consider GH therapy (Fig 2).

It is worth noting that, with advances in genomic analysis, the classification of ISS may be evolving. The population-level height distribution is essentially gaussian, implying that 2.3% of the "normal" population lies in the left tail of the population height curve and is below −2 SDs. Through genetic and genomic analyses of this tail of the curve, both monogenic and polygenic variants associated with short stature have been identified. Thus, children previously classified as having ISS may actually harbor single-gene mutations that affect growth and the growth plate, including mutations and deletions in short-stature homeobox *(SHOX)*, aggrecan, and natriuretic peptide receptor B *(NPR2)* genes, among others. In contrast to single-gene disorders, recent genome-wide association studies have yielded combinations of single-nucleotide polymorphisms that associate with short stature. For instance, Wood and colleagues identified 697 single-nucleotide polymorphisms that account for 20% of the phenotypic variance of adult height. (9) As laboratory-based studies of the genetic basis of diseases continue to progress, it is conceivable (and perhaps even likely) that children previously classified as having ISS may ultimately be found to have a clear monogenic or polygenic etiologic origin. As the cost of next-generation sequencing techniques (including whole-exome and whole-genome techniques) continues to decline, it is certainly possible that such genomic techniques may ultimately be integrated into the diagnostic evaluation for children with short stature. (10)

Chronic Illnesses

Many chronic, systemic childhood illnesses result in growth failure. Some disorders lead to growth failure by causing malnutrition, while in other cases, poor growth may be a consequence of treatment. Celiac disease, which has a prevalence of up to 1% of children, may have an insidious onset in children and lead to short stature. A Finnish cohort of 530 children with biopsy-proven celiac disease reported growth failure as the sole presenting sign in 8% of children and demonstrated that growth failure was present in 34%. (11) Growth failure is also extremely prevalent in children with Crohn disease, affecting approximately 30% of children with the disorder, although this is often reversible with optimal treatment of the gastrointestinal disease. Children with chronic kidney disease may also have growth failure as the presenting sign, which can be profound and multifactorial. rhGH therapy is beneficial in height optimization for children with chronic kidney disease. Further, childhood malignancies, pulmonary disease, and immunologic disease are all associated with growth failure, and therapies with CNS radiation, chemotherapy, and corticosteroids can further contribute to growth deceleration.

Genetic Syndromes

Numerous genetic syndromes have a described association with short stature, including chromosomal disorders, skeletal dysplasias, and other monogenic disorders. A number of these disorders are further described in Table 1.

EVALUATION OF SHORT STATURE

In children with short stature, obtaining a through medical history is essential, paying particular attention to clues that may indicate one of the conditions mentioned previously. Birth and pregnancy history should be noted for SGA infants, as well as any complications in the neonatal period, such as hypoglycemia or prolonged jaundice (associated with GH deficiency), meconium ileus (associated with cystic fibrosis), or poor muscle tone or feeding difficulties (associated with

US Food and Drug Administration–approved Indications for Recombinant Human Growth Hormone (GH) Therapy
GH deficiency
Growth failure secondary to chronic renal insufficiency
Growth failure secondary to being born small for gestational age without catchup growth
Turner syndrome
Noonan syndrome
Prader-Willi syndrome
Idiopathic short stature
SHOX deficiency
AIDS-related cachexia or wasting
Short bowel syndrome
Adults with childhood- or adulthood-onset GH deficiency

Figure 2. US Food and Drug Administration–approved indications for rhGH therapy.

TABLE 1. **Genetic Syndromes and Chromosomal Alterations Associated with Short Stature**

	APPROXIMATE INCIDENCE RATE	CLINICAL FEATURES	DIAGNOSTIC TESTING	TREATMENT AVAILABLE
Down syndrome	1/700 live births	Up-slanting palpebral fissures, epicanthal folds, neonatal hypotonia, developmental delay At risk for thyroid disorders and celiac disease Decreased length in infancy; diminished height in childhood and adulthood Diminished pubertal growth velocity	Prenatal screening Karyotype	rhGH treatment is controversial and not commonly administered Levothyroxine if needed for hypothyroidism Adherence to gluten-free diet if celiac disease is present
Turner syndrome	1/2,500 live births	Webbed neck, wide carrying angle, widely spaced nipples, nail hypoplasia, high-arched palate Short stature can occur in the absence of other clinical features Associated with chronic otitis media, left-sided cardiac defects, genitourinary abnormalities At risk for autoimmune thyroiditis and celiac disease Growth failure in 95%–100%	Karyotype	rhGH improves final adult height Estrogen therapy for ovarian replacement Levothyroxine if needed for hypothyroidism
Noonan syndrome	1/1,000–1/2,500 live births	Hypertelorism, ptosis, down-slanting palpebral fissures, low-set ears, broad/webbed neck, pectus deformity, scoliosis Right-sided cardiac defects (pulmonary vein stenosis most common) Short stature in 50%–70% of patients	*PTPN11* gene analysis mutation found in 40% of pateints	rhGH improves adult height
Prader-Willi syndrome	1/30,000 live births	Neonatal hypotonia, cryptorchidism, developmental delay, scoliosis Hyperphagia develops in childhood Hypothalamic hypogonadism GH insufficiency and short stature	Fluorescence in situ hybridization for 15q11 deletion If negative, DNA methylation analysis	rhGH improves adult height and body composition
Silver-Russell syndrome	1/3,000–1/10,000 live births	Clinical diagnosis based on Netchine-Harbison score Postnatal growth failure, feeding difficulties, protruding forehead (triangular facies), body asymmetry SGA with relative macrocephaly Body asymmetry	Methylation analysis of 11p15.5, 7p, and 7q, among others Detected in 60% of patients with clinical diagnosis	rhGH improves growth, body composition, and risk of hypoglycemia
18q deletion	1/40,000 live births	Hearing loss Hypotonia Developmental delay Short stature in 64%	Chromosome analysis (karyotype)	rhGH therapy
SHOX mutation	2%–7% of children with ISS diagnoses	Madelung deformity (malformation of wrists) Phenotypic variation, from ISS to Léri-Weill dyschondrosteosis (mesomelic dwarfism)	*SHOX* gene testing	rhGH therapy improves adult height

Continued

TABLE 1. (Continued)

	APPROXIMATE INCIDENCE RATE	CLINICAL FEATURES	DIAGNOSTIC TESTING	TREATMENT AVAILABLE
Achondroplasia	1/25,000 live births	Dwarfism with proximal limb shortening (rhizomelic shortening), frontal bossing, trident hand configuration Caused by mutations in *FGFR3*	*FGFR3* gene testing available	rhGH not routinely administered

FGFR3=fibroblast growth factor receptor 3, GH=growth hormone, ISS=idiopathic short stature, rhGH=recombinant human GH, SGA=small for gestational age.

some genetic syndromes). Past medical history may reveal a major head trauma or meningitis (leading to pituitary insufficiency), chronic abdominal pain or diarrhea (malabsorption), or chronic pulmonary infections (cystic fibrosis). Family history should be geared toward height measurements and timing of puberty of parents and extended family members, as well as any chronic illnesses or autoimmune diseases. Particular attention should be paid to prior and current medications that could affect growth or appetite (particularly glucocorticoids), as well as stimulant medications for the treatment of attention-deficit/hyperactivity disorder. The clinician should solicit a detailed dietary history, as well as any difficulties in school or learning disabilities. The review of systems should include screening for any chronic medical condition that may not yet be diagnosed, as well as chronic headaches, vision changes, energy levels, cold intolerance, chronic cough, diarrhea or constipation, chronic abdominal pain, easy bleeding or bruising, and timing of pubertal signs, if applicable. In the physical examination, pay attention to body proportions, features of genetic syndromes (Table 1), and pubertal staging.

In children with growth failure, screening laboratory tests should be performed, including complete blood cell count with differential, comprehensive metabolic panel, TSH and free T_4 tests, erythrocyte sedimentation rate, C-reactive protein level, celiac screening with anti-tissue transglutaminase testing, immunoglobulin A and total immunoglobulin A tests, IGF-1 test, IGF-BP3 test, and urinalysis (for identification of renal tubular acidosis). A left-hand radiograph should be obtained for assessment of bone age. Additional testing should be guided by any identified clinical signs or symptoms that may lead the practitioner to suspect a specific etiologic origin (see Table 2 for a summary of etiologic causes of short stature).

TREATMENT OF SHORT STATURE

When possible, treatment for short stature should focus on therapy for an identified underlying etiologic origin (such as hypothyroidism, glucocorticoid excess, or chronic illness). In some cases, initiation of GH therapy (under the guidance of a pediatric endocrinologist) can be considered (see Fig 2 for a listing of US Food and Drug Administration–approved indications). In true GH deficiency, treatment with exogenous rhGH can be effective and allow many children to reach adult height within the predicted mid-parental height range. The data for GH therapy in other indications, such as ISS, are more varied, but overall, rhGH therapy appears to have a small but positive effect in these patients.

CONDITIONS ASSOCIATED WITH TALL STATURE

Tall stature is most commonly attributed to constitutional (or familial) tall stature or overnutrition. While tall stature can be a sign of underlying pathologic processes (as discussed herein), relatively few children will have a pathologic cause identified.

Constitutional Tall Stature

In constitutional tall stature, neonates are born with an appropriate size for gestational age. They then have an increase in growth velocity, causing them to cross length or height percentiles to greater than the 97th percentile until about the age of 4 years, when they settle into their own growth channel that parallels the growth curve. The physical examination findings are normal, with normal arm span and upper to lower segment ratio. The bone age is also typically congruent with chronological age. Family history will likely reveal a similar growth pattern in one parent and tall stature in the family. The underlying cause of constitutional tall stature is heterogeneous. GH has been implicated in some subgroups. Insulin-like growth factor 2 levels have also been shown to be higher, and this may play an important role. Genetic polymorphisms in the GH secretagogue receptor (ghrelin receptor), IGF-1, and IGF-BP3 genes and

TABLE 2. **Conditions Associated with Short Stature**

ETIOLOGIC ORIGIN OF SHORT STATURE	MANIFESTATION
Normal variant	Constitutional delay of growth and puberty Familial short stature Small for gestational age with catchup growth
Hormonal/endocrine disorder	Hypothyroidism Glucocorticoid excess Growth hormone deficiency
Chronic illness	Celiac disease Chronic kidney disease Congenital heart disease Pulmonary disease Immunologic/inflammatory disease Malignancy Malnutrition
Genetic syndrome/chromosomal abnormality	See Table 1

Routine diagnostic tests include complete blood count with differential; comprehensive metabolic panel; urinalysis; thyroid-stimulating hormone and free thyroxine levels; erythrocyte sedimentation rate and C-reactive protein level; anti-tissue transglutaminase antibody testing, immunoglobulin A level, and total immunoglobulin A level; insulin-like growth factor 1 (IGF-1) testing, IGF-1 binding protein 3 testing, and bone age. Consider karyotype analysis in female patients. Additional testing should be guided by the suspected etiologic origin.

haplotypes at the *GH1* gene have also been implicated in constitutional tall stature.

Hyperthyroidism

Hyperthyroidism causes accelerated linear growth with weight loss, resulting from a hypermetabolic state. The most common cause of hyperthyroidism is autoimmune Graves' disease. Subacute thyroiditis, a thyroid hormone–secreting nodule or hot nodule, and the hashitoxicosis (hyperthyroid) phase of chronic lymphocytic thyroiditis are also possible etiologic origins. Patients may present with a goiter, tachycardia, hypertension, tremor, lid lag, exophthalmos, heat intolerance and anxiety, and sleep disturbances, in addition to growth derangement. Hyperthyroidism is assessed with measurement of serum TSH, free T4, total triiodothyronine, and thyroid-stimulating immunoglobulins. A radioactive iodine-123 uptake scan or technetium-99m scan can also aid in diagnosis. Hyperthyroidism is most commonly diagnosed by means of a suppressed TSH level, with increased T4 and triiodothyronine values.

Precocious Puberty

Estrogens are responsible for the pubertal growth spurt and epiphyseal fusion in both girls and boys. Estradiol levels are low in early puberty, with a subsequent increase that leads up to peak growth velocity. In central precocious puberty, the hypothalamic-pituitary-ovarian/testicular axis is turned on prematurely, resulting in increased estrogen and testosterone production in girls and boys, respectively. This leads to outward signs of breast development in girls and testicular enlargement in boys. Growth acceleration is caused by increased estrogen production in girls and by both the aromatization of testosterone to estrogen and the smaller, direct effects of testosterone on the growth plate in boys. The effect of estrogen levels on growth is varied and depends on an individual's sensitivity to estrogen at both the level of the growth plate and the hypothalamic-GH axis, as sex steroids have an important role in increasing GH secretion during puberty. Peripheral causes of early puberty (ie, not mediated by gonadotropin-releasing hormone [GnRH] secretion) include late-onset congenital adrenal hyperplasia, McCune-Albright syndrome, and familial male-limited precocious puberty.

Bone age assessment is markedly advanced in precocious puberty. Morning values of luteinizing hormone, follicle-stimulating hormone, and estradiol in girls or testosterone in boys may be increased and consistent with central precocious puberty; however, GnRH agonist stimulation testing is frequently needed to differentiate central from peripheral puberty. Dedicated pituitary magnetic resonance imaging is performed in cases of central precocious puberty. If adrenarchal signs, such as pubic and axillary hair, are primary symptoms identified in children with advanced bone age, then ACTH stimulation testing is performed to evaluate the presence of adrenal etiologic origins. If

precocious puberty is left untreated, epiphyseal closure may occur early and ultimately lead to a smaller-than-expected adult height.

GH Excess

GH excess, a rare cause of tall stature in the pediatric population, can be caused by a hormone-secreting pituitary adenoma, McCune-Albright syndrome, multiple endocrine neoplasia type 1, or Carney complex. Increased GH levels cause accelerated linear growth when growth plate epiphyses are still open. Patients will also frequently have enlarged hands, feet, and jaw. In children with GH excess, IGF-1 levels will be increased for age and pubertal status. Prolactin levels may also be increased, as co-secreting adenomas are common. GH suppression testing with an oral glucose load is performed for confirmation. Dedicated pituitary magnetic resonance imaging is typically performed after the diagnosis of GH excess is confirmed, with additional diagnostic testing for McCune-Albright syndrome, multiple endocrine neoplasia type 1, or Carney complex performed as guided by associated signs and symptoms.

Familial Glucocorticoid Deficiency

Familial glucocorticoid deficiency is an ACTH-resistant state that is associated with tall stature. A detailed history and physical examination will reveal features concerning for adrenal insufficiency, including nausea, weight loss, fatigue, bronzing of the skin, and darkening of the hand creases and buccal mucosa. While it has been postulated that increased levels of ACTH, as well as ACTH receptor mutations, could contribute to additional growth, the exact mechanism for the excess growth is not known. In primary adrenal insufficiency, laboratory evaluation will reveal low morning cortisol levels with increased ACTH levels. A complete blood cell count will frequently show eosinophilia, and plasma dehydroepiandrosterone sulfate levels will also be low. If morning cortisol and ACTH values are inconclusive, then an ACTH stimulation test can be performed to further evaluate the possibility of adrenal insufficiency.

Chromosome Duplication Syndromes

Klinefelter syndrome (47,XXY) occurs in about 1 of 600 male newborns and demonstrates variable phenotypes at presentation. Early studies of this disorder demonstrated tall stature, a eunuchoid body habitus, and gynecomastia. However, the clinical presentation can actually be subtle, especially in early childhood. An increased copy number of the *SHOX* gene on the X chromosome is associated with tall stature. Although tall stature was part of the original description of Klinefelter syndrome, a retrospective study of boys with this disorder demonstrated that only 25% of boys in younger childhood (age <11 years) and 32% of boys in older childhood (age 11–19 years) had tall stature (defined here as height >90th percentile) as part of their phenotype. (12) *SHOX* gene triplication has also been recognized in cases of tall stature, long limbs, and gonadal dysgenesis.

Boys with an extra Y chromosome (47,XYY) typically exhibit tall stature beginning at approximately 6 years of age. Other common features of this disorder include clinodactyly, hypertelorism, macro-orchidism, and tremor. Intelligence is typically normal if the diagnosis is assigned prenatally, although there is an increased incidence of autism, attention-deficit/hyperactivity disorder, motor tics, and other behavioral problems. Finally, duplication of 15q, which contains the IGF-1 receptor gene, has also been associated with tall stature.

Abnormal Paracrine Signaling

The C-type natriuretic peptide, through binding with its cognate receptor *NPR2*, forms a paracrine signaling pathway that has demonstrated a role in skeletal growth. Gain of function mutations in *NPR2* are inherited in an autosomal dominant fashion and have been found to cause tall stature in multiple members (across generations) within a family. Other abnormalities in paracrine signaling have also been identified, including loss of function mutations in the fibroblast growth factor receptor 3, which positively affects linear growth and leads to tall stature.

Genetic Syndromes

Sotos syndrome, or cerebral gigantism, is described as tall stature prenatally and in childhood. It is associated with advanced bone age, macrocephaly, cardiac and genitourinary abnormalities, benign and malignant tumors, brain malformations, developmental delay, and dysmorphic facial features. Deletions in the nuclear receptor binding SET-domain 1, or *NSD-1*, gene, which lead to loss of function, account for most cases in Japanese populations, while *NSD-1* mutations occur more frequently in non-Japanese populations.

Weaver syndrome, which is caused by mutations in histone-lysine-N-methyltransferase, manifests with tall stature, characteristic facial features, intellectual disability, clinodactyly, scoliosis, and hearing loss. Growth is accelerated in both the pre- and postnatal periods, and bone age is typically advanced. Patients with DNA methyltransferase 3A mutations present similarly to Weaver syndrome, with typical facial features, tall stature, and intellectual disability.

Marfan syndrome, an autosomal dominant disorder of the fibrillin-1 gene, is characterized by tall stature, ectopia

lentis, and aortic root dilation. While homocystinuria may have a presentation similar to that of Marfan syndrome, it is an autosomal recessive disorder of the cystathionine β-synthase gene. These patients are also predisposed to thromboembolic events, as well as psychiatric and learning disorders. Other syndromes associated with overgrowth include Beckwith-Wiedemann, Marshall-Smith, and Simpson-Golabi-Behmel. If a child with tall stature also has accompanying dysmorphic features, learning disorders, or behavioral concerns, he or she should be evaluated for a genetic cause of tall stature. An assessment of sitting height and arm span can be helpful, as eunuchoid proportions are consistent with Marfan syndrome, homocystinuria, Klinefelter syndrome, and hypogonadism, whereas Sotos and Weaver syndromes, by contrast, have proportional growth.

Overnutrition

Overnutrition that leads to obesity can increase linear growth in childhood, although adult height is not greater than expected. These patients can also manifest earlier-than-average puberty and advanced bone age. The mechanism regulating this pattern of growth is not fully understood. GH levels are typically low, but IGF-1 levels are normal. Ghrelin, leptin, GH secretagogue receptor, and hyperinsulinemic state all likely play a role in this complex system.

EVALUATION OF TALL STATURE

The evaluation of tall stature begins with a detailed history and physical examination. The patient's age and pubertal status, as well as the timing of the child's growth acceleration, are particularly important in guiding the differential diagnosis. The history should include a detailed family history (including the heights of the immediate and extended family members) and review of other associated symptoms and medical conditions. The physical examination should include a careful evaluation for dysmorphic features and disproportional growth. A routine diagnostic evaluation is less well defined, but initial laboratory evaluation may include assessment of GH signaling by measuring IGF-1 level, and radiologic evaluation may include a bone age assessment. Further diagnostic testing is guided by the history and physical examination findings, should a specific etiologic origin be suspected.

TREATMENT OF TALL STATURE

Treating the underlying cause of tall stature is the mainstay of management. Hyperthyroidism is treated with methimazole, an anti-thyroid medication. Central precocious puberty is treated with GnRH agonists, while congenital adrenal hyperplasia and adrenal insufficiency are treated with glucocorticoid replacement. GH excess can be treated medically, surgically, and with radiotherapy.

Treatment of tall stature with sex steroids is controversial. Testosterone therapy at doses ranging from 500 to 1,000 mg per month for 6 months to greater than 12 months has been used with consequent reduction in expected future growth by 50%. Lower doses administered for a shorter duration likely have similar effectiveness, although there are no prospective studies in which different treatment regimens have been compared. Side effects of high-dose testosterone include acne, edema, and gynecomastia. There have not been any identified long-term effects with therapy, relating to infertility or gonadal dysfunction. However, for girls treated with high-dose estrogen, fertility issues related to primary ovarian insufficiency have been identified. High-dose estrogen also causes weight gain, nausea, benign breast disease, excessive vaginal discharge, ovarian cysts, and thrombosis. Initiation of treatment should be carefully considered and weighed against potential risks, typically under the guidance of a subspecialist.

Summary

- On the basis of strong research evidence, height is a heterogeneous trait with marked variation in the population and is largely attributable to genetic variability. (9)
- On the basis of strong research evidence, growth velocity describes the pattern of growth over time, and, together with measurements of height and/or length, must be factored into clinical decision-making when evaluating children with abnormal growth and stature. (1)(2)
- On the basis of some research evidence, as well as consensus, evaluation of short and tall stature includes a thorough history and physical examination, along with laboratory and radiologic examinations dictated by pertinent history, symptoms, and physical findings. Particularly for the evaluation of short stature, an initial set of screening laboratory studies should be performed. (2)(3)
- On the basis of some research evidence, as well as consensus, timely referral to a pediatric endocrinologist is important when bone age is advanced and predicted adult height is compromised and in situations when growth hormone therapy may be indicated. (8)

References and Suggested Readings for this article are at http://pedsinreview.aappublications.org/content/38/7/293.

PIR Quiz

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1. Rose is a 6-year-old girl brought to the clinic by her parents for a health supervision check. At her 4-year health supervision examination, she was at the 25th percentile for height. Today, she is noted to be at the 5th percentile for height. Her weight has been consistently at the 25th percentile for age. Both her parents have average height. There is no history of fatigue, cold intolerance, or constipation. She is taking no medications. Her physical examination findings are unremarkable. A workup for growth failure is initiated, including free T4 and TSH, among other laboratory studies. Free T4 and TSH tests showed findings consistent with hypothyroidism. Which of the following is the most likely cause of growth failure in this patient?
    A. Congenital goiter.
    B. Congenital hypothyroidism.
    C. Familial short stature.
    D. Hashimoto thyroiditis.
    E. Thyroid hormone receptor deficiency.
2. A 15-year-old boy is brought to the clinic by his parents for follow-up. He has a history of severe asthma, for which he has been using an inhaled corticosteroid daily for the past 2 years. He is at the 25th percentile for height. His asthma has been well controlled, and he has not had any hospitalizations for his asthma in the past 2 years. His parents are concerned about the effects of long-term corticosteroids on his adult height and ask if the treatment should be continued. Which of the following is the most appropriate response regarding his chronic inhaled corticosteroid use?
    A. Addition of daily albuterol treatment will help decrease the need for long-term steroids.
    B. He can expect to lose, on average, 5.0 cm in his final adult height if he continues using inhaled corticosteroids.
    C. He has constitutional growth delay, and his growth will catch up.
    D. He has familial short stature and will likely remain at the 25th percentile for height.
    E. It is important to weigh the effects of long-term steroid use on height against the benefit of steroids in preventing severe asthma exacerbations.
3. A 15-month-old boy is referred for delayed growth. He had a normal birth length and weight. His postnatal course was significant for prolonged jaundice and hypoglycemia. He has crossed height percentiles, from the 15th to the 5th percentile, during the past 6 months. His weight is at the 25th percentile for age. He has global developmental delay. In addition to delayed tooth eruption, physical examination is most likely to show which of the following clinical signs in this child?
    A. Hepatomegaly.
    B. Low-set ears.
    C. Micropenis.
    D. Transverse palmar crease.
    E. Webbing of the second and third toes.
4. A 6-year-old girl is brought to the clinic because of early breast development. She is evaluated for precocious puberty. Laboratory tests demonstrated increased luteinizing hormone, follicle-stimulating hormone, and estradiol levels. The need to treat her condition is discussed with her parents. If left untreated, which of the following sequalae is most likely to occur in this patient?

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	EPIPHYSEAL CLOSURE	ADULT HEIGHT
A.	Early	> Expected height
B.	Early	< Expected height
C.	Late	At Expected height
D.	Late	> Expected height
E.	Late	< Expected height

5. A 16-year-old girl is referred for evaluation of tall stature. She is 6 ft 2 in (188 cm) tall. Her father was 6 ft 4 in (193 cm) tall and died suddenly at age 40 years. At physical examination, she has long arms and lower extremities, long fingers, and pectus excavatum. A cardiac workup showed enlarged aortic root, and ophthalmology evaluation demonstrated a dislocated lens.

   Which of the following is the most likely diagnosis in this patient with tall stature?
   A. Beckwith-Wiedemann syndrome.
   B. Homocystinuria.
   C. Marfan syndrome.
   D. Sotos syndrome.
   E. Weaver syndrome.

Additional Resources for Pediatricians

AAP Textbook of Pediatric Care, 2nd Edition

- Chapter 193: Short Stature - https://pediatriccare.solutions.aap.org/chapter.aspx?sectionId=109663743&bookId=1626&resultClick=1

Point-of-Care Quick Reference

- Short Stature - https://pediatriccare.solutions.aap.org/content.aspx?gbosid=165466

Parent Resources from the AAP at HealthyChildren.org

- When a Child is Abnormally Tall: https://www.healthychildren.org/English/health-issues/conditions/Glands-Growth-Disorders/Pages/When-a-Child-is-Unusually-Short-or-Tall.aspx
- When a Child is Unusually Short: https://www.healthychildren.org/English/health-issues/conditions/Glands-Growth-Disorders/Pages/When-a-Child-is-Unusually-Short.aspx
- Tips for Parents About Growth Hormone Injections: https://www.healthychildren.org/English/health-issues/conditions/Glands-Growth-Disorders/Pages/Growth-Hormone-Injections.aspx

For a comprehensive library of AAP parent handouts, please go to the *Pediatric Patient Education* site at http://patiented.aap.org.