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A General Pediatric Approach to Evaluating a Short Child

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Objectives After completing this article, readers should be able to:

1. Describe the most critical test for evaluating the growth of a child.
2. Discuss the implications of decreased growth velocity after age 3 years.
3. Name the two most common normal variations resulting in short stature during childhood.
4. Characterize the growth velocities of children who have constitutional delay of growth and adolescence or familial short stature during the first 2 or 3 years after birth.
5. Recognize what a low weight-for-height ratio suggests.
6. List clues suggestive of syndromic or genetic disorders.
7. Describe how children who have congenital growth hormone deficiency may present in the newborn period.

Definition

A child's growth pattern is a strong indicator of his or her general health. However, it may be difficult to distinguish between normal and abnormal growth. The purpose of this review is to highlight differences between growth patterns seen in normal variations of growth and those seen in pathologic conditions. In this review, growth patterns associated with normal variations or pathologic conditions are presented in the context of growth velocity, weight-for-height, and dysmorphic physical features.

The most critical factor in evaluating the growth of a child is determining growth velocity (regardless of the absolute height). The simplest method of identifying whether a growth velocity is normal for age is to observe whether the child's height pattern is "crossing" percentile lines on a linear growth curve. (The most up-to-date growth curves can be found on the Web site of the Centers for Disease Control and Prevention at www.cdc.gov/growthcharts.) Accurate height measurements performed at 6-month intervals and plotted to the year and month of age on the growth curve are an inexpensive means of identifying whether growth velocity is normal. Still more precise determinations of growth rate can be determined by using growth velocity charts.

In addition to growth velocity, consideration of "absolute height" is important. In this regard, one might ask, "What height is 'short?'" Definitions include population-based definitions based on normative data, such as "shorter than the 5th percentile" or "shorter than two standard deviations below the mean (2.5 percentile)." Other definitions are influenced by societal expectations, such as "too short for basketball" or "shortest in the class." A biologic definition of short stature is obtained from analysis of the child's height in the context of the expected genetic potential conferred by the parents or the

Abbreviations

- ACTH:** adrenocorticotrophic hormone
- BA:** skeletal or bone age
- CA:** chronologic age
- CDGA:** constitutional delay of growth and adolescence
- CNS:** central nervous system
- FSS:** familial short stature
- GH:** growth hormone
- GHD:** GH deficiency
- GHBP:** GH binding protein
- GHRH:** GH-releasing hormone
- IBD:** inflammatory bowel disease
- IGF:** insulin-like growth factor
- IGFBP:** IGF binding protein
- IUGR:** intrauterine growth restriction
- MRI:** magnetic resonance imaging
- SD:** standard deviation units from mean for age and sex
- SGA:** small for gestational age or intrauterine growth restriction
- SRIH:** somatotropin release inhibiting hormone
- T4:** thyroxine
- TS:** Turner syndrome
- TSH:** thyroid-stimulating hormone
- U/L:** upper-to-lower body segment ratio

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mid-parental height or target height (the average of the parents' height percentiles). For example, a boy at the 5th percentile for height might be the shortest in his class, although this would not be unexpected if his mother and father were 4 feet 11 inches and 5 feet 4 inches tall, respectively.

Finally, short stature should not be confused with failure to thrive. Failure to thrive is associated with greater impairment in weight gain than linear growth (resulting in a reduced weight-for-height ratio). Although failure to thrive may be associated with short stature or slow growth velocity, it primarily represents an inability to gain weight appropriately and only secondarily an impairment in linear growth.

Pathogenesis

Physiology of Growth

Normal somatic growth results from a complex interaction among genetic, nutritional, and hormonal factors in a cellular environment conducive for growth. In examining the causes of poor growth and short stature, it is important to understand the important basic ingredients of normal growth, including nutrition (calories, protein, calcium, minerals, vitamins), oxygen, hormones, the absence of toxins, and the more general components of a healthy environment for children, including adequate sleep, exercise, and psychosocial factors (positive attitude, self-esteem, sense of security, sense of being loved). Hormonal factors, in particular, are required in the right amounts and at the right times for optimal growth. Growth hormone (GH) and insulin-like growth factor-I (IGF-I) play key roles in this process. Other hormones (eg, thyroid hormone, insulin, sex steroids, and glucocorticoids) also affect growth, in part through their interactions with the hypothalamic-pituitary-GH-IGF axis.

Hypothalamic-Pituitary Development

The pituitary gland develops in two parts. The anterior pituitary develops as an invagination of the primitive foregut ectoderm to form the Rathke pouch. This pouch is "pinched off" from the foregut by about 8 weeks' gestation and assumes an anatomic position directly adjacent to the posterior pituitary. The anterior pituitary communicates with the hypothalamus through a capillary plexus. The posterior pituitary arises as a downward extension from the brain and retains direct neuronal connections with the hypothalamus.

The pituitary gland develops as a result of a sequential cascade of programmed gene expression of transcriptional factors triggered by contact between the fetal brain

tissue and oral ectoderm. Several of these genes have been identified and their functions defined, including *Hesx-1*, *Lhx-3/Lhx-4*, *Prop-1*, *Pit-1*, *SF-1*, *Dax-1*, and *GATA-2*. Although much is known about genes involved in normal pituitary development and function, only approximately 12% of hypopituitary children have a definable gene defect; approximately 6% of those have a *PROP-1* defect.

GH Secretion and Action

GH, a polypeptide (191 amino acids), is secreted by the anterior pituitary in pulsatile fashion. GH pulses occur during sleep, exercise, and physiologic stress. These pulses represent the net interaction between two opposing hypothalamic peptides that regulate the synthesis and secretion of GH from the somatotrope: GH-releasing hormone (GHRH) and somatostatin (somatotropin release inhibiting hormone) (SRIH). GH secretion also is regulated by other neurotransmitters that act directly or indirectly through GHRH or SRIH and by negative feedback systems involving GH and IGF-I. Ghrelin (endogenous GH secretagogue) is secreted from the stomach in increasing concentrations as time extends after the prior meal, leading to hunger and a significant rise in GH secretion through the stimulation of GH secretagogue receptors located in the hypothalamus and pituitary. GH circulates in either free form or bound to a binding protein (GHBP) that is structurally similar to the extracellular portion of the GH receptor. GH exerts most of its biologic effects through binding to the GH receptor and stimulating secretion of IGF-I from the liver and other tissues.

IGFs and IGF Binding Proteins

Many of the growth-promoting actions of GH are mediated by IGF-I, which exerts its actions through both endocrine and local effects. IGFs influence fetal growth independently of GH. The IGFs circulate and exert biologic effects, in large part, through interaction with binding proteins (IGFBPs). GH stimulates both IGF-I and IGFBP3 production by the liver. Circulating concentrations of IGF-I are low during the first 5 years after birth; they slowly increase to peak concentrations during adolescence. IGFBP3 values (highly GH-dependent) are not as low as those of IGF-I in the young child, but also increase during childhood and adolescence. GH also acts directly on the growth plate and stimulates local IGF-I production in all tissues. IGF-I blood concentrations also are influenced by malnutrition, chronic renal and liver disease, and hypothyroidism.

Changes With Development

The role of hormonal factors on growth depends on age and developmental stage. Although GH and thyroid hormone are of major importance in the process of normal growth in childhood, their roles in the control of fetal growth are relatively minor. This is illustrated clinically by most infants who have congenital GH deficiency and hypothyroidism being of normal weight and length at birth. The most important factors involved in the control of fetal growth are uterine function and size, maternal nutrition, insulin, and the IGFs and IGFBPs.

Postnatal growth is characterized by rapid linear growth velocity that declines progressively after birth (approximately 25, 12, and 8 cm/y during the first 3 postnatal years). Thereafter, until the onset of puberty, linear growth occurs at a relatively constant rate of 4 to 7 cm and weight gain occurs at approximately 2.5 kg annually in both sexes. A small linear growth deceleration often is seen before the onset of puberty. Throughout childhood, GH and thyroid hormone exert major influences on the process of normal growth, with nutrition and insulin also playing important roles.

At puberty, sex steroids (testosterone, estrogen) act in concert with GH, thyroid hormone, and nutrition, resulting in an accelerated rate of growth known as the pubertal growth spurt. In addition, spontaneous GH levels increase during puberty, most likely in response to estrogen and androgen. The first sign of puberty in females (typically, breast enlargement) precedes the onset of puberty in males (typically, testicular enlargement) by only about 6 months. However, the pubertal growth spurt is a relatively early event in girls and a relatively late event in boys. Thus, the pubertal growth spurt in girls occurs approximately 2 years earlier than in boys, usually at pubertal stage 3 for breast development in girls and pubertal stage 4 in boys. Peak height velocity is slower in girls (8.3 cm/y) than in boys (9.5 cm/y). This factor, combined with a 2-year longer duration of growth in boys, results in an average 13-cm difference in adult height between the two sexes. Growth ultimately ceases following puberty, a result of estrogen-induced epiphyseal maturation and closure in both sexes.

Documenting normal growth velocity is the most valuable tool to exclude a significant growth disorder. However, large infants born to small parents tend to have late deceleration, often during the second year after birth. Small (but otherwise healthy) infants born to large parents tend to experience early growth acceleration, typically during the first 6 postnatal months. An abnormal growth velocity documented after age 3 years, regardless of absolute height, almost always is abnormal

and requires careful evaluation and investigation. During puberty, children again may cross growth channels (either up or down), depending on when the particular child begins his or her pubertal growth spurt relative to that of the normal reference population.

Analysis of the Growth Curve

An appropriate analysis of the growth curve is the most important step in evaluating a child who has a growth problem. Four specific aspects of the growth curve should be examined closely.

Reliability of Measurements

Obtaining and plotting height and weight measurements do not require expensive or sophisticated equipment, but they do require some training and attention to details. The importance of this step cannot be overemphasized; two of the most common reasons for misdiagnosis of growth disorders and inappropriate referral to a specialist are measurement errors and inaccurate plotting of measurements on the growth chart.

Absolute Height

The absolute height of a child bears some relationship to the likelihood of a pathologic condition (ie, a child whose height is three standard deviations [SD] below the mean is more likely to have a pathologic condition than is a child whose height is only 1 SD below the mean). However, most children whose heights are below the lowest percentile (either 3rd or 5th percentile on the height curve) do not have pathologic conditions.

Growth Velocity

The most important aspect of a growth evaluation is the repeated measurement of a child's height over time to assess growth velocity. Most children's linear growth does not occur steadily and continuously; rather, it occurs in small increments. For this reason, as well as inherent inaccuracies in measurements of linear growth when using conventional equipment, accurate determination of growth velocity requires at least 3 and preferably 6 months of observation.

Weight-for-Height Ratio

Determination of the weight-for-height ratio has some diagnostic value in identifying the cause of growth retardation in a short child. Endocrine disorders (including GH or thyroid hormone deficiency or glucocorticoid excess) usually are associated with relatively preserved weight gain or frank obesity in a short child. In contrast, most "systemic" disorders resulting in poor linear

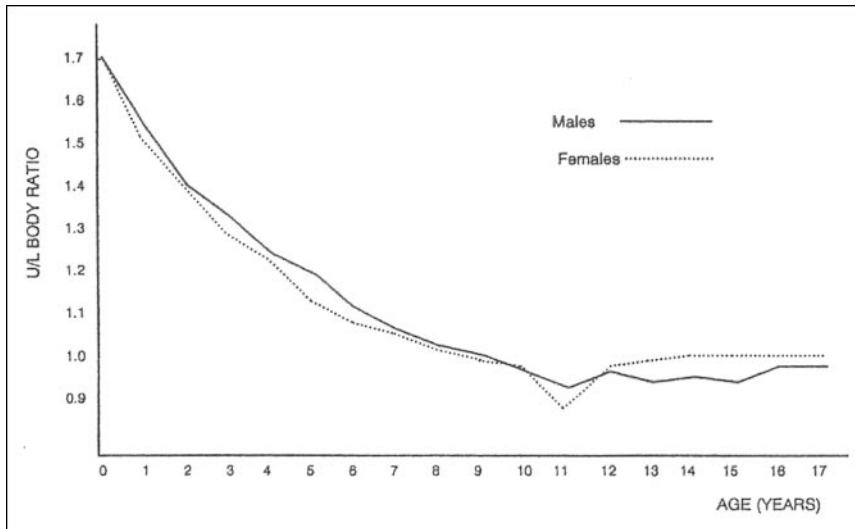


Figure 1. The upper-to-lower (U/L) body ratios of male and female children of various ages. Adapted from Lifshitz F. *Textbook of Pediatric Endocrinology*. 2nd ed. New York, NY: Marcel Dekker, Inc; 1990.

growth are associated with greater impairment of weight gain than linear growth, and affected children tend to be thin for their short stature.

Additional Helpful Parameters for Evaluation Target Height

The height of a child can be judged to be inappropriately short only in the context of his or her genetic potential. One simple method of distinguishing the child who is short, but appropriate for genetic potential, is to determine the target height of the child by using the formula:

$$\frac{[\text{father's height (cm)} + (\text{mother's height (cm)} + 13)]}{2}$$
 for boys

$$\frac{[(\text{father's height (cm)} - 13) + \text{mother's height (cm)}]}{2}$$
 for girls

Calculation of the target height provides a rapid and reasonably accurate index of a child's genetic growth potential. Most children achieve an adult stature within approximately 10 cm of their target height. A child whose current height percentile differs greatly from his or her target percentile is considered "inappropriately" short for his or her genetic potential and deserves a thorough evaluation to exclude an underlying pathology.

Skeletal Maturation

During normal childhood, the process of growth involves an increase in the length of the bones, proceeding in parallel with the rate of skeletal maturation. Bone age (BA) radiography is a method of assessing skeletal matu-

riety. The appearance of representative epiphyseal centers obtained on radiography is compared with age-appropriate published standards. The method used most commonly to assess BA is that of Greulich and Pyle, which examines epiphyseal maturation of the hand and wrist. Methods examining other epiphyseal centers (including the knee or hemiskeleton radiographs) may be especially helpful in infants whose hand and wrist growth plates are too immature for determining an accurate BA by using the hand radiograph alone.

Most conditions that cause poor linear growth also cause a delay in skeletal maturation and a retarded BA. Thus, observation of even a profoundly delayed BA is never di-

agnostic of a specific diagnosis. A delayed BA merely indicates that the associated short stature is to some extent "partially reversible" because linear growth continues until epiphyseal fusion is complete.

In contrast, a BA that is not delayed in a short child is of much greater concern and may, in fact, be of some diagnostic value under certain circumstances. Shortened metacarpals, "coned" epiphyses, or rachitic changes may point toward specific diagnoses, including syndromes, chondrodysplasias, or rickets.

Body Proportions

The upper-to-lower body segment (U/L) ratio indicates whether the short stature is proportionate (ie, involves both the trunk and the lower extremities) or disproportionate (ie, involves one more than the other). The lower segment is obtained by measuring the distance between the upper border of the symphysis pubis and the floor in a standing patient (not wearing shoes). The upper segment is determined by subtracting the lower segment from the standing height. The resulting U/L ratio is compared with normal values for age and sex (Fig. 1).

The U/L ratio normally declines progressively from birth, reaching a nadir during early puberty. With the onset of pubertal growth, the U/L ratio increases slightly until epiphyseal fusion. Skeletal dysplasias involving primarily the spine (eg, spondylodysplasias) often are associated with a decreased U/L ratio for age. Those dysplasias involving especially the long bones (eg, achondroplasia) frequently are associated with an increased

U/L ratio. Because puberty is associated with relatively greater truncal than limb growth, an increased U/L ratio for age may be seen in precocious puberty. A decreased ratio for age (eunichoidism) may be seen in delayed or incomplete puberty (eg, Klinefelter or Kallmann syndrome).

Arm span is approximately equal to height in children 8 years of age or older. Arm span can be measured as the distance from left fingertips to right fingertips in a patient standing, arms spread, against a wall. Arm span can be used as a surrogate for height measurement and for monitoring growth velocity in children who have scoliosis, spina bifida, or leg contractures or after spinal irradiation.

Clinical Entities Associated With Short Stature

The large number of clinical conditions associated with short stature or growth retardation can make the task of identifying a specific diagnosis particularly challenging. The following method may help determine the likelihood of a normal variation in growth or point toward a specific diagnosis if growth pathology is suspected, by using several simple bedside observations and tests.

Normal Variations in Growth

The growth of a child who has constitutional delay of growth and adolescence (CDGA) is characterized by: 1) slowing growth velocity during the first 3 years after birth, typically with both weight and height crossing growth percentiles downward; 2) a normal or near-normal growth velocity, with height below but parallel to the 5th percentile during prepubertal years; 3) delayed BA and pubertal maturation; and 4) adult height usually within the normal range, although occasionally lower than expected for parental height (Fig. 2).

Typically, the child who has CDGA is an otherwise healthy boy who has no phenotypic abnormalities and is described as a “late bloomer.” There often is a positive family history, with the father commonly being short as a child and experiencing a late pubertal growth spurt. BA is always delayed; height plotted against BA often corresponds to the height age. Although CDGA also occurs in

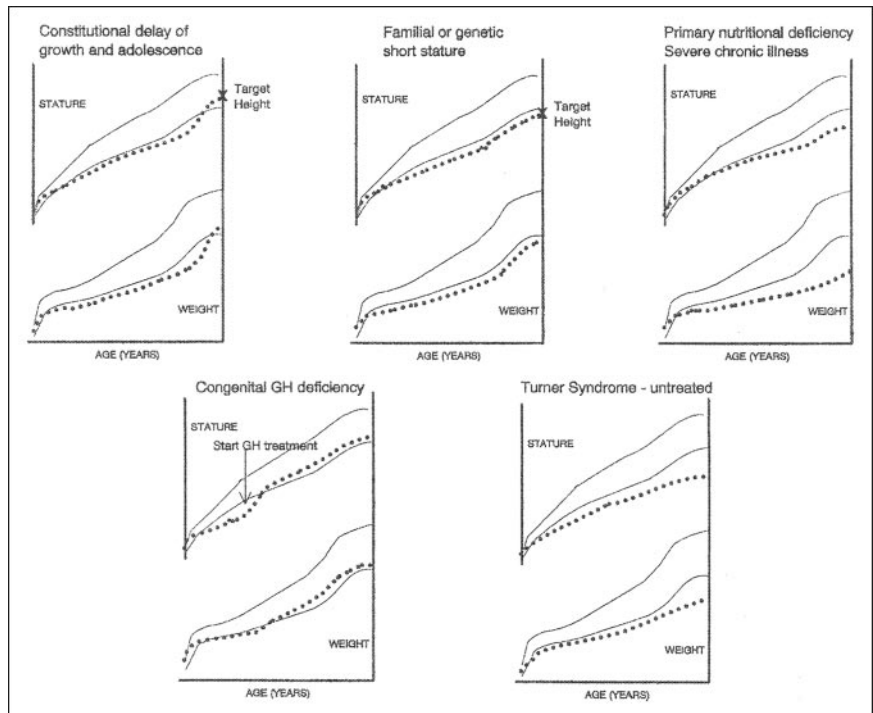


Figure 2. Schematic demonstration of height and weight growth curves in various conditions associated with short stature.

girls, they may be less likely to seek medical evaluation for the associated short stature or pubertal delay.

During infancy and until puberty, children who have familial (genetic or intrinsic) short stature (FSS) grow in a pattern similar to that of most children who have CDGA (Fig. 2). By definition, these children have no evidence of an endocrine or systemic disorder and have a family history of short stature. Most children who have FSS are of normal weight and length at birth. Most cross linear growth percentiles downward during the first 3 years after birth until they reach their genetic-appropriate linear growth percentile, then experience steady growth below but parallel to the normal linear growth curves. BA typically is not delayed and is consistent with chronologic age (CA). Onset of puberty and its rate of progression are normal for CA. Adult height is short, but by definition, appropriate for parental heights.

Proportionate Short Stature With Increased Weight-for-Height Ratio

This group includes children in whom an endocrinopathy should be suspected, such as hypothyroidism, glucocorticoid excess, and GH deficiency (GHD).

GHD. GHD can be congenital or acquired and may occur in association with other pituitary hormone defects. Congenital GHD occurs in two well-described patterns. The first is related to perinatal asphyxia because often affected infants have a history of perinatal distress, breech delivery, cesarean section, and low Apgar scores. The second pattern of GHD presenting in infancy is associated with early prenatal embryologic malformations, including central nervous system (CNS) malformations (eg, septo-optic dysplasia), midface abnormalities (eg, coloboma of the eye, midface hypoplasia, cleft palate and lip, median cleft face, and single central incisors), and in males, micropenis. Many of these infants have a characteristic neuroradiologic picture on magnetic resonance imaging (MRI), with interruption of the pituitary stalk and displacement of the posterior pituitary bright spot (ectopic posterior pituitary). Otherwise, findings on MRI of the brain in GHD may be normal or, alternatively, may show abnormal anatomy such as a small pituitary gland, pituitary stalk agenesis, empty sella, or sellar or suprasellar mass. A small minority (approximately 12%) of children who have congenital hypopituitarism can be shown to have gene mutations involving either the organization and development of the pituitary gland or one or more of the pituitary cell types.

The postnatal clinical course is similar in all types of GHD, with prolonged jaundice and hypoglycemia often present. Failure to thrive, with relatively normal growth velocity, may be present initially. Subsequent linear growth deceleration and normal weight gain typically develop after the first postnatal year (Fig. 2).

Acquired GHD occurs most commonly as an idiopathic diagnosis, but may result from tumors (craniopharyngioma, glioma, germinoma), traumatic head injury, CNS infection or irradiation, or surgical damage to the pituitary and hypothalamus. The physiology usually is that of hypothalamic deficiency of GHRH, rather than pituitary deficiency of GH. Deficiencies of thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), or pubertal hormones or diabetes insipidus also may be present. Although specific clinical features vary according to the cause, slow growth rate is prominent and an overriding feature in most cases.

Clinically, a child who has untreated GHD has short stature, slow growth velocity, a facial phenotype resembling a younger child, delayed BA, and low IGF-I and IGFBP3 values. The biochemical definition of GHD classically has been a peak stimulated GH concentration of less than 10 ng/mL (10 mg/L) in response to two GH stimulation tests (arginine, insulin, clonidine, glucagon). Variations in GH assay methodology influence the

measured GH values. With the recent advent of GHRH as a diagnostic agent, a GH response of less than 18 ng/mL (18 mg/L) to a combined arginine-GHRH stimulation test also has been proposed as a biochemical criterion for the diagnosis.

For a child who has GHD, the rest of the pituitary function must be evaluated to identify potential combined anterior pituitary hormone deficiencies (TSH, ACTH, prolactin, or gonadotropin deficiencies or diabetes insipidus). Children who have severe head injury and children who are long-term survivors of cancer merit longitudinal monitoring of their growth and pubertal development because GHD, primary or central hypothyroidism, ACTH deficiency, and hypogonadism may develop over time.

Recent research has focused on the effects of GHD in adults, who are no longer capable of linear growth. Metabolic effects of GHD include increases in body fat and cholesterol and reductions in lean body mass, bone mineral density, cardiac function, stamina, and quality of life. Thus, GHD has clinical importance not only in growing children but in adults. GH currently is approved by the United States Food and Drug Administration for use in GH-deficient children and adults, those who have Turner syndrome or renal insufficiency, adults who have acquired immunodeficiency syndrome wasting or Prader-Willi syndrome, children born small for gestational age (SGA) who have not reached the 5th percentile by age 2 years, and children who have idiopathic short stature and are not expected to reach an adult height in the normal adult range.

GH INSENSITIVITY. GH insensitivity syndrome is an autosomal recessive syndrome caused by defects of the GH receptor. The phenotype of affected patients is similar in many respects to that of patients who have GHD. Biochemically, such children have elevated serum concentrations of GH and low serum concentrations of IGF-I, IGFBP3, and GHBP.

HYPOTHYROIDISM. Congenital hypothyroidism is identified most often through newborn screening. However, many cases of primary hypothyroidism are acquired after the newborn period. Acquired hypothyroidism in childhood usually is an autoimmune condition (lymphocytic or Hashimoto thyroiditis) but occasionally is related to an inborn error of thyroid hormone metabolism or late failure of an ectopic or hypoplastic thyroid gland, undiagnosed at the time of newborn screening.

In untreated hypothyroidism, congenital or acquired, the growth velocity is slow and BA is delayed relative to

CA. Normal intelligence typically can be expected in acquired hypothyroidism developing after 2 years of age and in children who have congenital hypothyroidism detected within the first 2 or 3 months after birth, although the risks of mental retardation and learning deficits are related directly to the length of delay in diagnosis. Children who have a gradual onset of even severe hypothyroidism may be remarkably asymptomatic (with only mild symptoms such as constipation, dry skin, decreased stamina, with or without a goiter) or may be profoundly symptomatic. Whether a child who has severe primary hypothyroidism attains a normal adult stature depends primarily on the duration of untreated hypothyroidism, the adequacy of replacement therapy after diagnosis, and the confounding effects of the onset of puberty.

GLUCOCORTICOID EXCESS. Glucocorticoid excess usually is iatrogenic, caused by pharmacologic treatment of a concurrent disease such as renal or connective tissue disease or cancer. Rarely, it may be caused by endogenous steroid production because of an adrenal adenoma or ACTH-secreting pituitary adenoma. In states of glucocorticoid excess, growth velocity is slow, BA is delayed relative to the CA, and weight gain and elevated blood pressure typically are present. In contrast, weight gain in endogenous obesity usually increases the growth velocity slightly. Whether the child exposed to high doses of glucocorticoids attains a normal adult stature depends on the steroid dose, the duration of exposure, and the confounding skeletal maturing effects of sex steroids, either from the intervening onset of puberty or sex steroids cosecreted (in the case of endogenous Cushing syndrome) with glucocorticoids.

Proportionate Short Stature with Decreased Weight-for-Height Ratio

This group includes most children who have growth disorders due to a variety of systemic diseases, most notably undernutrition or malnutrition. Children who have nutritional deficiency (eg, starvation, anorexia nervosa, malabsorption, or poorly controlled type 1 diabetes mellitus) typically show weight loss or a decline in the rate of weight gain that is more pronounced than the decline in linear growth (Fig. 2). These children also typically exhibit delayed sexual development and delayed skeletal maturation proportionate to the severity of the underlying malnutrition or systemic disease activity.

Malnutrition (protein, calorie) is the most common cause of short stature internationally. Short stature may be associated with single-nutrient malnutrition (calcium, vitamin), disinterest in eating, fear of obesity or fear of

cholesterol, or anorexia nervosa. With restoration of adequate nutrition, growth usually accelerates (catch-up growth), although adult height may be compromised if the malnutrition is profound, especially in the first few years after birth.

Malabsorption and inflammatory bowel disease (IBD) should be emphasized as causes of growth disorders because both can be missed during a cursory history. IBD may result in growth retardation or failure to thrive even prior to the development of overt gastrointestinal symptoms.

The cause of growth retardation in socially neglected children usually is nutritional and related directly to inadequate caloric intake. Affected children typically present with failure to thrive that involves a more severe compromise of weight than height. However, an occasional neglected child develops a clinical picture characteristic of GHD, known as psychosocial dwarfism. Psychosocial dwarfism results from a disturbed parent-child relationship and has a characteristic behavior pattern. Infants and children may demonstrate bizarre behavior (eg, encopresis, personality disorders, aggressive food- and water-seeking habits). They also may have abnormal pituitary hormone responses to provocative testing. Growth velocity is slow, and BA is delayed relative to CA. Typically, such children resume normal growth when removed from the adverse home environment.

Virtually any chronic systemic disease can attenuate growth to a degree dependent on the severity and adequacy of management of the underlying disease. The systemic diseases most likely to be “silent” or subtle include gastrointestinal disorders (IBD, celiac disease), which can impair growth years prior to gastrointestinal symptoms, and some kidney diseases. Renal tubular acidosis or nephrogenic diabetes insipidus may be present from birth and typically present with a clinical picture of failure to thrive. In contrast to many cases of subtle renal and gastrointestinal disease, most growth failure associated with other chronic diseases (heart, pulmonary, immunologic, connective tissue, neurologic) is evident clinically and obviously related to the status of the underlying disease. For example, a small heart murmur not associated with exercise intolerance or cyanosis is unlikely to be the cause of growth failure in contrast to the growth impairment seen with recurrent episodes of congestive heart failure.

Disproportionate Shortening and Dysmorphic Features: Genetic or Syndromic Causes of Short Stature

Skeletal dysplasias and clinical syndromes are diagnosed most commonly because of abnormalities evident on a

careful physical examination. These abnormalities, including short stature, may be evident at birth or may become more evident progressively throughout childhood. Skeletal dysplasias usually are associated with relatively more shortening of the limbs than the spine (eg, typical achondroplasia) or vice versa (eg, spondylodysplasia), although some dysplasias may affect the spine and limbs equally. Those conditions that affect spine or limb growth primarily are evident clinically as disproportionate shortening, resulting in an abnormal U/L segment ratio for age. Children who have a skeletal dysplasia may have normal appearances or that of characteristic phenotype, and BA often is not delayed relative to CA. Diagnosis is usually made by radiology, although genetic markers have been identified for many conditions.

Short stature also is an integral part of numerous clinical syndromes (some clinically definable and others not) and chromosomal disorders, most notably Turner, Down, and Prader-Willi syndromes. Clues to this diagnostic category include dysmorphic features such as webbed neck, simian creases, ear abnormalities, and facial abnormalities.

Special consideration should be given to Turner syndrome (TS) because short stature may be the only clinical manifestation. As a result, a karyotype should be considered in any short girl, especially one whose puberty is delayed. For girls who have TS, the *SHOX* gene is present in only half of its normal dose, and part or all of one X chromosome is missing. Because the *SHOX* gene is essential for normal growth, it is not surprising that growth velocity in TS is slow (Fig. 2). Girls who have TS may have an entirely normal physical appearance or may have a typical phenotype that includes webbed neck, characteristic facies, short metacarpals, shield-shaped chest, and hyperconvex finger- and toenails. Gonadal dysgenesis results in an incomplete or absent puberty, with no pubertal growth spurt, and the BA usually is minimally delayed relative to CA.

Finally, it should be emphasized that only a small minority of infants born SGA or having intrauterine growth restriction (IUGR) have a definable genetic or chromosomal abnormality. Approximately 90% of infants born SGA demonstrate catch-up growth by 2 years of age; 10% never catch up. Those who remain short throughout life typically demonstrate dysmorphic features (eg, fetal alcohol, Russell-Silver, Prader-Willi, Down, Cornelia deLange syndromes).

Diagnostic Approach to the Short Child

Evaluation of a child who has short stature begins with a detailed medical history that focuses on potential causes

Table 1. The Medical History

Family History

- Parents' and siblings' heights, age of onset and tempo of puberty, age of attaining adult height
- Medical problems (parents, siblings, grandparents)
- History of consanguinity or familial congenital anomalies

Birth History

- Maternal problems during pregnancy
- Birthweight and length (presence or absence of intrauterine growth restriction)
- Preterm birth, difficult birth, or breech delivery
- Postnatal problems or complications

Development

- Developmental milestones
- Age of tooth eruption and loss
- School performance

Nutrition

- Calcium
- Protein
- Calories
- Vitamins

Medications

- Methylphenidate or other stimulants
- Anticonvulsants
- Antidepressants

General Health

- Frequent ear infections
- Urinary tract infections
- Constipation
- Poor appetite
- Diarrhea
- Stomach aches

Activity

- Physical activity
- Exercise tolerance
- Stamina

Age of Pubertal Development

- Body odor or deodorant use
- Acne
- Breast development
- Genital development
- Axillary and pubic hair development

Significant Medical Events

- Examples: head injury, surgery, illnesses

Other Persistent Symptoms

- Headaches
- Vision or hearing problems
- Dry skin
- Cold intolerance (covers at night)
- Allergies

Table 2. The Physical Examination

- Facial appearance and apparent maturation; abnormal facies
- Dysmorphic features: palate shape, ear placement, size and shape of hands and feet
- Skin: acne, facial hair, skin temperature, birthmarks
- Body proportions: arm span, upper-to-lower ratio, head circumference
- Hands: short metacarpals, nail beds <80% of fingertip width, palmar creases, clinodactyly
- Chest: widely spaced nipples, pectus excavatum, shield-shaped chest
- Breast development: breast buds (male or female) or breast stage
- General examination: heart, lungs, abdomen, neurologic
- Genitalia:
 - Female: pubic hair stage, clitoris size, labia, vagina, estrogen effect
 - Male: pubic hair stage, genital stage, including phallic and testicle length (>2.5 cm maximum length signifies entry into puberty)

of pathologic short stature (Table 1). The physical examination requires a systematic examination of all body systems (Table 2), particularly including a careful search for dysmorphic features and a calculation of the U/L ratio to exclude disproportionate shortening.

After completion of a thorough history and physical examination, the growth curve should be analyzed, including assessment of the reliability of measurements, calculation of growth velocity, and analysis of weight-for-height in the context of target height. If the growth velocity is unknown, the most important next step is to document growth rate by measuring a second height in 3 to 6 months. If prior nutrition was poor, calories, protein, calcium, and vitamins should be maximized during this interval of growth velocity assessment.

Deceleration of Linear Growth in a Well-nourished or Obese Child

This is the typical growth pattern of a child who has an endocrinopathy (GHD, hypothyroidism, or glucocorticoid excess). The evaluation should begin by measuring serum free thyroxine (T₄) and TSH, determining BA, determining a karyotype in a short girl, and measuring serum IGF-I (if the child is older than 4 y) and IGFBP3. Elevated TSH with low or low normal free T₄ values indicate primary hypothyroidism.

Normal thyroid function test results, a markedly delayed BA, and low IGF-I and IGFBP3 values for age in a

well-nourished child are consistent with a diagnosis of GHD. Depending on these initial results, additional tests may be indicated, including GH stimulation tests, a low-dose ACTH test to assess for cortisol sufficiency, and measurement of the diurnal pattern of TSH (the TSH surge test), which can confirm or exclude central hypothyroidism.

The short, well-nourished child whose thyroid function test and screening tests for GHD results are normal may require more extensive testing for glucocorticoid excess, particularly if the blood pressure is elevated, including measurement of 24-hour urinary free cortisol and creatinine as well as midnight salivary cortisol or an overnight dexamethasone test.

Deceleration of Linear Growth in a Thin Child

A low weight-for-height or an initial decline in weight gain followed by decreased growth velocity may indicate primary gastrointestinal, nutritional, renal, or other chronic systemic disease. In the absence of an obvious systemic medical disorder, the evaluation should focus on excluding silent malabsorption or evidence of an inability to concentrate or acidify the urine (eg, nocturia, enuresis, or polyuria). Although many other chronic systemic illnesses may have similar patterns of growth failure, most are clinically obvious and do not require an extensive laboratory evaluation. When the cause of growth failure remains obscure, a complete blood count with sedimentation rate may help identify patients who have a silent cause such as IBD, and a serum tissue transglutaminase measurement may exclude celiac disease. In addition, measurement of serum electrolytes and a first-void morning urinalysis (including pH and specific gravity) may identify renal tubular acidosis or nephrogenic diabetes insipidus.

The Short Child Who Has Dysmorphic Features or Disproportionate Short Stature

For a short girl or a child who has dysmorphic features, a karyotype should be obtained and referral to a geneticist made. If disproportionate shortening is found, a skeletal dysplasia radiologic survey (read by an experienced pediatric radiologist) can help establish a diagnosis of bone dysplasia.

Deceleration of Linear Growth in Adolescence

Delayed puberty is part of the growth pattern of CDGA, and deceleration of linear growth relative to the growth curve occurs as age-matched peers enter a pubertal growth spurt and the child who has CDGA does not. Children who have pathologic causes of delayed puberty

(eg, Kallmann and Klinefelter syndromes) typically are not short in the prepubertal years, but may cross percentiles on the linear growth curves at ages 12 to 15 years, as age-matched peers experience a pubertal growth spurt. The physical examination confirms delayed sexual maturation, and a low U/L ratio may help identify the truly hypogonadal patient, especially during and after the teen years. Because hypothalamic and skeletal maturation usually go hand in hand, the BA is delayed in nearly all children who have delayed puberty. Elevated serum gonadotropin levels indicate primary gonadal failure; normal or low levels are consistent with either CDGA or gonadotropin deficiency.

Normal Growth Velocity in a Short Child

This clinical scenario is most common in children who have CDGA and FSS. The child is proportionately short and otherwise healthy, and his or her linear growth is below but parallel to the lower percentiles of the growth curve. A delayed BA, a target height in the normal adult range, and a family history of delayed puberty all point to CDGA. BA consistent with CA and a low target height (mid-parental height) suggest FSS.

Conclusion

Although a number of simple diagnostic measurements (including analysis of weight relative to height and calculation of U/L ratio) and associated clinical findings (including dysmorphic features and SGA) are helpful, the most useful test in distinguishing the short normal child from one who has a pathologic condition is the collection of accurate height measurements over time and calculation of growth velocity. Most apparently healthy children who have short stature but are growing at a normal growth velocity are normal and healthy. On the other hand, any child whose growth velocity is declining, regardless of absolute height, merits careful evaluation. During the first 3 years after birth, most channel changes on the linear growth curve are normal. Examples include the large infant born to small parents or the small infant born to tall parents growing into a more “genetically appropriate” growth channel or the child who has CDGA or FSS adjusting to his or her own channel at the lower percentiles. Height channel changes during the teen years may be normal and indicative of variations in the onset and tempo of puberty among normal individ-

uals. A subnormal growth velocity at any other time indicates disease until proven otherwise. Indeed, the process of linear growth is a sensitive and powerful reflection of the general health of a child. The physician who understands a few simple concepts distinguishing normal from abnormal growth patterns can reassure the anxious parent of a healthy short child and is well prepared to embark on a focused and efficient screen for pathologic causes and to make appropriate referrals to a pediatric endocrinologist.

Suggested Reading

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

9. In which of the following conditions is the bone age consistent with chronologic age (ie, not delayed)?
- Acquired hypothyroidism.
 - Constitutional delay of growth and adolescence.
 - Familial short stature.
 - Glucocorticoid excess.
 - Psychosocial dwarfism.
10. Which of the following statements regarding growth in children is *true*?
- Crossing height percentiles in the first 3 years after birth can be normal.
 - The best indicator of the appropriateness of a child's growth is the comparison of the child's actual height with the target height.
 - The pubertal growth spurt occurs later in puberty in girls than it does in boys.
 - The upper-to-lower body segment ratio is at its highest during puberty.
 - The weight-for-height ratio has little importance in the evaluation of a child who has short stature.
11. You are evaluating a 6-year-old girl for short stature. Her growth chart reveals a birth length at the 60th percentile and a current height at the 5th percentile. Her growth velocity over the last 2 years has been 3 cm/y. Her weight is at the 50th percentile. Findings on her physical examination otherwise are within normal limits, and her intelligence appears normal. There are no midline defects or dysmorphic features. Her bone age is 4 years. Of the following, the *most* likely diagnosis is:
- Congenital hypothyroidism.
 - Crohn disease.
 - Growth hormone deficiency.
 - Spondylodysplasia.
 - Turner syndrome.
12. A 15-year-old boy is brought to your clinic by his mother. He tells you that he is concerned that he is the shortest boy in his class at school. His mother's height is 155 cm (61 inches), and his father's height is 178 cm (69 inches). His height is 158 cm (62 inches), which is between the 5th and 10th percentiles. You think that he likely has either constitutional delay of growth and adolescence or familial short stature. In addition to an evaluation of his pubertal development, the assessment that is *most* likely to give you the information you need to distinguish between these two conditions is:
- Bone age.
 - Calculation of his target height.
 - Calculation of his upper-to-lower body segment ratio.
 - Growth hormone assay.
 - Growth velocity measurement.
13. You are evaluating a 2-year-old girl who is new to your clinic. Her mother is worried that she seems small. She has had no recurrent infections, and her mother says that her daughter's appetite is good. Her mother appears petite and says that her height is 5 feet 1 inch. The child's weight is 9 kg (below the 3rd percentile), and her height is 78 cm (3rd percentile). She is appropriately interactive with her mother and shows no obvious behavior abnormalities. Findings of her physical examination are normal except for very little subcutaneous fat. Her bone age is 12 months. Of the following, the *most* likely explanation for her growth failure is:
- Celiac disease.
 - Familial short stature.
 - Growth hormone deficiency.
 - Psychosocial dwarfism.
 - Turner syndrome.

A General Pediatric Approach to Evaluating a Short Child

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