CME

Growth and Growth Disorders in Children and Adolescents

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Evaluation of a child's growth is one of the most important aspects of the general pediatric visit. Concerns about abnormal growth are the leading reasons general pediatricians refer patients to a pediatric endocrinologist.[1]

There is wide variation in normal growth patterns and an even greater variety of conditions that manifest with growth abnormalities. Here, we review patterns of normal growth in the pediatric and adolescent populations. We then review abnormal patterns of growth that require further evaluation and possible treatment.

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CME EDUCATIONAL OBJECTIVES

1. Describe typical variations in normal growth patterns encountered in children and adolescents.
2. Identify abnormal growth patterns in children and adolescents.
3. Discuss conditions associated with growth failure in children and adolescents.

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NORMAL GROWTH PATTERNS

Assessing Growth

The mainstay of monitoring pediatric growth is obtaining and maintaining accurate measurements of the child. To measure growth properly, the pediatrician should have well-calibrated equipment in the office that includes weighing scales (both for infants and older children), a stadiometer for assessing height, and a tape measure.[1]

The height or length of a patient should be measured at every office visit. The stadiometer should be appropriate for the patient's age, with a recumbent stadiometer being used for children younger than 3 years of age (to measure length) and a standing stadiometer being used for children older than 3 years (to measure height).[1]

It is inappropriate to measure a child standing before 3 years of age because it is difficult for these children to understand how to stand properly against the stadiometer for an accurate measurement. Ideally, three measurements should be taken in succession and then averaged. The measurements should then be transferred to the appropriate growth chart for sex, population, and diagnosis. Lipman and colleagues showed that only 30% of children measured in 55 different primary care offices utilized the proper technique.[2]

The growth charts most commonly used in pediatric practice in the US are those published by the Centers for Disease Control and Prevention (CDC). In 2010, new recommendations were released regarding whether to use CDC growth charts or charts produced by the World Health Organization (WHO). The WHO charts are growth standards, describing how children should grow based on longitudinal data from various locations around the world under ideal growth conditions. These charts are used for ages 0 to 59 months and reflect growth patterns expected for breast-fed infants.

The CDC charts are growth references, specific to the US, and obtained from cross-sectional data of all children born between certain time periods. The reference ranges for what is considered underweight/short stature or overweight/tall stature are different between the two charts, with WHO limits set at the 2.3rd and 97.7th percentiles (equivalent to <–2SD and >2 SD below and above the median, respectively), and CDC limits being set at the 5th and 95th percentiles.

The latest recommendation from the CDC is that WHO charts be used for children younger than 2 years of age, while the CDC charts should be used from 2 years to 20 years of age. This recommendation was based on the WHO charts taking into account that breast-feeding is the preferred method of feeding for infants, and reflect how breast-fed infants should grow.[3] It has been shown that prevalence of overweight, underweight, and short children is altered when the CDC cutoff points are used for the WHO charts. It is, therefore, important to use the appropriate cutoffs.[4]

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Requirements for Normal Growth

When children are not growing appropriately, several steps must be taken to ensure that the minimum requirements for proper growth are being met. First, the nutritional status of the patient must be assessed. Inadequate nutrition is the most common cause of growth failure worldwide.[1,5] Adequate calories must be provided to a child for proper growth.

Keeping a detailed, accurate food log for at least a week for older children and adolescents is a good strategy for assessing the number and quality of calories consumed daily. Should a patient be growing poorly despite apparent adequate caloric intake, one must screen for both malabsorption and other underlying chronic illnesses.

Laboratory studies should include a complete blood count to look for anemia, an erythrocyte sedimentation rate to exclude inflammation, and a comprehensive metabolic panel to assess electrolyte balance, renal, and liver functions.

When a child presents with unexplained growth failure, one must keep in mind that inadequate growth may be the initial presentation of malabsorptive diseases such as celiac disease or of inflammatory conditions such as Crohn's disease.[5]

Patients who are not growing normally should also be screened for thyroid disease by thyroid-stimulating hormone (TSH) and free thyroxine (T4) measurements to exclude hypothyroidism. Girls with apparent growth failure should have a karyotype to assess for possible Turner's syndrome or Turner's mosaicism, even in the absence of obvious physical features of Turner's syndrome.[1,6]

Variations in Normal Growth

Familial Short Stature

Most patients are referred to the pediatric endocrinologist for concerns about short stature and slow growth. However, there are instances where being short is considered normal for a particular patient. One such instance is familial short stature. As implied in the name, patients with familial short stature have parents who are short. The expected height for the patient based on midparental height calculation is, therefore, smaller than a significant portion of the general population.

Patients with familial short stature are differentiated from patients with growth failure based on the fact that they do not cross growth curves, but rather grow at an age-appropriate rate that is at the lower end of the normal growth curve (Figure 1, see page e5). Patients with familial short stature have bone ages that are relatively close to their chronologic age.[5]

One must not forget, however, that a patient with short stature in a short family may still have an inherited form of pathological growth. The diagnosis of familial short stature should be one of exclusion, with other causes of poor growth being ruled out before a final diagnosis is made.

One must also keep in mind that there are familial causes of short stature that do not necessarily fit the diagnosis of familial short stature (eg, achondroplasia). The role of intervention in the

case of familial short stature is controversial, but many endocrinologists feel that in the absence of a pathological cause for the short stature, treatment is not warranted.

Constitutional Delay in Growth and Puberty

Another reason patients are often referred is for short stature combined with absent puberty at an age when puberty is expected to have started. Typically, 95% of girls manifest at least one sign of puberty by 13 years of age. Boys should begin puberty by 14 years of age. In patients with delayed puberty and slow growth, a careful family history is needed to determine if the patient may be displaying constitutional delay of growth and puberty.

There is often a history of a family member who also did not begin puberty until late into the teenage years. These patients can be difficult to diagnose because they may appear to be slowing in growth as they cross growth percentiles around the time of the anticipated pubertal growth spurt. However, this pattern can be deceiving. These patients actually grow at a normal prepubertal growth velocity for longer than their pubertal peers whose growth velocity increases at the time of the normal growth spurt. As a result, patients with constitutional growth delay fall behind their peers initially, but have an increased growth velocity later when puberty progresses.

To differentiate patients with constitutional delay from those with familial short stature, especially when a child is prepubertal, a bone age X-ray can be performed. Patients with constitutional growth delay have a bone age that is delayed compared to the chronologic age. The bone age will be appropriate for height age (Figure 2, see page e6). Similar to familial short stature, patients with constitutional delay usually do not require treatment.

ABNORMAL GROWTH PATTERNS

There are many conditions for which short stature represents true pathology that need further evaluation and possible treatment (Sidebar, see page e7). In some patients, growth failure is a manifestation of other syndromes, whereas in others, a reason for growth failure cannot be found.

Evaluation of the GH/IGF-1axis

Growth hormone (GH) is secreted from the anterior pituitary in a pulsatile fashion. Its secretion is influenced by many factors, but it is mainly stimulated by the release of hypothalamic growth hormone-releasing hormone (GHRH) and inhibited by somatostatin. There is also a GH secretagogue receptor located in the pituitary gland that is stimulated by the hypothalamic and gastric substance ghrelin.

Ghrelin has been shown to stimulate the release of GH independently.[5,7] GH concentrations are highest during slow-wave sleep and its pulsatility changes if the sleep pattern is altered.[5,8] The GH receptor has extracellular, transmembrane, and intracellular domains. The extracellular portion circulates in the blood and can be measured as growth hormone-binding protein (GHBP). GH binds its receptor in bone, adipose tissue, muscle, and the liver and induces dimerization of the receptor.

At the liver, JAK2, a tyrosine kinase, phosphorylates and activates several STAT transcription factors as well as SHC, an intracytoplasmic signaling molecule that results in the sequential activation of several other transcription factors such as serum response factor (SRF) and ternary complex factor (TCF).[5]

These series of reactions eventually result in the production of insulin-like growth factor 1 (IGF-1), insulin-like growth factor binding protein 3 (IGF-BP3), and acid labile subunit (ALS). These three compounds form a trimer for transport to areas of IGF-1 action, including the growth plates.[5]

It is impractical to measure random GH concentrations because of its pulsatile release. Instead, patients are usually screened for GH deficiency by measuring serum IGF-1 and IGF-BP3 levels since they are released at steadier rates. Should these levels be low for age in a poorly growing child, GH provocative testing is then often performed. GH stimulation testing usually involves administering two agents known to cause GH secretion from the pituitary (L-dopa, clonidine, arginine, insulin, glucagon). Serial blood samples are taken to detect the point of maximal serum concentration of GH.

There are several limitations to stimulation testing. Results are often dependent on which assay is used to analyze blood samples. There is poor reproducibility of results even when using the same assay. Due to the normal increase in GH in children going through puberty, there is also debate as to whether prepubertal children should be "primed" with sex steroids before testing to maximize GH secretion.[5,9-10]

Nevertheless, if one combines the results of stimulation testing with the patient's height, growth velocity, physical examination, screening tests, and IGF-1 and IGF-BP3 levels, one may get a more complete clinical picture that allows for proper diagnosis and treatment.

Most patients found to be GH deficient during stimulation testing have isolated idiopathic GH deficiency. However, it is important to examine total pituitary function because growth failure may coexist with one or more other pituitary hormone deficiencies.

Children initially found to be only GH deficient should be monitored periodically for development of other pituitary hormone deficiencies. Patients found to be GH deficient should undergo a brain MRI to evaluate for the possibility of inherited or acquired hypothalamic-pituitary abnormalities. Intracranial lesions such as

Figure 1. Growth Chart Showing Familial Short Stature

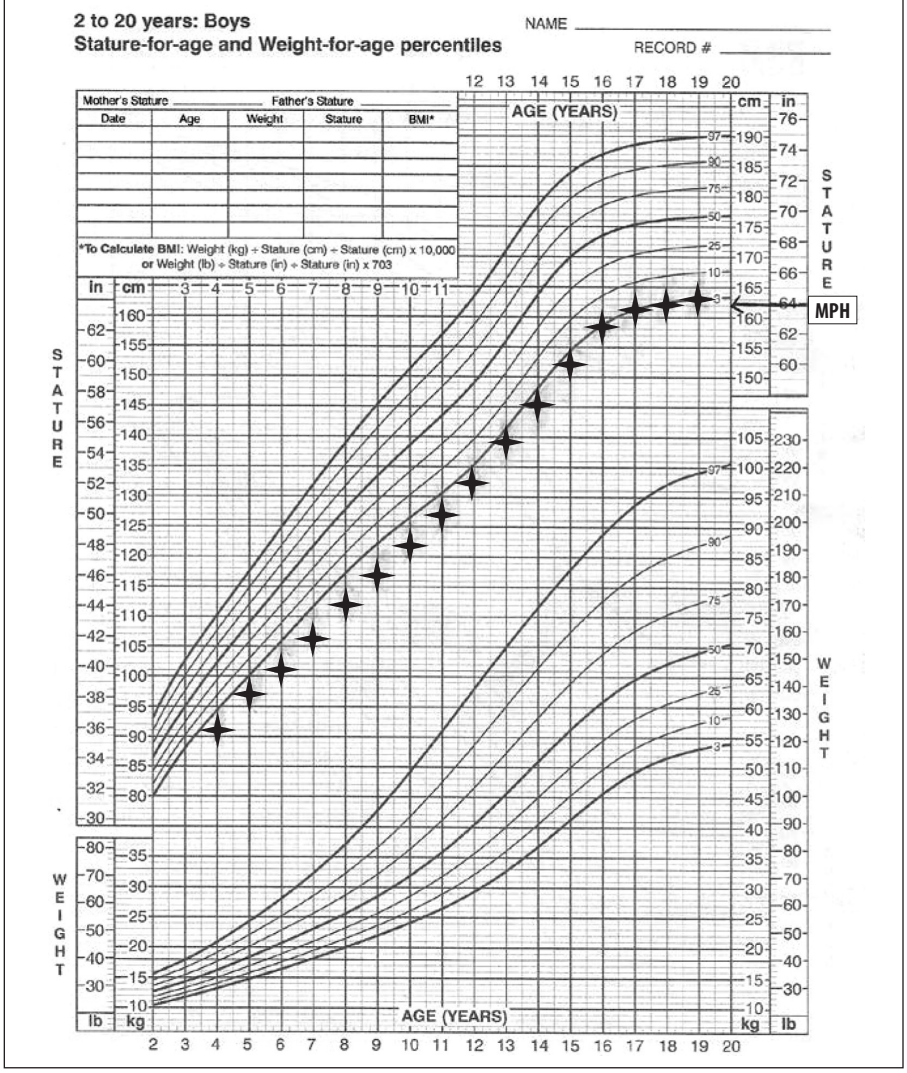

Figure 1. Adapted from the CDC; Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). www.cdc.gov/growthcharts. *Source: Graber E, Rapaport R. Reprinted with permission.* MPH = mid-parental height.

craniopharyngiomas may present with growth failure as the first symptom.

Treatment for GH deficiency involves daily injections of recombinant human GH. GH-deficient children whose baseline heights were as low as –2.7 SD below the mean achieved adult heights between –0.5 to –1.5 SD when treated with growth hormone.[11,12] GH therapy is continued through adolescence until the height velocity decreases to 2 cm/year or until a bone age X-ray reveals fused epiphyses.

A GH-deficient patient who reaches adult height should be taken off GH for 1 to 3 months. An IGF-1 level should then be assessed. If the IGF-1 level is low for the patient's age, a repeat GH stimulation test should be performed. Most patients with initial isolated idiopathic GH deficiency have normal GH peaks on repeat testing and do not need to continue their GH therapy into adulthood. Those with multiple pituitary hormone deficiencies or structural abnormalities of the pituitary are at risk for persistent GH deficiency.[13]

Patients who are found to be deficient should be restarted on GH and continue therapy into adulthood to achieve the metabolic benefits it provides. These benefits include increased lean body mass, improved lipid profiles, and improved bone mineral density as compared with GH deficient patients who do not continue GH therapy.[13-14]

Children with GH deficiency usually present with growth failure. However, any of the steps involved in the GH/IGF-1 pathway may be altered and may also result in growth failure. For example, in Laron syndrome, there is resistance to GH due to a defect in the GH receptor.[15.]

GH-binding protein is the extracellular potion of the GH receptor and may be measured in the blood, but defects in the other portions of the receptor have also been reported. STAT5b, a major transcription factor produced along the JAK2 cellular pathway that is involved in the production of IGF-1, may also be abnormal in children with growth failure.[16] Further downstream, there may be defects in production or binding of IGF-1, IGF-BP3, or, rarely, acid labile subunit.[17]

CONDITIONS ASSOCIATED WITH GROWTH FAILURE

Small for Gestational Age

To be defined as small for gestational age (SGA), patients must have a weight or a length at birth less than –2 SD from the mean for gestational age.[18] These patients must be distinguished from those with intrauterine growth restriction (IUGR). IUGR is defined as having a rate of intrauterine growth slower than expected based on two ultrasound evaluations.[18] Not all patients who are growth-restricted are born SGA, depending on when the intrauterine insult occurs. Kramer and colleagues demonstrated that maternal diabetes, pregnancy-related hypertension, prior history of low birth-weight infants, and maternal cigarette smoking are all risk factors for IUGR.[19]

Infants who are severely growth restricted during gestation tend to be born with larger heads and lengths compared with their weights.[19] Regardless of birth size, patients with IUGR may require future monitoring of growth.[18]

Children born SGA are at risk for disordered growth. Most infants born SGA are expected to catch up in length/height to their appropriate for gestational age peers by 2 years of age, except in the case of very premature infants, who may take longer. Up to 90% of children born SGA show catch-up growth and reach a stature above –2 SD from the mean for age by age 1 year. It is recommended that children who do not catch up should be referred for endocrine evaluation.[18]

Children born SGA who do not catch up spontaneously benefit from treatment with GH. Hokken-Koelega and colleagues found that children born SGA who were treated with GH doses of 1 mg/m^2 or 2 mg/m^2 per day, administered 7 days per week, attained normalization of both their childhood and adult heights. They also had an increase in bone mineral content and lean body mass when compared with non-treated controls.[20]

In the US, Rapaport and colleagues demonstrated a gain in height of 0.8 SD over a 12-month period in SGA patients treated with the FDA approved dose of GH of 0.48 mg/kg/week. Patients who were underweight responded as well as those who were of normal weight.[21] A recent meta-analysis showed that the adult height of SGA patients treated with GH was 0.9 SDS higher than non-treated controls.[22]

Many studies have demonstrated non-growth correlates of being born SGA. The increased rate of weight gain seen in patients born SGA with catch-up growth has been implicated in eventual insulin resistance and decreased bone mineral density in adulthood.[23-24] Reinehr and colleagues demonstrated that being born SGA was an independent risk factor for development of the metabolic syndrome.[25] More studies are needed to validate this finding.

Figure 2. Growth Chart Showing Constitutional Delay of Growth and Puberty.

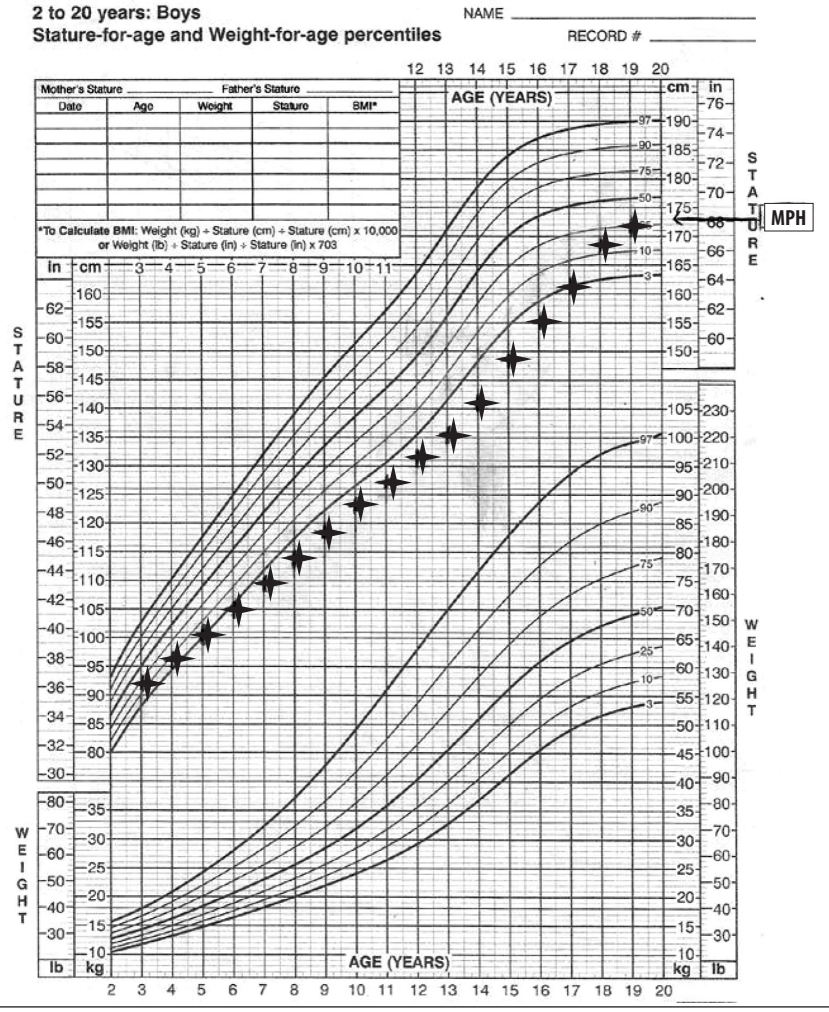

Figure 2. Adapted from the CDC; Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). www.cdc.gov/growthcharts. *Source: Graber E, Rapaport R.* Reprinted with permission. MPH = mid-parental height.

Turner's Syndrome

Turner's syndrome occurs in approximately one in 2,500 live births. Patients with Turner's syndrome can have any one of several genotypes, including 45 X, 45 XX with a loss of part of the X chromosome containing pseudoautosomal genes, or 45 X/46 XX mosaicism.[5,26-27]

Patients with Turner's syndrome almost universally suffer from growth failure that may begin prenatally and manifest as IUGR. The adult height of these patients has been found to be as much as 20 cm below that of the general population.[5,26-27] When plotting the height of a patient with Turner's syndrome, one should use the specialized Turner's syndrome growth charts.

Treatment with GH for Turner's syndrome was approved by the FDA in 1996 and is now standard treatment.[26] Traditionally, GH therapy has been recommended for girls with Turner's syndrome starting in mid-to-late childhood. Recent studies demonstrated significant increases in growth when GH is started at a younger age. One study demon-

SIDEBAR.

FDA-Approved Indications for Recombinant Human GH Treatment in the Pediatric and Adolescent Populations

1985 – Growth hormone deficiency
1993 – Chronic renal insufficiency
1996 – Turner's syndrome
2000 – Prader-Willi syndrome
2001 – Small for gestational age
2003 – Idiopathic short stature
2006 – Short stature homeobox-containing gene (*SHOX*) deficiency
2007 – Noonan's syndrome

Source: Graber E, Rapaport R. Reprinted with permission.

strated achievement of normal height by 6 years of age in girls treated with GH starting between 9 months and 4 years.[28]

Another recent study demonstrated that girls with Turner's syndrome who received GH before 4 years of age had height standard deviation scores 1.09 SDS higher than untreated controls by a mean age of 6.6 years.[29] There are also several studies that have shown that adding low-dose estrogen to the treatment regimen, along with GH, may help to optimize the adult height of girls with Turner's syndrome.[30-31]

Noonan's Syndrome

Noonan's syndrome is an autosomal dominant disorder that occurs in one in 1,000 to 2,500 live births.[26,32] It is phenotypically similar to Turner's syndrome but has a different genetic basis and occurs in males and females equally. Fifty percent to 70% of patients with Noonan's syndrome may have growth failure and short adult stature.[32]

Unlike Turner's syndrome, patients with Noonan's syndrome usually have normal intrauterine growth. Patients with Noonan's syndrome should be plotted on Noonan's syndrome specific growth charts when evaluating their growth. In 2007, the FDA approved the use of GH in this patient population.[26] Studies that demonstrate adult height outcomes in Noonan's syndrome patients treated with GH are limited, but they do demonstrate that better outcomes are achieved with earlier initiation and longer duration of GH treatment.[32]

SHOX Gene Haploinsufficiency

The short stature homeobox-containing gene (*SHOX*) is found in the pseudoautosomal region of both X and Y chromosomes and does not undergo X inactivation.[33] Under normal circumstances, an individual should have two copies of the *SHOX* gene regardless of sex. This gene has been found to be involved in extremity development during prenatal life and appears to also be involved in chondrocyte differentiation and proliferation.[26,34] *SHOX* haploinsufficiency is thought to be the etiology of short stature in girls with Turner's syndrome. This is due to the fact that these patients have only one functioning X chromosome, and therefore, only one functioning *SHOX* gene.

It is estimated from various reports that 1% to 15% of patients with apparent short stature of unknown etiology actually have *SHOX* haploinsufficiency.[26,33] The FDA approved the use of GH for treatment of growth failure due to *SHOX* haploinsufficiency in 2006.[26]

Idiopathic Short Stature

Idiopathic short stature (ISS) is defined as having a height < –2 SD below the mean for age, sex, and population group without any discernable evidence of other pathology.[6,26] ISS may exist as a primary diagnosis alone or may be subcategorized to include ISS with familial short stature or constitutional delay of growth and puberty.[6] Patients with ISS are often predicted to have an adult height below that expected based on midparental height.

The FDA approved the use of GH in this population in 2003 with the conditions that the height of the child be more than –2.25 SD below the mean, the predicted adult height is less than 5 feet 3 inches for men and 4 feet 11 inches for women, and there be no other reason for the child to have short stature (with the possible exception of familial short stature or constitutional delay of growth and puberty).[6,26]

It is thought that GH may increase the adult height of patients with ISS by 3.5 to 7.5 cm when compared with controls.[9,35] Additional considerations for treatment in conjunction with GH include gonadotropin-releasing hormone (GnRH) analogs and aromatase inhibitors. Both of these classes of medications seek to decrease bone age maturation while allowing the child to continue to grow.[6]

In one study, histrelin, an implantable GnRH agonist, slowed bone age advancement from 1.7 ± 0.5 years to 0.6 ± 0.4 years after 9 months of treatment. However, growth velocity was significantly reduced during treatment as well.[36] These agents are still considered experimental when used for improving growth and more studies are needed.

IGF-1 has received some attention recently as a potential treatment for ISS. Currently, IGF-1 is only approved for those patients with proven IGF-1 deficiency (IGF-1 levels –3 SD from the mean) with heights below –3 SD from the mean for age that have normal stimulated GH levels.

There is a lack of prospective studies that show clear benefit of IGF-1 for ISS. IGF-1 has also been associated with potential side effects, including hypoglycemia, headaches, lymphoid tissue

hypertrophy, and coarsening of facial features. Further studies must be performed before IGF-1 can be considered a treatment option for ISS.

The concept that short stature alone is a problem that must be treated often leads to patients seeking treatment for cosmetic, rather than medical, reasons to attain an adult height the patient feels is appropriate.[37] It is important to stress that short stature itself is not necessarily a medical problem. However, a pattern of growth consistent with growth failure (decreasing growth velocity, growth velocity consistently <50 percentile) regardless of height percentile should be evaluated further.

If an underlying cause of growth failure cannot be found, we propose that it is appropriate to use a term such as "idiopathic growth failure" or "growth failure of unknown etiology" (GFUE) rather than "idiopathic short stature." These terms take the focus off stature as the overriding problem and place it on an element all can agree needs investigation and, if persistent, needs intervention for its reversal. Height predictions always, but especially in the face of subnormal growth rates, are likely to be inaccurate and should be provided with a great deal of caution.[38] We believe familial short stature and constitutional delay of growth and puberty should be removed from the current overall category of "ISS"[6] and placed under the "normal variant category."

CONCLUSIONS

Abnormal growth is a major concern for both pediatricians and families alike. Certain populations of children are at increased risk for growth failure and should be evaluated carefully. Others may appear to be short and possibly growing abnormally but may fall within the spectrum of what is normal for the family. For those that have true growth failure, nonendocrine causes must be considered.

If an endocrine etiology is the cause of growth failure, several treatment options are currently approved to aid in reversing the process. These therapies should be administered by an experienced pediatric endocrinology team to ensure correct diagnosis, appropriate treatment, and avoidance of potential side effects. ■

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