Normal Variant and Idiopathic Short Stature

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Key Points

- Familial short stature and constitutional delay of growth and puberty are normal physiologic variants of growth.
- Familial short stature, constitutional delay of growth and puberty, and idiopathic short stature do not have an organic etiology. Idiopathic short stature is distinguished from normal variant short stature in that predicted adult height is below the genetic target height range.
- In 2003, the FDA approved growth hormone for the treatment of idiopathic short stature which generated controversy within the medical community.
- Height outcome data for growth hormone treatment of children with idiopathic short stature is variable with a mean gain in height of 4–7 cm.

3.1 Introduction

Short stature is defined as a height ≤−2 standard deviations (SD) below the mean for age, sex, and population. Height in a given population follows a normal Gaussian distribution; therefore, it is expected that the height of 2.3% of a population will fall 2 SD below the mean for age and sex [1]. Among this 2.3% of the population, the majority of these individuals will have a normal variant of short stature or idiopathic short stature, while some may have pathological causes of short stature.

Normal variant short stature is comprised of familial short stature (FSS) and constitutional delay of growth and puberty (CDGP).These individuals attain a final adult height consistent with their target genetic height, while individuals with idiopathic short stature have predicted adult heights below their target height range. Frequently, FSS and CDGP are considered as subtypes of ISS. Since the growth patterns of individuals with FSS and/or CDGP are usually consistent with that of a first degree relative and their final adult height conforms with their target height, these diagnoses most suitably represent "normal variants" of growth [2].

Normal variant and idiopathic short stature constitute forms of nonpathologic short stature, meaning that the short stature is not caused by intrauterine growth restriction, chronic disease, an endocrine disorder, skeletal dysplasia, or genetic disorder.

3.2 Auxologic Methods to Assess Growth

3.2.1 Length and Height Measurement

Accurate length and height measurements are critical for assessing a child's growth pattern. Until a child can stand, an infant or adult horizontal measuring board is used to measure length. The infant or child is placed supine on the board with one person holding the head in the Frankfort plane, flush with the headboard (Fig. 3.1). The Frankfort plane is defined as the linear plane created by the intersection of the outer epicanthus of the eye with the upper 1/3 of the ear. The second person should maintain the infant's knees fully extended and feet upright and parallel to the footboard. Height is measured with a wall-mounted stadiometer, and the child is positioned with their head, shoulders, back, buttocks, and heels flush against the back of the stadiometer. The child's knees are extended with their feet together and head positioned in the Frankfort plane (Fig. 3.1) [3]. To improve the accuracy of length and height measurements, a minimum of three measurements should be obtained and the mean of the three measurements used. Weight, length, weight for length, and head circumference should be plotted on the Centers for Disease Control and Prevention (CDC) growth charts from birth through age 3. When the child is able to stand for a height measurement, weight, height, and body mass index should be plotted on the CDC growth charts for children age 2–20 [4].

Within the first 2 years of life, it is common for an infant's weight and length to cross growth percentiles, gravitating toward percentiles consistent with their genetic potential. Thereafter, crossing length or height percentiles should not occur, with the exception of children with CDGP, who may continue to exhibit a decline in length or height percentile until ages 3–4. Thereafter, they maintain a normal linear growth velocity and will grow at a consistent percentile. Height measurements are 1 cm less than length measurements which frequently accounts for the apparent

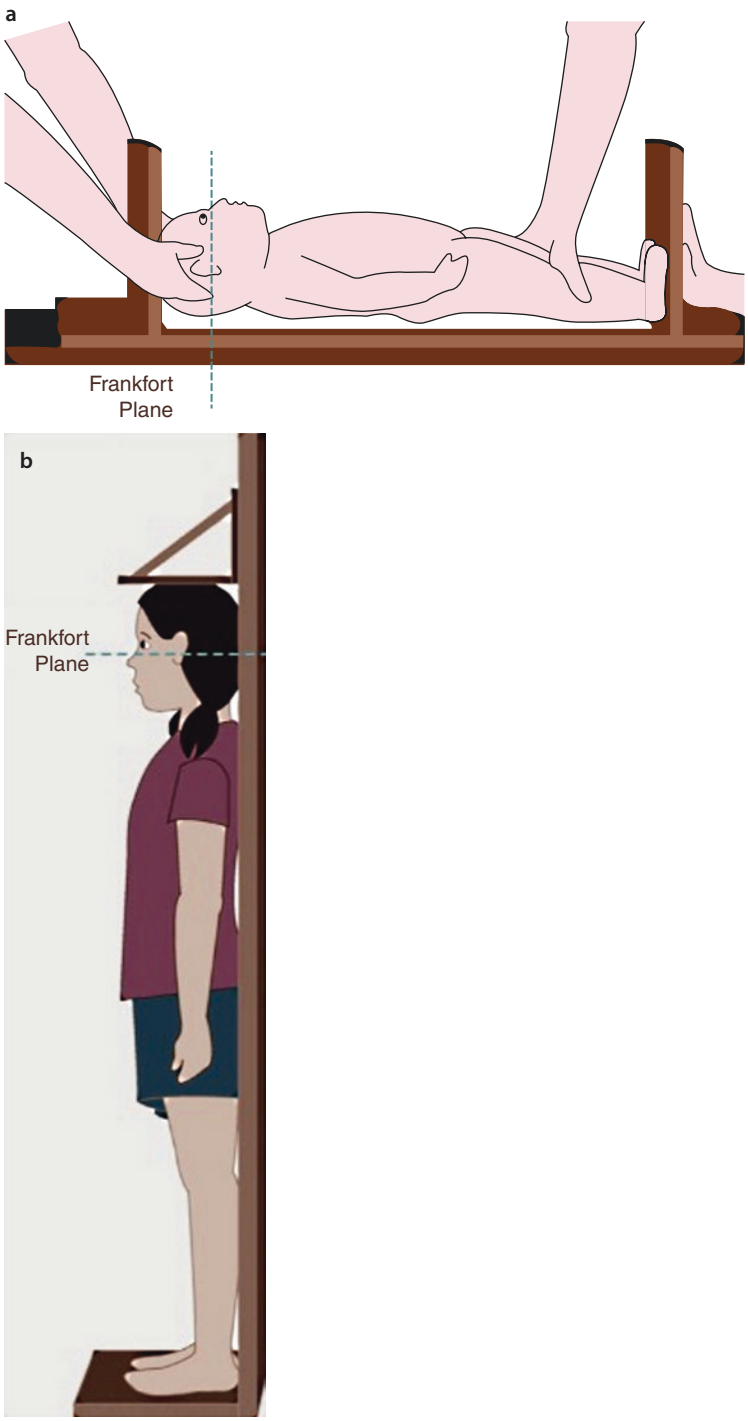

Fig. 3.1 Length and height measurements with an infant board and wall-mounted stadiometer. Note the position of both the infant's **a** and child's **b** heads in the Frankfort plane (From Foote et al. [3]. Reprinted with permission from Elsevier)

decline in growth rate when a child is transitioned from a length measurement to a standing height.

Assessing a child's pattern of weight gain, linear growth, and gain in head circumference from their growth chart is an important part of an evaluation for short stature. Pathological causes of poor growth secondary to nutritional causes or chronic disease initially affect weight gain and then linear growth followed by head circumference. In contrast, children with endocrine disorders typically present with normal or increased weight gain and poor linear growth. Sometimes,

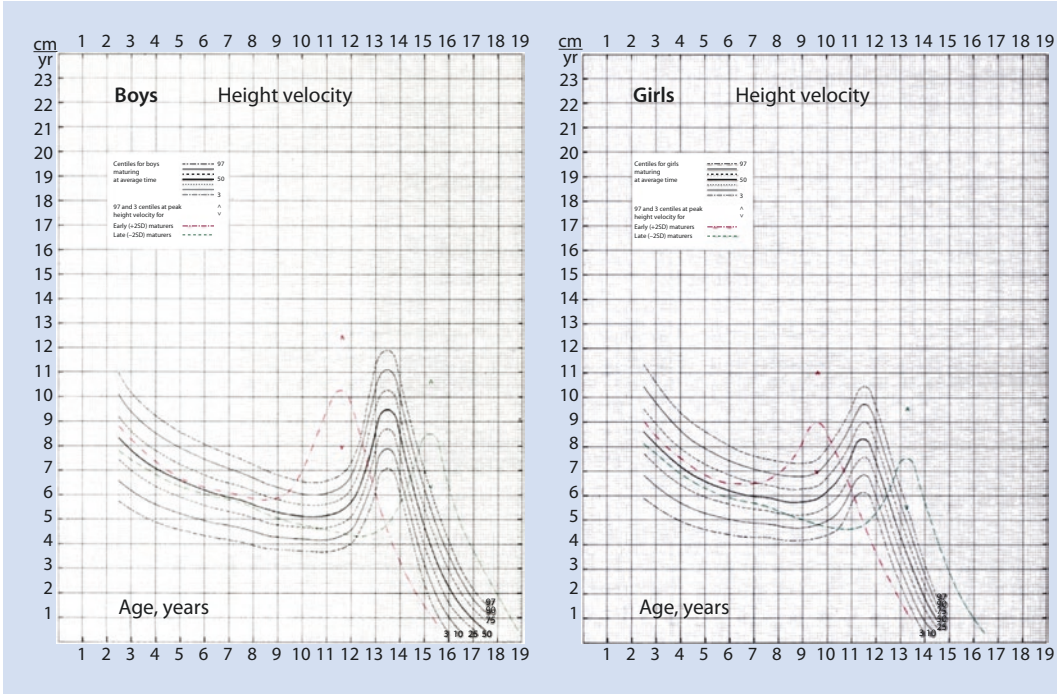

Fig. 3.2 Height velocity charts for boys and girls (From Tanner and Davies [5]. Reprinted with permission from Elsevier)

disorders of malabsorption, such as celiac disease, may initially present with normal weight gain, but poor growth.

3.2.2 Growth Velocity

Determination of growth velocity, expressed as growth rate per year, is essential in the evaluation of a child's growth. In the first year of life, infants grow at a rate of 23–27 cm/year, and by the second year of life, their growth rate declines to 10–14 cm/year. Between 2 and 4 years of age, the growth rate further declines to 7 cm/year and by age 5 to 5 cm/year until the onset of puberty. The pubertal growth spurt in girls peaks at Tanner stage 3 with a growth rate of 6–10 cm/year, while in boys the growth rate peaks at Tanner stage 4 with a growth rate of 7–12 cm/year. Figure 3.2 illustrates the growth velocity charts devised by Tanner et al. for North American boys and girls to assess growth rates throughout childhood and adolescence. These growth velocity charts also contain separate growth rate curves for early and late maturers who achieve their peak growth velocity 2 SD earlier or later than the general population [5].

3.2.3 Anthropometric Measurements

The evaluation of a child with a height 2 SD below the mean for age and sex should include anthropometric measurements of lower segment or sitting height, arm span, and occipitofrontal head circumference to assess for a skeletal dysplasia. Arm span is measured with the child standing in an erect position against a wall with outstretched arms. The distance between the tips of the middle phalanges is measured. In prepubertal children, the arm span is shorter than height, and after midpuberty the arm span exceeds height. In an adult male, arm span exceeds height by 5.2 cm and in an adult female by 1.2 cm. Ethnic differences exist as well, with longer arm spans noted in the African American population. A sitting height (SH) is measured with the child seated on a chair flush against the stadiometer. The sitting height provides the height of the trunk and when subtracted from the child's standing height (HT) provides the value of their lower segment (LS). The SH/HT ratio or SH/LS ratio can be plotted on their appropriate charts to determine whether these body proportions are

suggestive of a skeletal dysplasia. An alternative approach is to measure the child's lower segment from the symphysis pubis to the floor and subtract this value from the child's standing height for their truncal height. The upper to lower segment ratio decreases throughout childhood and adolescence. Due to an increased truncal length relative to limbs, infants have an upper to lower segment ratio of 1.7. By age 3 the upper to lower segment ratio decreases to 1.3, by age 10 this ratio decreases to 1, and in pubertal children the ratio is <1. Children with CDGP have increased leg length and shortened truncal height which accounts for their decreased upper to lower segment ratios of 0.8–0.9.

3.2.4 Bone Age

Skeletal maturation is evaluated by assessing epiphyseal maturation on bone age films, which can be determined by the methods of Greulich and Pyle or Tanner-Whitehouse. The former method compares a child's left hand radiograph to standard bone age radiographs of the left hands of boys and girls from birth through age 18 [6]. The Tanner-Whitehouse method assigns a value to each of the 27 epiphyses in the hand and wrist and sums these values for the skeletal maturity score, which correlates with specific bone ages as determined for select populations [7]. Bayley-Pinneau also provides a table for the percent of adult height achieved at given bone ages which can be used to calculate a child's predicted adult height [8]. Variations in bone age readings among providers and inaccurate height measurements can limit the accuracy of a child's height prediction.

3.2.5 Dental Age

Loss of the primary teeth and eruption of permanent teeth correlate with specific ages and bone ages but vary due to environmental influences. Tooth calcification as determined on an orthopantomogram is less variable and corresponds better with dental age [9, 10]. GHD, hypothyroidism, and CDGP are associated with delayed dental age and bone age.

3.2.6 Target Height

In the 1970s, Tanner et al. defined target height as either the addition or subtraction of 6.5 cm from the mean parental height for a boy or girl, respectively, with 2 SD representing 10 cm above or below the calculated target height [11]. The target height is used to determine a child's expected adult height based on their genetic potential. Measuring the parents' heights at the child's visit improves the accuracy of the target height. Starting in the 1990s researchers devised alternative formulas to calculate the target height because the method of Tanner was determined to either underestimate or overestimate the height of a child with either short or tall parents, respectively. These formulas also tried to account for population mating trends and secular height trends. The 2008 consensus statement from the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology Workshop recommended using a corrected target height SD in lieu of the Tanner method. The corrected target height is calculated as 0.72 X average of father's and mother's height SD with the lower limit of the target height as the corrected target height minus 1.6 SD [12].

The evaluation of a child with short stature requires a review of their previous growth data, accurate length and/or height measurements, a calculated target height, bone age, predicted adult height and possibly arm span, and upper to lower segment ratio. Analyzing auxologic data in conjunction with a detailed history and physical examination is essential for determining whether a child's short stature is a *normal variant* or due to an underlying disorder.

3.3 Etiology and Clinical Presentation

3.3.1 Normal Variant Short Stature

3.3.1.1 Constitutional Delay of Growth and Puberty

In CDGP, within the first 2–3 years of life growth rate declines, crossing percentiles on the growth chart. Usually, by age 3–4 growth proceeds at a normal growth rate. Other features include a

delayed bone age (often a 2–3 SD delay), normal growth velocity, delayed pubertal onset, and eventual attainment of an adult height consistent with genetic heights. Most children with CDGP exhibit a pattern of weight gain that mirrors their linear growth at less than 2 SD below the mean for age, sex, and population. Individuals with CDGP are frequently referred to as "late bloomers" and often have either a first- or second-degree relative(s) with a history of delayed onset of puberty (defined as the onset of puberty for males as >13 years of age and for females as >12 years of age) and a similar growth pattern.

Prior to the onset of puberty there is a normal decline in growth velocity as seen on the growth velocity charts devised by Tanner et al. [5] (◘ Fig. 3.2). Individuals with CDGP commonly have a more pronounced or longer decline in their growth rate, which is usually more pronounced in boys than girls, causing their height to deviate further away from their prepubertal height percentile. The growth velocity of children with CDGP should be plotted on the growth velocity curves for late maturers and interpreted with respect to a child's bone age as opposed to chronologic age.

Forty percent of children with constitutional delay of growth and puberty also have familial short stature [13]. Even with a strong family history of CDGP, as with FSS, other identifiable causes of short stature and delayed puberty should be excluded which is discussed in the ▶ Sect. 3.4.

Several studies report a 2:1–5:1 male to female predominance of CDGP [14, 15]. Wehkalampi et al.'s retrospective study evaluated the prevalence of a positive family history in children with CDGP. The findings in this study challenge this male predominance because a nearly equal number of mothers as fathers had CDGP. The authors suggest that referral bias may account for the reported male prevalence in CDGP. The data from this study and others support an autosomal dominant pattern of inheritance for CDGP [14–16]. Heterozygous mutations in the growth hormone secretagogue receptor gene (GSHR), a ghrelin receptor gene, were identified in two females with CDGP, suggesting an autosomal dominant mode of inheritance with incomplete penetrance. Further studies are needed to better define the association of mutations in this gene with CDGP [17]. Researchers have not found mutations in the acid labile subunit, leptin, or the leptin receptor in individuals with CDGP [18, 19].

3.3.2 Familial Short Stature

Children with FSS have normal linear growth at ≤−2 SD below the mean for age, sex, and population with a predicted adult height consistent with their target height. They also have a bone age consistent with their chronologic age, a normal growth velocity, and onset of puberty, and either one or both of their parents have short stature.

Extreme cases of FSS in which a parent's height is near or below 3 SD below the mean for age and sex should elicit an evaluation for a genetic disorder other than normal variant short stature. To establish a diagnosis of FSS, one should discern that the patient and/or parent's short stature is not due to familial isolated growth hormone deficiency, a skeletal dysplasia, or some other identifiable etiology (refer to the ▶ Sect. 3.4). Factors that may have affected a parent's height should be considered, such as a history of precocious puberty, acquired hypothyroidism, chronic disease, or malnutrition. ◘ Figure 3.3 represents a normal growth chart of a girl with FSS.

3.3.3 Idiopathic Short Stature

As with normal variant short stature, ISS is defined as a height ≤−2 SD below the mean for age, sex, and population. ISS is discerned from normal variant short stature by a predicted adult height more than 2 SD below the child's target height range. The term "idiopathic" implies that the etiology of the short stature is unknown and should be established in the absence of FSS, CDGP, or other identifiable cause as discussed in detail in the ▶ Sect. 3.4).

Molecular defects in the growth hormone receptor gene, STAT 5, acid labile subunit, and IGF-1 gene have been described in patients with a prior diagnosis of ISS [20]. Whole exome sequencing led to the identification of genetic causes of short stature in 5 of 14 children with prior diagnoses of ISS with a height at or ≤−3 SD below mean for age and sex. Prior to the whole exome testing, these children had extensive testing, including standard genetic testing, that did not identify a cause for their short stature. Two of the five patients had the progeroid form of Ehlers-Danlos syndrome, and the other diagnoses included 3-M syndrome (overlapping features with Russell-Silver syndrome), Floating-Harbor

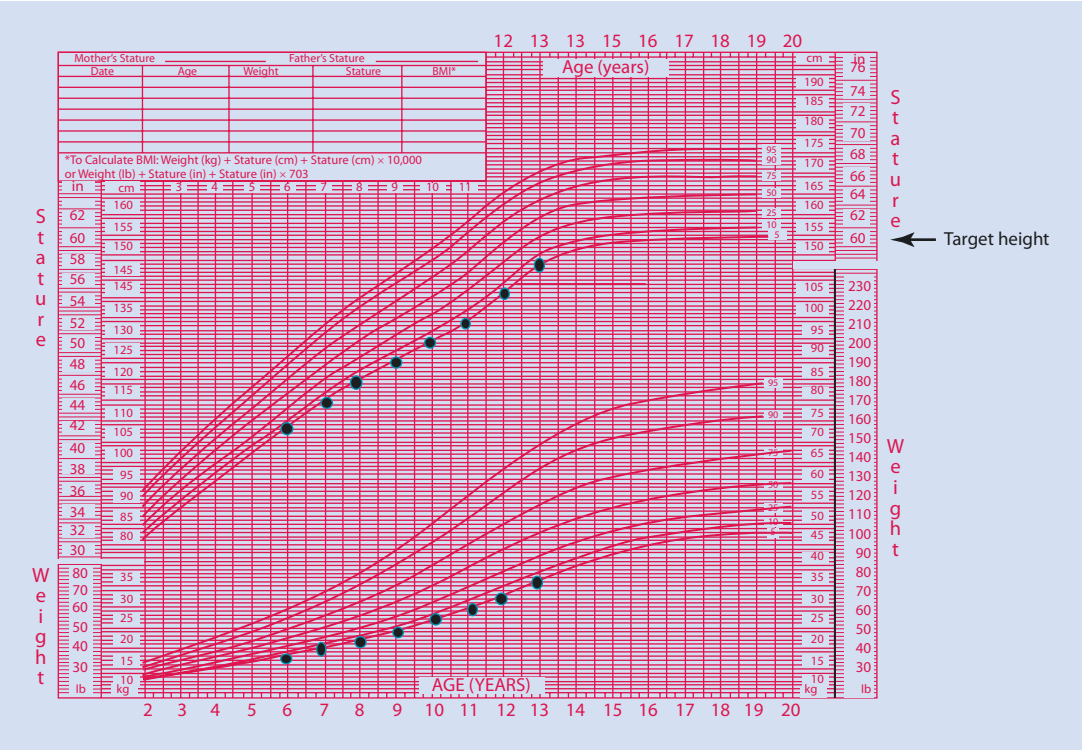

Fig. 3.3 Weight and height data for a girl with familial short stature plotted on the CDC growth chart [4]. Note the normal growth velocity along the 5th percentile

syndrome, and a variant of the Kenny-Caffey syndrome with normocalcemia. In addition to short stature these patients had dysmorphic features and/or other medical conditions [21].

In summary, ISS is also a diagnosis of exclusion, determined after a comprehensive evaluation fails to find an identifiable etiology for the short stature. Rare genetic disorders should be considered as a cause for the short stature in children with a height at or ≤−3 SD below the mean for age and sex, especially in the presence of dysmorphic features and/or other medical diagnoses.

3.4 Diagnostic Evaluation

The evaluation of a child with a height ≤−2 SD below the mean for age, sex, and population should include a comprehensive history and physical examination with anthropometric measurements. A detailed history should assess for risk factors for hypopituitarism, such as a traumatic birth, postnatal hypoglycemia, jaundice, and/or a microphallus in male infants. A low birth weight may suggest short stature secondary to small for gestational age or Russell-Silver syndrome. A history of lymphedema, pedal edema, and/or cardiac anomalies may suggest Turner syndrome or Noonan syndrome. In girls with short stature, it is well established that Turner syndrome should be excluded even in the absence of overt clinical findings. A karyotype is not routinely done in boys but should be considered when predicted adult height is below target height, because 45X/46 XY may present with a normal phenotype and short stature. Growth hormone treatment is indicated for this condition [22]. Determining whether to test for a SHOX gene mutation is best determined by the established clinical scoring system for this condition. Rappold et al. found that an increased body mass index, SH/HT ratio, decreased arm span/height ratio, Madelung's deformity, short bowed forearms, dislocation of the ulna at the elbow, and muscular hypertrophy were most predictive of this gene mutation [23]. Children with a history of developmental delay and findings suggestive of a chromosomal disorder warrant further evaluation with a geneticist. Furthermore,

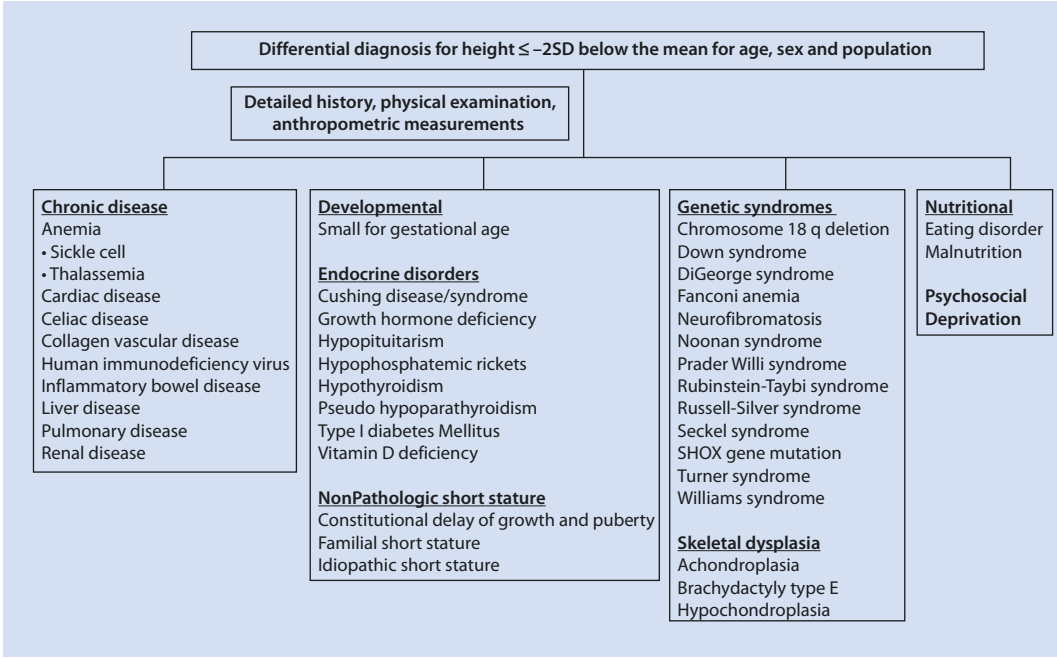

Fig. 3.4 Diagnoses to consider when evaluating a child with short stature

the evaluation should include an assessment for endocrine disorders such as Cushing disease/syndrome, hypothyroidism, and isolated growth hormone deficiency. Other causes of short stature to consider are chronic diseases, eating disorders, and psychosocial deprivation.

Physical examination findings of shortened metacarpals may indicate Turner syndrome, pseudohypoparathyroidism, brachydactyly type E, or other associated disorder. Some of the brachydactyly type E skeletal dysplasias are of autosomal dominant inheritance or may be caused by a spontaneous new mutation. Determining a diagnosis may be facilitated by examination of the parents for the presence of similar findings, especially if parental height is near or ≤−3 SD below the mean for age and sex [24]. A skeletal survey to evaluate for a skeletal dysplasia should be considered in the presence of abnormal body proportions and/or height SD significantly below target height. Figure 3.4 shows the different diagnostic categories to consider when evaluating a child for short stature.

If the comprehensive history, physical examination, and auxologic data are not suggestive of a specific disorder, then screening studies (electrolytes, alkaline phosphatase, calcium, phosphorous, albumin, CBC, TSH, free T4, IGF-1, IGF BP-3, ESR, and celiac panel) to exclude an identifiable etiology are indicated [12]. The diagnostic studies to consider when evaluating a child with short stature are listed below. A retrospective chart review of 235 asymptomatic patients (defined as normal history, review of systems, and physical examination) referred to a large academic pediatric endocrinology center for short stature (height at ≤−2 SD below the mean for age, sex, and population) determined that performing these screening studies had a low yield for organic disease and was not cost-effective. Only 37% of the patients had prior growth records available as part of their evaluation. The authors suggest reconsidering the recommendations from the 2008 Consensus Statement on the Diagnosis and Treatment of Children with Idiopathic Short Stature (ISS) in that in asymptomatic children a height velocity should be monitored over a 6 month period, and if abnormal for age and sex then proceed with screening studies [25].

Assessing these children for growth hormone (GH) deficiency is an important part of the evaluation. Since GH is secreted in a pulsatile fashion throughout the day with more frequent pulses overnight, random GH levels are usually low. GH mediates the production of IGF-1 and IGF BP-3 from the liver, and these levels are stable throughout the day, serving as a better screening test for GH deficiency. Normal ranges for IGF-1 and IGF BP-3 are based on age and Tanner stage in prepubertal and pubertal children, respectively. Low or low/normal IGF-1

Diagnostic Screening Studies for Evaluation of Short Stature and/or Delayed Puberty

Screening studies for height ≤−2 SD mean for age, sex, and population

- CBC
- Electrolytes
- Calcium, phosphorous, alkaline phosphatase
- ESR
- Celiac panel (total IgA and tissue transglutaminase IgA)
- TSH, Free T4
- IGF-1, IGF BP-3
- Karyotype for girls (consider for boys)
- Bone age
- Consider skeletal survey based on anthropometric measurements and/or growth rate

Screening studies for delayed puberty

- Gonadotropins (*pedi-LH and pedi-FSH, recommend 3rd-generation assay)
- Testosterone or estradiol.
- Prolactin.
- Depending on the above results, a karyotype or head MRI may be indicated.

and/or IGF BP-3 levels should prompt further evaluation with provocative GH stimulation testing. GH is measured at several time points following the administration of a GH secretagogue, such as clonidine, arginine, L-Dopa, propranolol, glucagon, or insulin. A single GH value of ≥10 ng/ml on two provocative GH stimulation tests indicates GH sufficiency. In peripubertal and early pubertal children, priming with sex steroids, testosterone, or estrogen, prior to the testing, is indicated to prevent misdiagnosis of GH deficiency. Priming with sex steroids is controversial, because of concern for a missed opportunity to treat partial GH deficiency or underdiagnose GH deficiency [26–28]. An increase in GH amplitude and mean 24 h GH levels occur between Tanner stages 2–4 and 3–5 in girls and boys, respectively. Girls exhibit increased mean nocturnal GH levels and GH amplitude prior to the onset of breast development which coincides with the start of their pubertal growth spurt. In contrast, boys in the early stages of puberty have lower mean nocturnal GH levels and GH amplitude that are comparable to that of a prepubertal boy [29]. This data supports the role of sex steroids on GH secretion and explains the decline in growth rate exhibited in boys prior to the onset of puberty. Saggese et al. showed that lower growth hormone releasing hormone (GHRH) levels in children with delayed puberty may explain their subnormal GH response to stimulation tests. When retested in mid- to late puberty, these adolescents had a normal GH response, and their GHRH levels were comparable to the control group [30]. A prospective study in Turkey evaluated the final height of boys with a history of delayed growth and normal testosterone primed GH stimulation studies. These boys had normal final adult heights, consistent with their mid-parental heights [31]. Müeller et al. and others showed that children with true GH deficiency have an abnormal GH response to sex steroid primed provocative GH stimulation tests [32, 33].

Adolescents with delayed puberty should have additional analyses (gonadotropin levels, serum prolactin, estradiol, or testosterone) to assess for causes of pubertal delay. A girl with hypergonadotropic hypogonadism requires further evaluation with a karyotype for Turner syndrome, a common cause of primary ovarian failure and short stature with an incidence of 1 in 2500 live births. Often boys and girls with Noonan syndrome manifest delayed puberty, but boys more frequently have primary gonadal failure [34]. 46 XX SRY-positive males present with normal male external genitalia, short stature, and primary gonadal failure [35]. Other causes of primary gonadal failure include autoimmune primary ovarian failure, triple X syndrome, and Klinefelter's syndrome, but these disorders are associated with normal or tall stature. Primary gonadal failure may also be a sequela of radiation therapy and/or chemotherapy for childhood cancer.

Hypogonadotropic hypogonadism (HH) may be isolated or associated with other pituitary hormone deficiencies or genetic syndromes. Head trauma, CNS tumors, neurosurgical resection of a cranial tumor, cranial irradiation, or transcription factor mutations (PROP-1, HESX-1, LHX3 and SOX 3) can cause HH, frequently in association with other pituitary hormone deficiencies. A prolactinoma causes delayed puberty secondary to suppression of gonadotropin release and may or may not be associated with galactorrhea. Kallmann syndrome and isolated hypogonadotropic hypogonadism (IHH) due to mutations in the GnRH receptor cause IHH, although Kallmann syndrome is often associated with tall stature. Functional causes of HH include chronic illness, eating disorder, or other endocrine disorder (hypothyroidism, Cushing disease/syndrome). Genetic syndromes associated with HH and short stature include Prader-Willi syndrome and Werner syndrome. Table 3.1 shows the differential diagnosis and evaluation for delayed puberty.

Table 3.1 Diagnoses to consider in the evaluation of a child for delayed puberty

Differential diagnosis for delayed puberty	
Hypergonadotropic hypogonadism	**Hypogonadotropic hypogonadism**
Short stature Turner syndrome Noonan syndrome Normal male phenotype of 45 X/46XY 46XX SRY-positive male Gonadal radiation/chemotherapy for cancer (e.g., cyclophosphamide, ifosfamide, procarbazine)	*Short stature* Brain malformations (e.g., hydrocephalus) Brain tumor (craniopharyngioma, prolactinoma) Craniospinal irradiation Head trauma Hypothyroidism Neurosurgical treatment Pituitary transcription factor mutations (Prop-1, HESX-1, LHX-3 SOX-3)
	Short stature (GH deficiency excluded) Constitutional delay of growth and puberty Isolated hypogonadotropic hypogonadism
Normal/tall stature Primary ovarian failure Triple X syndrome Klinefelter's syndrome	*Normal/tall stature* Kallmann syndrome

Distinguishing idiopathic IHH from CDGP is often a challenge, because basal and stimulated levels of gonadotropins are low in both conditions until activation of the hypothalamic-pituitary-gonadal axis. Many studies, limited by a small number of study subjects, were conducted to determine whether basal and GnRH-stimulated FSH and LH levels, basal inhibin B levels, HCG-stimulated testosterone, and/or combinations of these tests can most effectively diagnose IHH. Binder et al.'s retrospective study showed that a combination of basal LH <0.3 IU/L and inhibin B < 111 pg/ml had a specificity of 100% and sensitivity of 98% in establishing a diagnosis of IHH [36]. Another retrospective study determined that a peak stimulated LH of 2.8 U/L and 4-day and 19-day HCG-stimulated testosterone cutoff peaks of 1.04 mcg/L and 2.75 mcg/L, respectively, had 100% sensitivity and specificity for diagnosing IHH [37]. Two prospective studies of basal inhibin B as a diagnostic test for IHH reported discrepant cutoff values. Further studies of basal inhibin B are indicated before establishing it as a routine test to discern IHH from CDGP [38–40].

3.5 Management of Normal Variant and Idiopathic Short Stature

Children with NVSS and ISS are healthy and do not have an identifiable cause for their short stature. Management should include reassurance and follow-up to monitor growth, pubertal development, and other auxologic growth parameters to confirm that the child follows the anticipated pattern of growth. Ongoing surveillance of the child's growth pattern is important because sometimes, despite, an extensive evaluation, a diagnosis such as a mild hypochondroplasia or pseudohypoparathyroidism may not be clinically and diagnostically evident until the child is older [41–43].

Treatment of children with normal variant short stature and ISS should be individualized and expectations of treatment clearly discussed with the family.

As peers progress through puberty and differences in pubertal development and stature become more apparent, despite reassurance, many boys with CDGP have a difficult time coping with this discrepancy. The short stature and/or delay in puberty from CDGP can significantly impact the psychological and emotional well-being of an adolescent, causing poor school performance and self-esteem, withdrawal from social activities, and even depression and anxiety [44].

Treatment with low-dose testosterone is an option for boys with difficulty coping with their short stature and delayed puberty. Boys treated with low-dose testosterone should have a bone age of at least ≥12 to prevent significant bone age advancement [45]. Depot testosterone enanthate

or cypionate 50 mg SQ or IM every 4 weeks for 3–6 months will frequently invoke an increase in growth rate and pubertal progression without bone age advancement. Testosterone enanthate contains a sesame seed oil and testosterone cypionate, a cotton seed oil, and should be avoided in individuals with allergies to these oils. The response to treatment should be evaluated within 4–6 months following the last testosterone dose. If the response is inadequate, then an additional 3- to 6-month course of testosterone 50–75 mg monthly may be administered [46, 47].

In contrast to boys, girls have a growth spurt in early puberty. Therefore, girls infrequently seek treatment for CDGP because their onset of puberty is accompanied by a pubertal growth spurt. In extreme cases of CDGP, a girl can be treated with either a low-dose oral estrogen, ethinyl estradiol 5 mcg daily, or low-dose estrogen transdermal patch, 3.1–6.2 mcg per 24 h (1/8 to ¼ of a 25 mcg patch), to initiate puberty [46].

Oxandrolone, a weak synthetic, non-aromatizing anabolic steroid derivative of testosterone, is an oral treatment option for CDGP. Oxandrolone 0.1 mg/kg/day for 3–4 months is recommended for pubertal initiation. Crowne and colleagues' double-blind, placebo-controlled trial showed comparable increases in growth velocity and testicular development in boys treated with either a 3-month course of oxandrolone 2.5 mg daily or testosterone 50 mg every 4 weeks [47].

Increased interest in aromatase inhibitors as a potential treatment option for boys with CDGP and ISS stems from its inhibition of the conversion of androgens to estrogen. Cessation of growth depends on estrogen-mediated fusion of the epiphyses; therefore, lower estrogen levels may preserve epiphyseal patency, improving final height prognosis. Many of the studies conducted to date included a small number of male study subjects with CDGP and/or ISS. Hero et al.'s prospective randomized, placebo-controlled study compared predicted adult height in 8 boys with CDGP treated with low-dose testosterone and placebo and 9 boys treated with testosterone and letrozole. Both groups were treated with a 6-month course of testosterone 50 mg every 4 weeks and either placebo or letrozole for 2 years. Initial study data, following 1 year of treatment, showed a gain of 5.1 cm in predicted adult height in the letrozole-treated group compared to the control group. After 2 years of treatment the cohorts were followed until near final height, defined as a bone age ≥15.75 years. The study group achieved a final adult height (175.8 cm) consistent with their target height (177.1 cm), while the control group's final adult height (169.1 cm) was less than their target height (173.9 cm) [48]. In a separate randomized controlled study in boys with ISS, Hero et al. compared the effect of 24 months of placebo vs. letrozole on predicted adult height and bone mineralization. In the letrozole-treated group, predicted adult height increased 5.9 cm, whereas the control group's predicted adult height was unchanged. Bone mineral density of the lumbar spine and femoral neck was comparable in the two groups, but the apparent bone mineral density was higher in the letrozole-treated cohort [49].

Another randomized, double-blind, placebo-controlled trial compared the effects of letrozole and oxandrolone on predicted adult height, pubertal development, bone mineral density, serum IGF-1, and blood lipoproteins in boys with CDGP and ISS. Following 2 years of treatment, predicted adult height in the letrozole-treated group improved by 6.1 cm, while the oxandrolone group's predicted adult height was unchanged. A greater increase in testicular volume and bone mineral density occurred in the oxandrolone-treated group compared to the letrozole- and placebo-treated groups. HDL was lower in the letrozole-treated group and unchanged in the oxandrolone group. The increases in IGF-1 levels were comparable in the oxandrolone and letrozole groups, significantly increased from that of the placebo group [50]. Currently, Dr. Nelly Mauras is conducting a 2–3-year randomized controlled trial in pubertal boys with ISS and a bone age <14.5 years, comparing three different treatment arms, an aromatase inhibitor (letrozole or anastrozole) vs. growth hormone alone (0.3 mg/kg/week) vs. combination therapy (aromatase inhibitor and growth hormone). Outcome measures include change in predicted adult height, bone density, bone markers, IGF-1, lean body mass, and the degree of estradiol suppression by the individual aromatase inhibitors [51]. In terms of adverse effects of aromatase inhibitors, there is only one published report of an increased incidence of vertebral deformities in 5 of 11 prepubertal/early pubertal boys with ISS treated with letrozole [52]. Karmazin et al. reported that 25% of study subjects treated with letrozole developed adrenal suppression determined by a low-dose ACTH stimulation test [53].

The aromatase inhibitor, anastrozole, increases sperm count in males with infertility, yet concern exists as to whether it can affect sperm production in adolescent males. Mauras et al. analyzed sperm counts in 11 young adults, age 18, with GH deficiency treated with anastrozole for 29 months. No difference was found in the sperm counts between the treated and untreated cohorts, but low sperm counts were found in both groups [54]. Currently, due to the paucity of data on side effects and final adult height, aromatase inhibitors are not recommended for the treatment of ISS and CDGP.

In 2003, the Food and Drug Administration (FDA) approved GH treatment (0.3–0.37 mg/kg/week) for children with ISS defined as a height of ≤−2.25 SDS (1.2 percentile) below the mean for age and sex "and associated with growth rates unlikely to permit attainment of adult height in the normal range, in pediatric patients whose epiphyses are not closed and for whom diagnostic evaluation excludes other causes associated with short stature that should be observed or treated by other means" [55]. The lower cutoff for the normal range adult height is defined as 160 cm (63 inches) for a male and 150 cm (59 inches) for a female. This statement issued by the FDA does not clearly exclude GH treatment for children with FSS and CDGP.

Prior to the FDA approval of GH treatment for ISS, several nonrandomized, longitudinal studies were published that used variable dosing regimens of GH. Hintz et al. reported final adult height outcomes in children with ISS treated for 2–10 years with a 0.3 mg/kg/week of thrice weekly GH. The data demonstrated a gain in height of 5 ± 5.1 cm for boys and 5.9 ± 5.2 cm for girls above the initial predicted adult height. The researchers did not find any predictive factors that correlated with an improved response to GH [56]. MacGillivray et al.'s 4-year open-label randomized study compared a daily regimen and thrice weekly regimen of 0.3 mg/kg/week of growth hormone in prepubertal children with ISS and found superior growth rates in the cohort treated with daily GH. No difference in bone age advancement or onset of puberty occurred between these groups. Skeletal maturation and pubertal onset did not differ between the placebo- and GH-treated cohorts [57]. The Cochrane Metabolic and Endocrine Disorders Group analyzed the data on 10 randomized controlled studies published between 1989 and 2004. Two of the studies reported on final adult height outcomes, and the remainder of the studies had short-term height outcome data. This analysis included the National Institutes of Health (NIH) randomized, double-blind placebo-controlled study that treated peripubertal children with GH 0.22 mg/kg/week divided into three doses per week. Adult height outcome data was available in nearly 50% of the cohort and showed a gain of 3.7 cm in adult height compared to the placebo-treated group. Intent-to-treat analysis for final adult height showed a similar gain in final adult height compared to the control group. The other randomized controlled study that reported final adult height outcomes was a small study with only 10 girls in the treatment group (GH 30 IU /m2/week of daily injections), 8 in the randomized control group, and 22 in the control group that refused to consent to randomization. A gain of 7.5 cm and 6 cm in final adult height was reported in the treated group compared to the randomized control and the nonrandomized control groups, respectively. The remainder of the randomized controlled studies evaluated short-term gains in height which ranged from no improvement to 0.7 SD improvement over 1 year [58, 59]. Other meta-analysis of randomized and nonrandomized controlled studies indicates a variable response with gains in height ranging from 2.3 to 8.7 cm in children [60, 61]. The GH adverse effect profile reported in these studies did not differ from that of children treated with GH for other conditions. Some studies suggest that adult height outcomes are optimized with earlier initiation of GH treatment and with higher doses [12, 62, 63]. Kamp et al.'s randomized controlled study analyzed the effects of 2 years of high-dose GH treatment in prepubertal children with ISS. Five years after initiation of treatment, when compared to the control group, for the GH-treated cohort, height improved (−1.4 SD vs. −2.2 SD), bone age advanced significantly (3.6 year/2-year chronologic age vs. 2 year/2-year chronologic age), and pubertal onset was earlier (11 of 13 GH-treated study subjects vs. 7 of 13 control subjects) [64].

GH treatment requires monitoring of growth velocity and adjustment of GH dose to achieve an adequate response. The 2007 international consensus meeting on ISS recommended monitoring IGF-1 levels to assess dosing, adherence and to prevent overtreatment, with a goal of a level above 0 SDS and within the normal limits for age [65].

Lee et al. calculated a cost analysis of treating a 10-year-old child with GH 0.37 mg/kg/week with an endpoint of a 1.9 inch gain in height over

5 years. The gain in height and GH dose used for this analysis was derived from the two studies that the FDA based its decision on to approve GH for ISS [59, 66]. The analysis revealed a cost of approximately $52,000 per inch of height gain [67]. An estimated 400,000 children would qualify for GH treatment based on the FDA's criteria for GH treatment of children with a height of <1.2nd percentile. Although the FDA statement that children with a "form of short stature that can be observed or otherwise managed by other means" is suggestive of children with FSS and CDGP, these diagnoses are not clearly excluded from the FDA indications for GH treatment for short stature. The exorbitant cost of GH weighed against treating an otherwise healthy child has generated controversy over the use of GH as a "lifestyle drug," a term used to refer to a "pharmaceutical product characterized as improving quality of life rather than alleviating disease" [68].

Conflicting study outcomes have been reported on the efficacy of combination treatment with GH and a GnRH agonist for pubertal children with ISS and SGA. Many of the studies are small and nonrandomized and do not include control groups. Kamp and colleague's randomized controlled study of combination treatment in pubertal children with ISS and SGA showed that predicted adult height in the treated groups improved by 8 cm in girls and 10.4 cm in boys [69]. These researchers also analyzed the final height and bone mineralization of 32 of the 40 participants who participated in the original 3-year study and found that the treated group had a net gain of 4.9 cm above their predicted adult and target heights compared to the control group. The bone mineralization was similar between the treated and control groups except for a lower lumbar spine bone mineralization SD score in the treated boys ($n = 6$) compared to the control group ($n = 2$) [70].

3.6 Outcomes and Possible Complications

Adult height outcome data in children with CDGP vary, with some studies showing impaired adult height and in others an adult height consistent with target height. These studies found that the Bayley-Pinneau method as opposed to the Tanner-Whitehouse method of height prediction correlated best with the child's adult height. Factors negatively impacting the adult height prognosis in children with CDGP included a shorter period of time between the onset of puberty and peak height velocity, a lower peak height velocity, a shorter sitting height, and a decreased duration of puberty [71].

Proponents of treatment advocate that short stature negatively impacts a child's psychosocial development [72, 73]. In contrast, others have shown that GH does not affect psychosocial function. The Wessex study, a longitudinal controlled study, evaluated whether short stature impacts a child's academic, social, and behavioral development. The study and control groups consisted of 5-year-olds recruited from two school districts in the South of England. The study group had a height at or below the 3rd percentile and was matched with a control group of peers of the same sex, age, and grade with normal stature (10–90th percentile). These cohorts had testing at ages 7–9, 11–13, and 18–20 years to determine whether their short stature effected their academic and psychosocial development. Analysis of the data from these studies showed that after adjusting for socioeconomic status, the study and control groups did not differ with respect to intelligence quotient, self-esteem, and behavior [74–76]. Other studies that examined participants referred to pediatric endocrinology clinics for evaluation of short stature indicated no effect on psychosocial function [77, 78].

The Sante Adulte GH Enfant (SAGhE) study led by French investigators reported on the long-term mortality of approximately 7000 GH-treated patients for diagnoses of isolated GH deficiency, ISS, and SGA. The mortality was evaluated 16.9 years following the cessation of GH treatment and compared to that in the general French population. This study found an increase in mortality due to cerebrovascular events and bone tumors among individuals treated with GH, in particular in those treated with higher doses of GH, exceeding 50 mcg/kg/day [79]. The SAGhE study design had several shortcomings that may have influenced these findings. In particular, mortality in the treated group was compared to the mortality rate in the general French population as opposed to an identical matched, untreated control group. Also, the reported association between the higher dose of GH and increased mortality was among a small number of the cohort, many of whom had a diagnosis of SGA [80]. A preliminary report from the EU SAGhE

Study conducted in Belgium, the Netherlands, and Sweden did not show an association between adult mortality in 2543 patients treated with GH during childhood for isolated GH deficiency, ISS, or SGA [81]. Due to the limitations of the SAGhe study design the FDA, Endocrine Society, Pediatric Endocrine Society, and Hormone Research Society concluded that it is safe to continue to treat children with ISS, isolated GH deficiency, and SGA with GH [80].

Case Study

LA was referred at age 16 to a pediatric endocrinologist for evaluation of short stature and delayed puberty. His growth chart below shows normal linear growth below and parallel to the 3rd percentile before the age of 12. Between ages 12 and 16, his growth velocity declined to 3 cm/year. A comprehensive history revealed no significant past medical history, and a complete review of systems was unremarkable. Family history was significant for CDGP; both the patient's father and brother completed their growth in their early to mid-20s. LA was doing well in school, but was upset by the lack of secondary sexual development. His physical examination revealed Tanner 2 pubic hair and genitalia with testicles measuring 4 ml. LA had a delayed bone age consistent with a 12-year-old boy. He had an extensive workup that revealed a normal CBC, complete metabolic panel, ESR, IGA 110 mg/dl, negative tissue transglutaminase antibody titer, TSH 1uIU/ml, free T4 1.2 ng/dl, IGF-1 201 ng/ml (normal Tanner 2: 56–432 ng/ml), IGF BP-3 4.4 mg/L (normal Tanner 2: 2.3–6.3 mg/L0), normal prolactin 9 ng/ml, and gonadotropins consistent with early puberty (FSH 3.9 uIU/ml, LH 0.94 uIU/ml, and testosterone 22 ng/ml).

How Should LA Be Managed?

LA was treated with low-dose testosterone 50 mg IM every 4 weeks for 6 months, and his growth velocity started to increase. At age 17 he had Tanner 3 genitalia and a growth rate of 5–6 cm/year and a bone age consistent with a 12.5-year-old boy. He was followed every 6 months to monitor his growth velocity (Fig. 3.5).

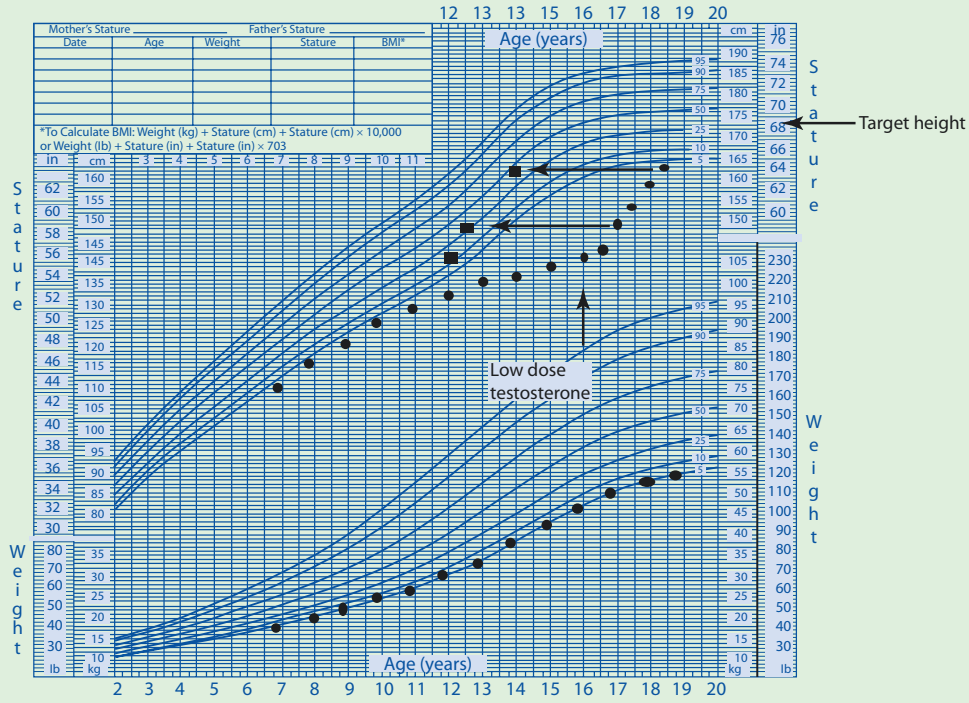

Fig. 3.5 Weight and height data for a boy with constitutional delay of growth and puberty treated with a 6-month course of low-dose testosterone. Data points are plotted on the CDC growth chart [4]. • represents height and ■ represents bone age

3.7 Summary

A comprehensive history, physical examination, current and past auxologic data, and diagnostic studies are essential for evaluating children with short stature to exclude an organic etiology. The growth patterns of children with normal variant short stature typically reflect a familial pattern of growth in that a child with FSS has at least one parent with short stature. Children with CDGP frequently have a family history of a first or second degree relative with a similar pattern of growth. Often children with CDGP also have FSS as the cause of their short stature. Children with normal variant short stature require reassurance and follow-up to ascertain that they follow the expected course of growth and pubertal development for these normal physiologic variants of growth. Low-dose testosterone treatment effectively initiates puberty in boys with CDGP without advancing their bone age and compromising their final adult height.

ISS is differentiated from normal short stature in that the predicted adult height falls below the target height range for that child. These children are GH sufficient and do not have an identifiable cause for their short stature. Treatment of ISS with GH remains controversial in the medical community because of the costs and variable response to treatment. GH treatment for ISS should be individualized and the growth expectations explained to families. Children who are treated with GH should be closely monitored for side effects and assessed for an adequate response by monitoring growth velocity.

Although the SAGhE study initially raised concern regarding a potential increase in long-term mortality from GH treatment of isolated GH deficiency, SGA, and ISS, the limitations of this study created an awareness that well designed controlled studies are needed to effectively determine the long-term safety of GH.

Review Questions

1. Which of the following findings distinguishes ISS from CDGP and FSS?
   A. Bone age
   B. Predicted adult height is less than target height range
   C. Family medical history
   D. Height ≤−2 SD below the mean for age, sex, and population
2. Based on the FDA 2003 approval of GH for the treatment of children with short stature, which diagnoses could potentially qualify for treatment with GH growth hormone?
   A. ISS
   B. FSS
   C. CDGP
   D. All of the above
3. Which of the following provisions were included in the FDA approval statement for GH treatment for children with short stature?
   A. Height at or below 1.2nd percentile for age and sex.
   B. Predicted adult height is below the 150 cm (4′11″) for a woman and 160 cm (5′3″) for a man.
   C. The short stature is not due to an identifiable cause.
   D. All of the above.
4. Which of the following is not an auxologic measure of growth?
   A. Growth velocity
   B. Head circumference
   C. Arm span
   D. Bone density
5. You are asked to evaluate a 5-year-old boy with both height and weight at the 1st percentile. Your evaluation includes a comprehensive history and physical examination. Which of the following data are *essential* for evaluating the child's short stature?
   A. Prior growth data, target height, and bone age
   B. Bone age, target height, and head circumference
   C. Target Height, bone density, and growth velocity
   D. Sitting height, arm span, and upper to lower segment ratio

Answers

1. (B) Individuals with ISS have a predicted adult height more than 2 SD below their target height. Individuals with CDGP and FSS have a predicted adult height within 2 SD of their target height.
2. (D) In 2003 the FDA approved GH for treatment of children with a height less than 2.25 SD below the mean for age,

sex, and population "and associated with growth rates unlikely to permit attainment of adult height in the normal range, in pediatric patients whose epiphyses are not closed and for whom diagnostic evaluation excludes other causes associated with short stature that should be observed or treated by other means." Based on this statement, children with ISS, FSS, and CDGP may qualify for treatment with GH based on these criteria.

3. (D) All of the above statements are included in the FDA 2003 criteria for growth hormone treatment of children with short stature.
4. (D) Bone density is not an auxologic measure of growth. Choices A, B, and C are all auxologic measures of growth.
5. (A) All three of these parameters provide essential information for the initial assessment of this child's short stature. Prior growth data provides information about growth velocity. Target height is an auxologic growth measure utilized to determine whether a child's growth potential falls within the expected range for their genetic potential and should be utilized cautiously as certain growth disorders are genetic. Lastly, bone age provides information about skeletal maturity and potential adult height. The auxologic growth parameters in the other choices would not be essential for the initial assessment.

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