Clinical Crossroads

Idiopathic Short Stature
A Clinical Review

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IMPORTANCE Approximately 2% of children are defined as having short stature. Deciding when to pursue recombinant human growth hormone therapy to increase adult height is controversial.

OBJECTIVE To review the management of children with idiopathic short stature, including diagnostic evaluation and therapeutic options.

EVIDENCE REVIEW Systematic literature search of PubMed, Embase, and the Cochrane Library databases. For height outcome, articles were limited to studies reporting adult height and to systematic reviews.

FINDINGS Recombinant human growth hormone therapy of children with idiopathic short stature increases height in some children. The estimated mean gain in adult height is 5.2 cm (2 in). The cost-benefit ratio is controversial. Treatment with growth hormone appears safe in the short term, while data on long-term effects are limited because studies of long-term efficacy were not powered to determine safety.

CONCLUSIONS AND RELEVANCE Growth hormone treatment may be considered in some children with idiopathic short stature.

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Dr Tess Miss W is a 9-year-old girl with short stature. She was always smaller than her peers, and her height began to decline from her growth curve after age 2 years, with a subsequent reduction in weight gain (**Figure 1**). Her growth velocity has fluctuated but most recently has been consistent with a normal delayed tempo of growth pattern (**Figure 2**).

Her growth rate remains slow at 4.83 cm/y (normal range for age, 4.2-7.3 cm/y).[1] She and her parents are considering growth hormone treatment. She is in third grade, does well in school, and is physically active and participates in sports.

At birth, she was full term, weighed 2640 g (approximately fifth percentile), and was 49.5 cm long (>10th percentile). She had early jaundice and feeding problems but appropriate progression through developmental milestones. She has migraine headaches, takes no medications, and has no allergies.

Her family history includes diabetes, hypothyroidism, hypertension, and hyperlipidemia in her grandparents. Her mother is 157 cm (5 ft 2 in) tall and had menarche at age 14 years. Her father is 168 cm (5 ft 6 in) tall, grew significantly his senior year of high school, and has had a mild stroke. Her brother is 6 years old, has been maintaining height at the 10th percentile, and is healthy.

On examination, her height is 115 cm (0.05th percentile; SD, −3.32) and her weight is 21.8 kg (1.99th percentile; SD, −2.06). Her body mass index is 16.5 (50.29th percentile; SD, 0.01). The remainder of her physical examination results were normal.

Miss W's laboratory test results were all normal, including free thyroxine level of 1.25 ng/dL (reference range, 0.8-1.9 ng/dL), thyrotropin level of 1.5 µU/mL (reference range, 0.7-5.7 µU/mL), insulinlike growth factor 1 (IGF-1) level of 183 ng/mL (reference range, 74-388 ng/mL; median for age, 169 ng/mL), insulinlike growth factor binding protein 3 (IGFBP-3) level of 4.6 µg/mL (reference range, 1.8-7.1 µg/mL; median for age, 3.6 µg/mL), and negative screening results for systemic illnesses. Chromosomal studies revealed a karyotype of 46,XX and *SHOX* gene mutational analysis was negative. Her bone age was 6 years 10 months according to the standards of Greulich and Pyle[2] at a chronological age of 9 years 0 months and height of 112.7 cm, predicting an adult height of about 147 cm (4 ft 10 in), below her mid-parental height of 156 cm (5 ft 1 in). Other evaluations have included normal results of endoscopy and ileoscopy with biopsy for abdominal pain.

Miss W: Her View

A lot of people tell me I'm small. Some people still tease me. I just ignore them or I just say, "That's who I am." Sometimes it is hard because my brother touches my toys on my shelf and I can't stop him.

I know if I was taller, I would be better at activities like basketball and gym. I could help my friends more too. [In the past, Miss W had complained of bullying, pushing, and exclusion from games because she was small.]

I'm not really sure what the medicine is, but I think it's going to help. The only thing that worries me is that if there is a needle like an IV or shot. I don't like those. Some people do, some people don't, but I don't like them and sometimes I get nervous about it.

The one thing I would like from my doctors is to do whatever they can to help me live a better life and succeed. To me that means being able to reach my stuff and play more active sports.

Miss W's Mother: Her View

One of the things that has been difficult for us as parents is watching our daughter when she cannot do something. A lot of people think that she and her brother are twins when he is really 3 years younger. I have to explain it to them, and then I see our daughter's head down and her shoulders rounded down. It is upsetting for her. It's hard as parents to approach a situation like this and to counsel her on how to handle it.

The next step would be growth hormone. We don't want to make her taller than what her body wants, but just the chance to catch her up to her peers. We do have some concerns about the treatment and we want to make sure we understand the long-term side effects; we want to make sure we do our homework and that we're doing the right thing.

Short Stature

Dr Cohen Miss W is an active 9-year-old girl who presented for evaluation of short stature. The medical evaluation for secondary causes was unrevealing, other than a delayed bone age. She and her parents now present to consider growth hormone therapy.

Search Methods

To determine the evidence for the use of growth hormone therapy in idiopathic short stature (ISS), PubMed, Embase, and the Cochrane Library databases were queried using the terms *adult height* OR *final height* AND *growth hormone* or its synonym and trade names AND *short stature* with the following limits: English language, humans, all children aged 0 to 18 years, and published from 1985 to December 2011. Additional relevant studies found in the bibliographies of the articles used in this analysis were also reviewed. A second PubMed search through March 2014 did not reveal new studies. The query excluded studies of pituitary-derived growth hormone because of their poor external validity for clinicians today. Adult height was selected as the primary outcome in the consideration of efficacy. To compare adult height data across studies, the parameter of adult height standard deviation score (SD score) minus initial height SD score was used or calculated from available data. The recommendation for the patient was made based on assessment of the quality of evidence using the American Heart Association level-of-evidence grading system.

CDGP *constitutional delay of growth and puberty*

GHD *growth hormone deficiency*

IGF-1 *insulinlike growth factor 1*

IGFBP-3 *insulinlike growth factor binding protein 3*

ISS *idiopathic short stature*

Clinical Bottom Line for Idiopathic Short Stature

- Short stature definition: 2 SDs or more below mean height for age, sex, and population
- Extreme short stature may be treated with recombinant human growth hormone
  - At least 2.25 SDs below the mean height (1.2nd percentile)
  - No underlying diseases
  - Requires 6 or 7 nights per week of subcutaneous injections for years
- Growth hormone therapy may result in an estimated mean gain in adult height of 5.2 cm (2 in), but response to therapy is highly variable
- Growth hormone therapy is safe in the short term; long-term safety is not well described because efficacy studies were not adequately powered to determine long-term safety
- The cost-benefit ratio for growth hormone is not known

Literature Search Results

A total of 531 citations were retrieved. Only studies that continued through adult or near adult height and had control data were reviewed (n = 12). Systematic analyses (n = 3) and consensus statements (n = 1) were also reviewed.

Definitions and Causes of Short Stature

In an initial evaluation of a child for short stature, determination if the child is truly short is the first step. Short stature is defined as a height that is more than 2 SDs below the mean for age, sex, and population,[3] so 23 per 1000 individuals have this diagnosis. Miss W meets this definition, as her height SD is −3.3.

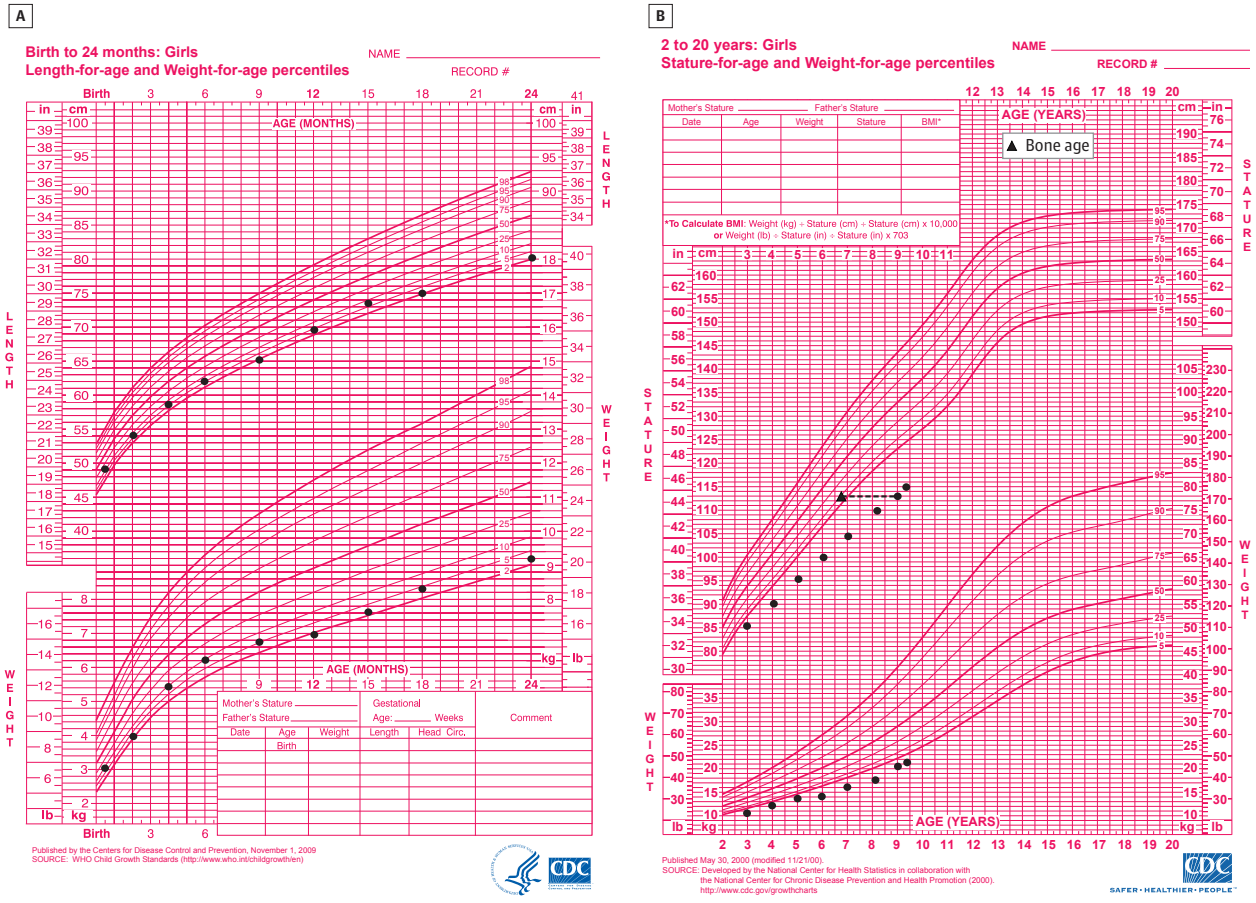
The second question is whether the child's height is appropriate for the family. To determine whether a child's height is consistent with his or her genetic potential, a target height can be calculated using the formulas in **Box 1**.

Most children's adult height will fall within 10 cm of their target height. Clinicians should be more concerned when a child's height percentile differs from the target range percentiles.[4]

The third question is what is the child's growth rate? Children who grow at a normal rate are more likely to represent normal variations of growth, while a poor growth rate may indicate an organic problem. Miss W's annualized growth velocity has ranged from low to low-normal over the past few years.[1]

While most children stay at approximately the same percentile when height is plotted on a standard cross-sectional growth chart, there can be normal variation, especially in infancy and adolescence. Longitudinal growth charts, such as those created by Tanner and Davies,[1] show variations in patterns of growth based on the timing of pubertal maturation. Children who end up at the same adult height may follow different patterns depending on whether they mature at an average age, early, or late. During the first 3 years of life, the length or heights of infants may cross growth percentiles as they transition from the effects of the intrauterine environment and early infant nutrition to their genetic potential.[4] During adolescence, an

Figure 1. Miss W's Growth Charts



A, Infant growth chart (World Health Organization Child Growth Standards). B, Childhood growth chart (National Center for Health Statistics; distribution of heights obtained from cross-sectional studies). Miss W's bone age according to Greulich and Pyle standards[2] (6 years, 10 months), obtained at 9 years, 0 months, is indicated by a triangle.

early-maturing child will move to a higher percentile because his/her growth spurt will be earlier than average, whereas a late-maturing child will move to a lower percentile as his/her peers start their growth spurts while he/she continues to grow at a prepubertal rate (constitutional delay of growth and puberty [CDGP]). Healthy children eventually return to their preadolescent height percentile.[5] Because children often have similar growth patterns and timing of onset of puberty as their parents, family heights and history of pubertal development should be obtained.

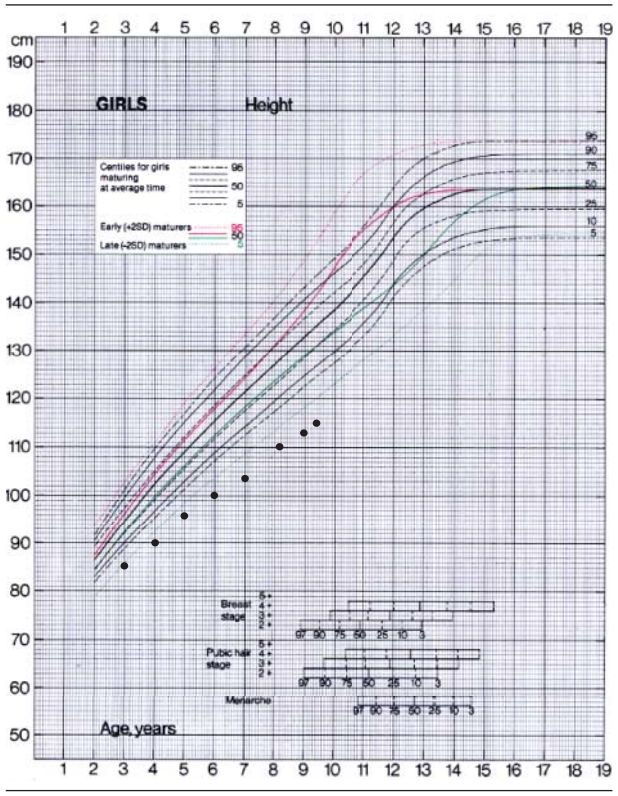
Nutritional, systemic (chronic diseases), endocrinologic, and syndrome/chromosomal abnormalities can all affect growth[4] (**Box 2**). When these conditions, including intrauterine growth retardation/small for gestational age, have been excluded, an individual is diagnosed as having ISS.[6]

Evaluation of Short Stature

Evaluation of a short child with a concerning growth pattern starts with a detailed medical history. Birth history should include gestational age, birth weight and length, and prenatal and perinatal complications. A delay in developmental milestones or poor school performance, past medical problems, or positive findings on a review of systems may suggest a specific pathology. Dietary recall is important for assessment of nutritional intake. Certain medications, such as stimulants used for attention-deficit/hyperactivity disorder, anticonvulsants, and antidepressants may affect growth.[4] A complete physical examination should be performed looking for signs of systemic illnesses and endocrinopathies, with special attention to dysmorphic features, metacarpal length, body proportions, and pubertal staging.[4]

Skeletal maturity is determined from a radiograph of the left hand and wrist (bone age) and is delayed in CDGP, endocrinopathies, nutritional deficiency, and chronic illness.[7] Laboratory screening should be tailored to the growth pattern (**Box 3**). In the case of a child who is simultaneously faltering in linear growth and weight gain, evaluation for both a systemic disorder and an endocrinopathy may be warranted. While screening algorithms generally include laboratory evaluation for renal and liver disease, review of published studies of children older than 3 years suggest these are not often causes of growth failure in otherwise asymptomatic children[10-12]; rather, growth hormone deficiency, hypothyroidism, celiac disease, Noonan syndrome (a genetic disorder due to mutations in genes in the RAS-MAPK pathway), and Turner syndrome (a genetic disorder due to a missing or abnormal X chromosome) are most common. Recent data suggest that screening tests seldom yield

Figure 2. Miss W's Height Chart With Centiles for Early, Average, and Late Maturers



Height chart with patterns of growth for North American girls based on the timing of pubertal maturation derived from data from the National Center for Health Statistics.[1]

a new diagnosis in short children with a normal growth rate and without any abnormality on history or physical examination, except possibly for celiac disease.[13]

A karyotype should be considered in girls with unexplained short stature to rule out Turner syndrome. While girls with Turner syndrome typically have physical findings such as webbing of the neck, low posterior hairline, short metacarpals, dysplastic nails, high-arched palate, and ptosis,[14] it is important to appreciate that short stature may be the only major sign.[4] Haploinsufficiency of the short stature homeobox-containing (*SHOX*) gene is thought to be the etiology of short stature in Turner syndrome through loss of normal chondrocyte function at the epiphyseal growth plate.[15] Gene mutations and deletions in the *SHOX* gene and its enhancer region downstream have also been found in children with unexplained ISS and, depending on the study, the prevalence has been estimated at 1% to 5%.[15-18] Recent guidelines suggest that screening for *SHOX* gene mutations should be reserved for children with any combination of the following physical findings: reduced arm span/height ratio, increased sitting height/height ratio, above-average body mass index, Madelung deformity (a wrist abnormality), cubitus valgus, short or bowed forearm, dislocation of the ulna at the elbow, or appearance of muscular hypertrophy.[19]

Growth Hormone Evaluation

A typical child with classic growth hormone deficiency (GHD) has increased subcutaneous truncal fat, an immature face with a large calvarium (frontal bossing), an underdeveloped nasal bridge, and delayed dentition. There is a positive correlation between the impairment in growth velocity and the severity of GHD. Distinguishing between mild growth hormone insufficiency and ISS is more difficult.

Box 1. Target Height Formulas

For girls

(father's height [cm] + mother's height [cm] − 13) ÷ 2

For boys

(father's height [cm] + mother's height [cm] + 13) ÷ 2

Because growth hormone secretion is pulsatile, a single growth hormone sample will often be low and not useful for diagnosis.[20] Screening for GHD may be performed by measuring IGF-1, the major growth hormone–dependent peptide, as its serum level is relatively stable throughout the day. However, there is considerable overlap in IGF-1 concentrations in healthy children younger than 6 years and in those with GHD.[21] Levels of IGF-1 vary with sex and ethnicity and may be reduced in malnutrition, hypothyroidism, hepatic disease, diabetes mellitus, and delayed puberty.[20,21] A literature review by Federico et al[22] determined that IGF-1 had a specificity of 100% and a sensitivity of about 70% to 90% in diagnosing GHD. The major serum carrier of IGF-1, IGFBP-3, is also growth hormone dependent but is less affected by nutrition.[20] In the initial report by Blum and Ranke,[23] IGFBP-3 showed excellent discrimination between GHD and normal growth, but other groups have reported that IGFBP-3 does not provide a good distinction between the 2 populations.[20] Because the normal ranges for IGF-1 are low in young children, IGFBP-3 may be more informative for children younger than 3 years.[3]

Provocative tests for growth hormone release are available but are challenging to interpret. Following administration of substances such as insulin, levodopa, arginine, glucagon, propranolol, or clonidine that provoke growth hormone release, growth hormone levels are measured over a period of time using antibody-based testing. Thresholds to make the diagnosis of GHD have varied from 2.5 ng/mL to 10 ng/mL, with specificity decreasing as the cutoff increases.[24,25] The current widely used cutoff is 10 ng/mL by immunoradiometric assay.

Other issues that affect interpretation of provocative testing include differences in epitope specificity of antibodies used in different assays and variable results with different stimuli or populations. Recent studies have shown that variability between assay results exceeds 100% because of heterogeneity of the analyte itself, the availability of different preparations for calibration, and the interference from matrix components such as growth hormone–binding protein.[26] The reliability of the growth hormone peak measured by comparing the results of 2 tests using different stimuli, or even the same stimuli, is poor (intraclass correlation coefficients <0.8).[27] Peak growth hormone response is blunted in obese persons and in prepubertal adolescents with CDGP.[28,29]

Assessment of spontaneous growth hormone secretion can be performed by obtaining 12-hour overnight growth hormone profiles during sleep, although it is time-consuming, invasive, and expensive. In retrospective studies, Radetti et al[30] noted a correlation between subnormal spontaneous growth hormone secretion and improvement in adult height with growth hormone

Box 2. Differential Diagnosis of Short Stature

- Normal patterns of growth
  - Familial (genetic) short stature
  - Constitutional delay of growth and development ("late bloomer")
- Abnormal patterns of growth
  - Disproportionate short stature: trunk is longer or shorter than expected in comparison with limbs
    - Skeletal dysplasias
    - *SHOX* gene mutations
    - Spinal radiation
  - Proportionate short stature: trunk is length expected in comparison with limbs
    - Intrinsic: inherent limitations on bone growth
      - Small for gestational age/intrauterine growth retardation
      - Genetic or chromosomal abnormalities
    - Weight loss or more pronounced decline in weight gain than in linear growth
      - Nutritional deficiency
      - Malnutrition (starvation, anorexia nervosa)
      - Malabsorption (celiac disease, inflammatory bowel disease)
      - Poorly controlled diabetes mellitus
    - Chronic diseases (renal, cardiac, pulmonary, hematologic)
    - Maintenance of weight
      - Endocrine causes (growth hormone deficiency, hypothyroidism, glucocorticoid excess)
      - Celiac disease or inflammatory bowel disease at times

Box 3. Laboratory Screening Tests for Evaluation of the Most Common Pathologic Causes of Short Stature

- Celiac disease: immunoglobulin A (IgA) tissue transglutaminase or IgA endomysial antibody immunofluorescence, with an IgA level[8a]
- Inflammatory bowel disease: complete blood cell count; erythrocyte sedimentation rate +/− C-reactive protein[9a]
- Hypothyroidism: thyroid function tests
- Growth hormone deficiency: insulinlike growth factor 1 (consider insulinlike growth factor binding protein 3 if age is <3 years)
- Turner syndrome (in girls with unexplained short stature after initial screening or with phenotypic features): karyotype

[a] May miss disease. If high index of suspicion, refer to a gastroenterologist.

therapy, while Diamond et al[31] found that indexes of spontaneous growth hormone secretion were not predictive of response to growth hormone therapy. Rogol et al[32] reported that serial growth hormone sampling did not add significant information to auxologic data, maximally stimulated growth hormone, and IGF-1 levels in predicting response to growth hormone therapy. Most clinicians still consider assessment of spontaneous growth hormone secretion a research tool.

Expected Outcomes of Use of Growth Hormone Replacement in Children With ISS

In 2003, the US Food and Drug Administration (FDA) approved the use of growth hormone for treatment of ISS in children whose height is more than 2.25 SDs (1.2nd percentile) below the mean for age and sex without evidence of underlying disease or GHD, such as Miss W. Although it was not part of the FDA criteria, the FDA issued a statement that these children should have "a growth rate that is unlikely to attain an adult height within the normal range," with a cutoff at the 1.2nd percentile, which is 160 cm (63 in) for men and 150 cm (59 in) for women.[33]

The FDA approval of growth hormone for treatment of children with ISS was based on 2 studies. Leschek et al[34] performed a randomized, double-blind, placebo-controlled study of peripubertal children and followed up with some of them until near adult height. Treatment effect was 0.51 SD score (95% CI, 0.10-0.92 SD score; *P*=.02) (3.7 cm). The growth hormone dose used, 0.22 mg/kg per week, is lower than that used in later studies, and the weekly dose was divided into 3 times weekly, which has been shown to be less effective than daily treatment for GHD.[35] Wit et al[36] performed an open-label randomized study investigating the effect of 2 doses of growth hormone, 0.24 mg/kg per week and 0.37 mg/kg per week, with a calculated dose-response effect of 0.57 SD score (±0.25 SD score; *P*=.03) (3.6 cm).

There are 3 prospective randomized controlled trials of growth hormone therapy and adult height in ISS: the study by Leschek et al,[34] a dose-response study by Albertsson-Wikland et al,[37] and a small study of girls by McCaughey et al[38] (**Table 1**). Data from these studies and from several of the nonrandomized, prospective and retrospective, controlled and uncontrolled studies show higher mean adult heights in treated participants.[39-44] Other studies did not find an effect of growth hormone treatment on adult height.[45-47] Treatment responses in these studies are highly variable. A limitation of these studies is variable growth hormone dosing and administration schedules. Three systematic reviews[48-50] (**Table 2**) concluded that growth hormone therapy can result in greater adult height in some children, but a height deficit may remain. In their review, Deodati and Cianfarani[50] analyzed the 3 randomized controlled trials and concluded that the mean height gain among children treated with growth hormone exceeded that of controls by 0.86 SD (5.2 cm [2 in]). A joint consensus statement from the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society (now the Pediatric Endocrine Society), and the European Society for Paediatric Endocrinology concluded that the shorter the child, the more consideration should be given to treatment with growth hormone, but the group stated that therapy would generally not be recommended for a short child who is unconcerned about his/her stature.[3]

Target Height

A major problem in the decision to treat a child with ISS is the inability to accurately predict adult height, which is based on the patient's current bone age. There are 2 commonly used methods for assessing bone age. The Greulich and Pyle method, the more commonly used method in the United States, compares the patient's radiograph with a reference image in an atlas. Studies have shown standard errors between readers of 0.55 to 0.82 years.[7] The Tanner-Whitehouse method applies scores to maturity indicators of the individual bones of the hand and wrist to derive bone age.[7] There are several algorithms used for predicting adult height from bone

Table 1. Overview of Randomized Controlled Trials of Recombinant Human Growth Hormone Therapy for Idiopathic Short Stature

	McCaughey et al,[38] 1998		Leschek et al,[34] 2004		Albertsson-Wikland et al,[37] 2008		
Trial Characteristics	Control[a]	Treatment	Control	Treatment	Control	Treatment 1	Treatment 2
Growth hormone dosage, mg/kg/wk	NA	~0.33	Placebo	0.22	NA	0.23	0.47
Dosing regimen	NA	Daily	3 times/wk	3 times/wk	NA	Daily	Daily
No. treated (M/F)	8 (0/8)	10 (0/10)	31 (24/7)	37 (29/8)	64 (50/14)	49 (40/9)	81 (63/18)
No. followed up to adult height (M/F)	6 (0/6)	7 (0/7)	12 (9/3)	22 (18/4)	19 (14/5)	18 (14/4)	31 (24/7)
Age, mean (SD), y							
At start of trial	6.14 (0.62)	6.24 (0.38)	NR	NR	NR	NR	NR
At start of treatment	NA	8.07 (0.48)	12.9 (1.1)	12.5 (1.6)	12.0 (1.6)	11.5 (1.3)[b]	
Height at start of trial, SD score (SD)	−2.55 (0.32)	−2.52 (0.26)	−2.8 (0.6)	−2.7 (0)	−2.76 (0.39)	−2.84 (0.56)[b]	
Predicted adult height at start of trial, SD score (SD)			−2.3 (0.8)	−2.1 (0.7)			
Treatment duration, y							
Median (range)	NA	6.2 (5.5-6.5)					
Mean (SD)			4.1 (1.7)	4.6 (1.6)	NA	5.64 (1.37)[b]	
Adult height, SD score (SD)	−2.37 (0.46)	−1.14 (1.06)	−2.34 (0.17)	−1.77 (0.17)	−2.2 (0.75)	−1.7 (0.68)	−1.5 (0.84)
Adult height SD score − baseline height SD score, mean (SD)	0.18	1.38	0.42 (0.07)	0.93 (0.16)	0.4 (0.62)	1.2 (0.82)	1.3 (0.73)
Adult height − predicted adult height, mean (SD), cm	−6.0 (1.7)	3.5 (4.4)					
Adult height SD score − predicted adult height SD score, mean (SD)			−0.14 (0.19)	−0.32 (0.12)			
Adult height − mid-parental height, mean (SD), cm	−10.6 (4.3)	1.9 (5.1)					
Adult height − mid-parental height, SD score (SD)			−1.02 (0.25)	−0.66 (0.19)	−1.0 (0.77)	−0.1 (0.64)	0.4 (1.03)
Intention-to-treat analysis performed	No		Yes		Yes		

Abbreviations: NA, not applicable; NR, not reported.

[a] Subsets that were randomized.

[b] Both treatment groups combined.

Table 2. Overview of Systematic Analyses of the Effect of Recombinant Human Growth Hormone Therapy in Idiopathic Short Stature

Source	Databases Searched	Study Selection	Findings
Finkelstein et al,[48] 2002	MEDLINE (1985-2000)	10 Controlled trials (434 children) 28 Uncontrolled trials (655 children)	Controlled trials: adult height in growth hormone-treated participants exceeded that of control participants by 0.84 SD score Uncontrolled trials: adult height exceeded predicted adult height by 0.56 SD score Average gain in adult height predicted to be 4-6 cm (range, 2.3-8.7 cm)
Bryant et al,[49] 2007	Cochrane Library issue 4, 2005 MEDLINE (Ovid: 1981-12/2005) Searches on 6/7/2006: PubMed, Science Citation Index, BIOSIS National Research Register, Current Controlled Trials	10 Randomized trials (741 children)	Only 2 studies followed up to near or adult height[34,38] (Table 1)
Deodati and Cianfarani,[50] 2011	Cochrane Central Register of Controlled Trials MEDLINE Bibliographic references from all retrieved articles describing such trials up to April 2010	3 Randomized trials (115 children) with adult height measurements 7 Nonrandomized trials (477 children) with adult height measurements	Randomized trials: height of growth hormone-treated participants exceeded that of control participants by 0.65 SD (~4 cm), with mean height gain of 1.2 SD vs 0.34 SD Nonrandomized trials: height of growth hormone-treated participants exceeded that of control participants by 0.45 SD (~3 cm)

age. The Bayley and Pinneau method is most often used in the United States; a predicted percentage of completed growth is determined based on the bone age result, sex, and whether the bone age is more than 1 year delayed from, within 1 year of, or more than 1 year in advance of chronological age.[51] Adult height may be overestimated in children with CDGP and underestimated in children with ISS using the Bayley and Pinneau tables, more so in boys than in girls.[7] Even in studies that have shown a good correlation between predicted adult height and actual adult height, individual variation can be large; Sperlich et al[52] showed that one-third of enrolled adults had a height that differed by more than 5 cm from the adult height predicted by the Bayley and Pinneau method.

Decision to Treat

Inherent in the decision to prescribe growth hormone is consideration of the consequences of no treatment. Although short stature may be a sign of underlying pathology, short stature itself is not a disease; it is considered a problem because it is perceived to be a disability. While severe short stature may be a physical disability, there is no clear evidence that there is a physical disadvantage to being mild to moderately short.[53] If short stature is truly a physical disability, then both short girls and short boys should equally be referred to pediatric endocrinologists. However, Grimberg et al[54] noted that twice as many boys as girls are referred for evaluation of short stature and of those referred, girls' heights are more impaired, with a median height of −2.4 SD score for girls and −1.9 SD score for boys ($P < .01$) and median deficits from mid-parental height of 1.9 SD score for girls and 1.3 SD score for boys ($P < .001$).

Is short stature psychologically disabling?[53] Children with ISS who are referred for medical evaluation have more psychosocial problems than children with normal stature or those with ISS who are not referred.[55] However, in the general population, there are only minor behavioral difficulties in short boys[56] and no association with adverse behavioral outcomes or peer relationships,[57] suggesting an ascertainment bias in the referred population.

Cost of Treatment

The cost of growth hormone therapy must be considered. Lee et al[58] created a decision analysis model. They estimated that the incremental cost-effectiveness ratio of growth hormone treatment was $52 634 per 2.54 cm (1 in) in 2004 US dollars, with an incremental height gain of 4.8 cm (1.9 in) over 5 years and an incremental cost per child of $99 959. Based on the FDA indication for treatment of children with ISS, 585 000 US children are eligible for growth hormone at a potential annual cost exceeding $11 billion.[59]

It is important to recognize that growth hormone therapy is administered to an otherwise healthy child. Treatments require administration of injections 6 to 7 nights per week for years until growth is near completed, with frequent medical visits and laboratory testing to monitor the treatment.

Safety of Growth Hormone Therapy

Known short-term complications include insulin resistance (with increased incidence of type 2 diabetes mellitus in children with other risk factors), pseudotumor cerebri, and slipped capital femoral epiphyses.[60] Data from the 2 studies used to obtain FDA approval for treatment of children with ISS showed similar or lower rates of adverse events as with children treated for GHD.[61] However, studies powered to estimate a treatment effect are typically underpowered to evaluate rare adverse events.[62] The National Cooperative Growth Study enrolled 8018 children with ISS and found no significant increase in adverse events or mortality at doses of 0.37 mg/kg per week or lower in treatment of children for ISS compared with GHD.[63,64] However, the outcomes were collected through reports from physicians rather than systematic monitoring, so underreporting or misclassification of adverse events could have occurred.[62] Long-term complications are less clear; adverse events may occur after end of follow-up and thus not be noted or reported.

There are concerns about a correlation between cancer risk and IGF-1 levels observed in nested case-control trials.[65] Recent interim results from the Safety and Appropriateness of Growth Hormone Treatments in Europe (SAGhE) highlight this possibility, but the data are conflicting and controversial. The investigators from France reported an increased risk of death in an adult population previously treated with growth hormone compared with the general population. The data showed an increase in mortality, even in those at low risk of mortality (idiopathic GHD, "neurosecretory" GHD, ISS, and small for gestational age), due to bone tumors (but not global cancer mortality) and due to cardiovascular events (mainly subarachnoid and intracerebral hemorrhage). Those who received higher mean doses of growth hormone (>0.35 mg/kg per week) had higher mortality rates.[66] The SAGhE data from Belgium, Scandinavia, and the Netherlands did not show an increase in mortality rate.[67] Both studies lacked statistical power, and long-term safety of growth hormone therapy remains unclear.

Other Treatments Available for Short Stature

Height growth of children with CDGP may decrease to more than 2.25 SDs below the mean during adolescence, concurrent with their peers having their pubertal growth spurt. Treatment of these children with low-dose androgens in boys increases growth velocity without rapidly advancing bone age or compromising adult height. There are no comparable studies on the effect of low-dose estrogen in girls.[68]

Gonadotropin-releasing hormone agonists have been used to halt pubertal progression, allowing for a longer period of growth. However, increases in adult height are often clinically insignificant.[69] Yanovski et al[70] performed a randomized placebo-controlled study showing that treatment with a gonadotropin-releasing hormone agonist for 3.5 years increased adult height over predicted adult height by 0.6 SD (95% CI, 0.2-0.9 SD) for an average increase of 4.2 cm (1.7 in). Significantly decreased bone mineral density in the treatment group was found, resulting in the risks of treatment outweighing the modest benefits. Others have used a combination of gonadotropin-releasing hormone agonist and growth hormone treatments. In the only randomized study to date, Van Gool et al[71] found no difference between treatment and control groups in adult height, although there was a greater height gain in treatment vs control (4.4 cm vs −0.5 cm).

Because estrogen mediates skeletal maturation and epiphyseal fusion in both sexes (testosterone is converted to estrogen via aromatase), aromatase inhibitors have been used to block conversion of androgens to estrogens in boys, alone or in combination with testosterone or growth hormone. These agents do not delay pubertal development. Most studies have not reported adult height, and treatment response appears to be related to the aromatase inhibitor used and the duration of treatment. Adverse effects include reduced high-density lipoprotein cholesterol, vertebral wedge deformities, and theoretical long-term effects on spermatogenesis and infertility.[72,73] At this time, the use of aromatase inhibitors is considered experimental. Oxandrolone, a nonaromatizable anabolic steroid with a high anabolic-to-androgenic ratio, has been used to stimulate growth in boys with CDGP. While its mechanism of action on growth is unclear, oxandrolone may increase growth hormone–IGF-1 axis activity and may have effects on the estrogen receptor. Increases in predicted adult height have been reported in some but not all studies, and there are no studies of adult height.[73]

Recommendations for Miss W

There is a high level of evidence that recombinant human growth hormone might be considered in children with ISS. This therapy is not effective in all children with ISS. Ideally, clinicians should identify children with ISS who are likely to respond to growth hormone therapy and treat only them. Predictors of better growth response to growth hormone in ISS include a greater height difference between a child and his/her parents and greater bone age delay.[37] Miss W had negative screening test results for celiac disease, inflammatory bowel disease, and other systemic illnesses; normal thyroid function test results; a normal karyotype; and no evidence for a *SHOX* gene mutation. She was not small for gestational age and she has no syndromic features. Her body proportions are normal. Her serum IGF-1 and IGFBP-3 levels are above the median for a prepubertal girl, which suggests that GHD is unlikely. Nevertheless, she has an adult height prediction of 147 cm (58 in); therefore, she satisfies the height criteria for treatment with growth hormone according to the FDA indication for children with ISS. Her shorter starting height, lower predicted adult height, and delayed bone age are positive predictors for response,[37,74] although her familial short stature is not.[37,75]

Albertsson-Wikland et al[37] recommended treatment to those "predicted to have a good growth response, and only after thorough discussion with the children and parents to determine, on a case-by-case basis, those who suffer substantially from their short stature, thus justifying this long-term therapy."[37] Miss W does not have clear evidence of psychological or physical disability. Thus, the modest benefits in adult height may not outweigh potential unknown risks of treatment.

Most recently, Miss W was tracking parallel to but below a normal growth curve. If her growth velocity declines, then growth hormone therapy should be reconsidered. Although starting growth hormone treatment at an earlier age is a factor in predicting growth hormone responsiveness,[76] Leschek et al[34] found that most of the catch-up growth in their study was noted in the first 2 to 3 years of treatment. Because of the peripubertal growth dip, low-dose estradiol may be appropriate treatment at the time of expected puberty, but this is not well studied.

Questions and Discussion

QUESTION Has anyone looked at the potential downstream effects of IGF-1 and other potential therapeutic targets for the future?

DR COHEN Recombinant human IGF-1 has been approved for the treatment of "severe primary IGF-1 deficiency" in children with a height SD score of −3.0 or lower, a basal IGF-1 SD score of −3.0 or lower, and normal or elevated levels of growth hormone.[77] Their growth response to recombinant human IGF-1 is lower than the growth response to growth hormone among children with GHD. This may be due to lower IGFBP-3 and acid labile subunit levels (also produced in response to growth hormone and necessary for IGF-1/IGFBP-3 binding) and thus decreased IGF-1 delivery to some target tissues; lack of growth hormone–induced proliferation of prechondrocytes in the growth plate; and absence of growth hormone–induced local IGF-1 production at the growth plate.[78] Common adverse effects involve hyperplasia of lymphoid tissue, accumulation of body fat, and coarsening of facies. Intracranial hypertension and papilledema may be more common than with growth hormone treatment. No data exist on long-term safety, which is of concern because circulating IGF-1 has been implicated in cancer pathogenesis.[78,79] Currently, there is a shortage of recombinant human IGF-1 in the United States.

ARTICLE INFORMATION

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