Evaluation of the Child with Short Stature

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Introduction

Children with short stature are encountered often in family practice. By definition, one child in 33 has height measurements below the third percentile for age. While this is often defined as the lower limit of "normal," most of these children are, in fact, healthy and growing adequately. Many will attain normal stature as adults. The practitioner's task is to identify the few children who are short as a result of medical conditions that lead to failure of normal growth.

Birth weight and length do not reliably predict ultimate height and weight. Tanner and co-workers (1) have reported a correlation co-efficient of only 0.25 between birth length and ultimate height. However, the correlation between height and two years of age and ultimate height is nearly 0.8.

Growth retardation may exist if

(1) Height is less than two standard deviations from the mean for age.
(2) Growth velocity is less than two standard deviations from the mean growth velocity for age or,
(3) A pubertal growth spurt fails to occur within two standard deviations of the usual time (2).

Causes of short stature

The causes of short stature are listed in (Table 1). An understanding of the typical pattern of growth seen in each of these conditions is helpful in evaluating the short child. Determining the level of epiphyseal maturation is also useful. The radiologic standards published by Gruelich and Pyle are used most widely and are based on the growth centres and epiphyses of the left wrist and hand (3).

Bone age is usually equal to chronological age in familial and primordial short stature, but is delayed in other causes of short stature. Its major value is prognostic, as children with delayed bone age have a better chance to attain normal adult height than do short children whose bone age is not delayed.

Table 1: Causes of short stature

Familial short stature
Constitutional growth delay
Chronic systemic disease
CNS abnormalities
Congenital heart disease
Respiratory disease (asthma, cystic fibrosis)
Gastrointestinal disease (inflammatory bowel disorder, celiac diseases)
Renal disease (renal tubular acidosis, chronic renal failure)
Immune deficiency
Chronic anemia
Primordial growth delay
Chromosomal abnormalities
Down syndrome
Turner syndrome
Skeletal dysplasias
Osteochondrodystrophies
Pseudohypoparathyroidism
Environmental causes
Malnutrition
Psychosocial deprivation
Endocrine disease
Hypothyroidism
Growth hormone deficiency
Cushing syndrome

Bone Age and Height Age

Bone age and height age are helpful in estimating a child's growth potential. The younger the bone age (the state of skeletal maturation), the greater the remaining growth potential. Bone age is determined by a radiologist, using standard tables. Height age is obtained on a growth chart by drawing a horizontal line from the patient's height to the 50th percentile line for height and then dropping a vertical line to the baseline to measure the age (4).

Although a child may have a delayed height age (HA) with respect to chronologic age (CA), if the bone age (BA) is proportionately delayed (CA > HA = BA), the ultimate height may be equal to that of the child whose chronologic age is equal to his height age and bone age (CA = HA = BA). Comparison of chronologic age, bone age and height age may be used to classify causes of short stature (5).

Height Prediction

Height prediction can be used to confirm suspicion of abnormal growth. To predict a target adult height, an adjusted midparental height is obtained by averaging the parents' heights after first adding 13 cm to the mother's height if the child is a boy or subtracting 13 cm from the father's height if the child is a girl. Projection of the child's anticipated growth along his or her growth percentile should yield an adult height that is within + 8.5 cm of the adjusted midparental height. If the projection of the child's growth is more than 8.5 cm below the adjusted midparental height, the growth of the child cannot be assumed to be secondary to parental short stature (6,7).

Evaluation of Growth Retardation

History and Physical Examination

If growth retardation is suspected, particular attention must be given to certain key aspects of the history and physical examination. The categories outlined in Tables 2 and 3 (pages 29 and 30) are touched on in the well-child examination. However, in the evaluation of growth retardation, each area must be more extensively considered. For example, a family tree can be used to plot family heights, ages of menarche and ages of pubertal growth spurts in search of familial short stature and constitutional delay of growth and maturation. Upper-to-lower segment ratios, usually not calculated in general physical examinations, should be included in all evaluations of growth in order to detect abnormalities of bone development (3).

Laboratory Evaluation

If growth retardation is suspected, the following routine screening tests should be performed: Complete blood count (anaemia); erythrocyte sedimentation rate (inflammatory bowel disease, which may be relatively asymptomatic except for growth retardation); urinalysis, blood urea nitrogen, serum creatinine and serum bicarbonate (renal disease); thyroid function tests (hypothyroidism) and hand films for bone age (helpful in determining whether growth is consistent with chronologic age and in excluding skeletal dysplasias) (9). If a child with growth failure is more than two years old, the plasma somatomedin-C (SM-C) level can be determined to screen for growth hormone deficiency. An SM-C level of less than 0.25 u per mL suggests a growth hormone deficiency. A value greater than 0.5 u per mL indicates that a growth hormone deficiency is unlikely. However, the SM-C level is not useful during the first two years of life because of the overlap of levels between normal and growth hormone-deficient patients (10).

If the SM-C level is abnormal or if there is strong suspicion of a hormonal deficiency (hypoglycemia in a short child), growth hormone stimulation tests should be done. Since baseline growth hormone levels are low, stimulation tests are required to separate subjects with hormonal deficiency from those with normal secretion (11).

Metabolic screening tests should be performed as needed to identify mucopolysaccharidosis, aminoacidopathies and galactosemia. Any girl with delayed bone age and unexplained shortness should have a karyotype done to rule out Turner's syndrome or one of its variants.

Differential Diagnosis

A useful way of approaching growth disturbances is by comparing chronologic age, bone age and height age (Table 5). A bone age that differs from height age by six months or less is not significant. However, a bone age that differs from height age by one year or more is significant (12).

Treatment

Treatment of short stature depends on the underlying cause. Children with chronic systemic disease will show improved growth if their medical status can be significantly improved. Growth failure because of dietary or environmental factors can also be reversed with appropriate intervention. Children with hypothyroidism usually show a rapid return to normal stature once hormone replacement is begun. For children with growth hormone deficiency, however, the results of treatment are seldom as dramatic, with most individuals remaining subnormal in height as adults.

There is no specific treatment for the other causes of short stature. Nevertheless, parents may enquire about the benefit of growth hormone treatment. When the child has constitutional delay, parents can be reassured that the adult height will be normal without intervention. Unfortunately, the same cannot be said for those with familial or primordial short stature. There is no evidence to show that the use of growth hormone results in any significant increase in final height for these children.

Growth hormone does seem to offer possible benefit to children with Turner syndrome. Although the results of long-term studies are not yet available, most girls with this condition who have been given growth hormone have shown an increase in linear growth that is expected to

Table 2: Important Historical Features in the evaluation of the Child With Growth Retardation

Historical Features	Diagnostic Implications
MATERNAL HISTORY Length of gestation, previous fetal abortions, complications of TORCH infection, pregnancy, smoking, alcohol and drug use	Fetal alcohol syndrome, hydantoin syndrome, intrauterine growth retardation secondary to placental insufficiency
ANTHROPOMETRIC VALUES Birth weight, birth length, dysmorphology	Intrauterine growth retardation, Turner's syndrome, Down's syndrome, other short stature syndromes
NEONATAL AND DEVELOPMENTAL HISTORY Neonatal hypoglycemia, hypothyroidism developmental milestones	Hypopituitarism,
NUTRITIONAL HISTORY Inadequate caloric intake	Failure to thrive
PSYCHOSOCIAL HISTORY Child neglect or psychological child abuse	Environmental
FAMILY HISTORY Genetic syndromes. Skeletal dysplasias (e.g. achondroplasia), inborn errors of metabolism (e.g. mucopolysaccharidosis, gangliosidosis type I, mucolipidosis II) Family height, ages of menarche,constitutional delay of maturation, ages of pubertal growth spurts	Familial short stature
REVIEW OF SYSTEMS Specific chronic organic diseases	Cardiac, pulmonary, hepatic, disorders
MEDICATION HISTORY Corticosteroids, stimulants	Drug-induced growth retardation

Referral to a pediatric endocrinologist seems appropriate when Turner syndrome is diagnosed.

In the second half of this paper I will present a charming child with short stature. The workup of this patient demonstrates the step that should be followed in investigation of short stature.

History and Physical Examination

Haifa was seen initially in Tripoli and was referred later to AUB where I saw the patient in the Family Medicine Practice Center. The investigations were done in Tripoli, AUB and Royal Hospital for sick children in London.

She was born in Tripoli in a maternity hospital, birth weight 3 kg, birth length 49 cm, following a spontaneous vertex delivery. Mother had been well during the pregnancy with no smoking nor alcohol intake. Mother is aged 36 with a height of 163.0 cm which is 50th centile. She reached menarche at age 13 years. Father, aged 37 years, is an agricultural land owner in good health. He is 183 cm tall, which would put him between the 9th and 97th centiles. There are four siblings, a boy aged 16 years who is 183 cm tall, a girl of nearly 13 years who has been menstruating for some six months, she is 167 cm tall, a girl of 10 years, said to be 154 cm, and a boy of 10 months, said to weigh 12 kg and be around 74 cm tall some two months ago. There is no history of stillbirth, neonatal death nor death in infancy.

In the past, Haifa has been in good health. She was breast fed for six months and solids introduced by seven to eight months of age. However, mother says that her appetite has always been bad and that she often has to force food into her. Bowels are open regularly once a day, said to have been of rather small volume but more normal of the last year and normal in colour. There have been no serious illnesses. Mother had no height records but thought that she had gained 5 cm over the last year and 8 cm the year before. She thinks her weight has been static over the last two years.

Table 3: Important Physical Findings in the Evaluation of the Child with Growth Retardation

Physical Findings	Diagnostic Implications
Upper-to-lower segment ratio	Disorders affecting bone growth (skeletal dysplasias) or resulting in infantile proportions, (hypothyroidism, hypopituitarism)
Head circumference	Evidence of poor cerebral growth, (malnutrition)
Goitre, prolonged jaundice, large posterior fontanelle, umbilical hernia	Hypothyroidism
Micropenis, visual disturbances	Hypopituitarism
Heart murmur, increased blood pressure, pallor, wasting	Evidence of chronic organic disease
Stigmata of short stature syndromes	
Cubitus valgus, webbed neck, low posterior hairline, edema of hands and feet	Turner's syndrome
Flat facies, inner epicanthal folds, upward lateral slant of palpebral fissures, short metacarpals and phalanges, simian crease	Down's syndrome

Table 4: Laboratory Evaluation

Initial Evaluation	Complete blood count Serum chemistry Urine analysis Wrist X-ray for bone age
Further Tests as Necessary	Chromosome analysis Lateral skull X-ray Thyroxin and thyroid Stimulating hormone Growth hormone level stimulation tests

On examination, Haifa was a delightful girl who looked well. She looked somewhat dysmorphic with coarse features, hypertelorism, rather square face with snub nose and coarse hair. Limbs superficially looked short with particularly short fingers and square hands with broad great toes. No abnormalities were found in the central nervous system with normal fundi, no cataracts, no squint. The cardiovascular system: There was a systolic murmur heard over the precordium at the left sternal edge and at the back with no thrill. There was no femororadial delay. There were no abnormalities in the respiratory system nor the abdomen. In particular, there was no hepatosplenomegaly. Genitalia were those of the normal female and there was no kyphoscoliosis. Triceps skinfold thickness was 6.2 mm (3rd centile), subscapular skinfolds 4.2 mm (3rd to 10th centile). Height 95.9 cm, which is well below the 3rd centile, sitting height 56.8 cm, and subischial leg length 39.1 cm, indicating that her back and limbs are proportionately small (-3.5 and -4 standard deviations, respectively).

Investigations

Haemoglobin, full blood count, showed no abnormality, with ESR of 10 mm/hr. Serum iron level was 12 mol/l (nl) with normal transferrin (2.6 g/l) and ferritin level (52 ug/l). Both vitamin B12 and folate level were within normal 824 ng/l and 10.6 ug/l, respectively with red cell folate of 371 ug/l (normal). Her electrolytes profile was normal including: Calcium 2.42 mmol/l, phosphate 1.38 mmol/l, creatinine 5.3 mmol/l. The plasma amino acid screen and organic acid urinary screen were normal as well. Qualitative urinalysis revealed trace of protein and ketones but no other abnormality. Mucopolysaccharidosis screen

Table 5: Differential Diagnosis of Growth Disorders by Comparing Chronologic Age, Bone Age, and Height Age

CA > BA = HA Hypopituitarism

Constitutional delay of growth and maturation
Nongrowth-hormone-deficient, growth-hormone-responsive growth failure (biologically inactive growth hormone, or growth hormone and/or somatomedin-C resistance)
Cushing's disease
Chronic malnutrition
Psychosocial deprivation
Chronic organic disease
Glucocorticoid excess

CA > HA > BA

Growth hormone deficiency (hypopituitarism)
Hypothyroidism

CA > BA > HA

Constitutional delay of growth and maturation with familial short stature
Intrauterine growth retardation
Turner's syndrome
Down's syndrome

CA = BA > HA

Familial short stature
Intrauterine growth retardation

KEY: CA = chronologic age; BA = bone age; HA = height age

revealed mucoolysaccharides of 19 mg/mmol creatinine (age related reference range 6-13 mg/mmol creatinine)

The pattern obtained from one dimensional electrophoresis does not support the diagnosis of mucopolysaccharidosis types I, II, or III. Her thyroxin was 165 nmol/l (normal) and prolactin 307 m u/l (normal).

Time	LH	FSH	TSH
Min	U/l	U/l	mU/l
0	<0.9	1.9	4.0
20	4.0	12.0	9.5
60	3.9	15.2	7.0

These are normal results though there is a somewhat exaggerated response of FSH of doubtful clinical significance.

Insulin hypoglycemia test: Plasma glucose fell from 4.7 mmol/l to a minimum of 1.8 mmol/l. Cortisol response baseline 409 nmol/l, maximum 814 nmol/l (normal response). Growth hormone rose to maximum of 16.5 mU/l (very slightly suboptimal response, but unlikely to be of clinical significance).

Jejunal biopsy: Two attempts failed, but stool culture negative. In addition, urine for reducing substances was negative.

Skeletal survey: There is abnormality of the hands and feet. This consists in the hands of short metacarpals, phalanges and a small carpal area. Similar changes are present in the feet. Long bones show only minor abnormality with slight loss of tubulation of the proximal humeri and tibiae. Remaining skeleton including the skull and spine, normal. Appearances are not of a mucopolysaccharidosis, but suggest a possible acrodysplasia.

Conclusion

It seemed very likely, on the first meeting with Haifa, that she had a syndrome diagnosis and I felt it quite possible that she would turn out to have either a mucopolysaccharidosis or a form of skeletal dysplasia. The investigations, however, have excluded a mucopolysaccharidosis and the measurements indicate that her short stature is proportional, with back and long bones equally short. The skeletal survey findings are not pathognomic of any particular syndrome and I would have expected the radiological changes to be more specific by her age in conditions such as acromesomelic dysplasia syndrome or brachydactyly syndrome type-E, although the latter does remain a possibility (14, 15).

The importance of making a specific syndrome diagnosis would be to provide genetic counselling and, of course, to be more specific about the prognosis. Most important, however, is the question as to whether any treatment is likely to influence Haifa's final height and, despite the marginally suboptimal growth hormone response to insulin hypoglycemia, there is nothing clinically about Haifa to suggest that she might respond to exogenous growth hormone treatment. There is nothing from our other investigations to suggest any other form of treatment that is likely to prove beneficial.

In summary, therefore, I think that Haifa is small because of a dysmorphic syndrome which we have been unable to positively identify. I think that it is very unlikely that any therapeutic intervention will improve her final height prognosis.

Final Comment

Growth is a manifestation of health in the young. As such, it is a parameter of the well-being of a child. A wide variety of disorders can affect the rate and the quality of growth. Thus, the ability to evaluate growth is a basic diagnostic skill that all physicians who provide care for children should possess. By focusing on key aspects of the history and physical examination, by performing the appropriate screening tests, by comparing chronologic age, bone age and height age, and by reviewing prior anthropometric measurements, the family physician can confidently evaluate the child with growth retardation.

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