Clinical update: Investigating short stature in children

Introduction

Short stature, or decreasing growth velocity, is a frequent reason for paediatric consultations. Children and parents have concerns both about the possibility of underlying disease and the perceived social consequences of short stature in respect of self-esteem (which can be affected by teasing or bullying), social relations and physical challenges. Short stature frequently goes unrecognised in early childhood, and its being diagnosed at a later age decreases the opportunities to intervene, improve health outcomes and optimise final adult height.1

Normal growth is the result of a complex interaction between genetic, hormonal, environmental and nutritional factors. Common normal variants of short stature are familial short stature, constitutional delay of growth and puberty, and idiopathic short stature. Approximately 5% of children referred for evaluation of short stature have an identifiable pathological cause, which when corrected will usually result in normalisation of growth. Endocrine disorders, when present, are highly treatable and the most common aetiologies are growth hormone deficiency (GHD), hypothyroidism, coeliac disease and Turner syndrome. Other causes of short stature include renal, hepatic and gastrointestinal diseases, and other genetic syndromes. The large number of clinical conditions associated with short stature can make identifying the cause challenging.1,2

To identify children with abnormal growth early, one requires good growth monitoring systems as part of preventive child health programmes, along with well-defined and accurate referral criteria using evidence-based guidelines for growth monitoring. The latter should have a high positive predictive value with an acceptable false-positive rate; good diagnostic work-up after referral is also required.3
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Learning Objectives

You will learn:

- Why the early identification of children with abnormal growth is important
- Common aetiologies of short stature in children
- How to recognise and assess a normal pattern of child growth
- When and how to refer a child because of short stature
- The role of growth hormone therapy in some children with short stature.

Recognising a normal pattern of growth

A child’s height/length is the product of initial length at birth and the rate (or velocity) of growth over time. Growth velocity is highest at birth and decreases progressively until the pubertal growth spurt brings about the adolescent increase in height. As epiphyseal fusion occurs, there is a sudden deceleration of growth velocity as final adult height is attained. Intermittent short growth arrests and spurts are frequent in child development. This natural pattern of saltatory growth and possible catch-up or catch-down growth contributes to the growth trajectories attained by individual children.

Normal growth, by definition, encompasses the 95% confidence interval for a specific population. Height, body weight, body mass index (BMI) and many other anthropometric parameters can either be described in absolute terms (e.g. cm, kg or kg/m²) or they can be referred, using percentiles or using a standard deviation score (SDS) scale, against a reference population chart for children of comparable age and sex. Transforming and plotting individual measurements into percentiles or SDS scales has been found favourable for clinical purposes.

When charting anthropometric parameters over time, percentile or SDS crossing is a ubiquitous physiological phenomenon in early human growth, but actually occurs at all ages. A newborn’s size and growth are the result of the intrauterine environment, and growth hormone does not play a major role. Between six and 18 months of age, children exhibit catch-up or catch-down growth until they reach their genetically determined growth curve based on mid-parental height (Box 1). By two years of age, growth hormone plays a predominant role. At this stage, children should track along a percentile and any variation should stay within two percentiles. In adolescence, growth is affected by the onset of puberty and sex hormones become the predominant factor.

Children with heights >2SD below the mean are generally classified as being of short stature, with variants of normal growth including familial short stature, constitutional delay of growth and puberty, and small-for-gestational-age with catch-up growth. The further below 2SD an individual’s growth falls, the more likely it is that there is a pathological condition keeping him or her from achieving their genetically determined height potential. Growth retardation refers to a downward deflection of the growth velocity, with the resultant growth curve crossing the SD lines or percentiles.

The growth of preterm children differs from that of children born at full term and is dependent on their gestational age. It is important to correct for premature birth and to use the corrected age, rather than actual age since birth. Evidence suggests that boys, in particular, may be vulnerable to the complications of preterm birth that influence growth.
Assessment of growth

The intrinsic biological complexity of human growth makes the use and interpretation of measurements of growth challenging. No real pathology is seen in as many as 95% of referrals, and yet several studies have reported a high frequency of diagnostic delays with regard to so-called classic target conditions, such as Turner syndrome and GHD. Appropriate referrals for diagnostic work-up for abnormal growth might improve patient outcomes with early diagnosis and treatment, while minimising unnecessary and stressful procedures and their related costs in disease-free children within normal variants of growth. Daily clinical practice can best be optimised by standardisation of growth monitoring with validated evidence-based tools.1,6

Growth charts

Cross-sectional distance charts provide percentiles for height, weight and other anthropometric parameters against age. Velocity charts provide percentiles for the differences in height, weight and other parameters against a standard time interval (usually 12 months). Tempor-conditional charts provide percentiles that allow for distinguishing between early- or late-maturing children and can only be applied when additional information on developmental tempo is available, i.e. when clinical signs of puberty are visible, or when bone age or the age of peak height velocity of that subject is known. As this information is not usually available, tempo-conditional growth charts are rarely used in routine clinical practice.5

Regional variations in adult height do exist and are, in large part, attributable to genetic factors; a child’s adult height can be predicted on the basis of mid-parental height. Growth charts are gender-, parameter- and population-specific and it is key that the correct chart is used for evaluation of individual growth. Accurate use of SD scores depends heavily on the appropriateness of the reference population data. The South African National Department of Health’s Road-to-Health booklet has been used nationally since 2011 and includes various growth (height, weight, BMI) and velocity charts for age, but not head circumference. The 2006 World Health Organization (WHO) international growth standard charts are representative of healthy children in optimal conditions. Of note, children were excluded according to many criteria, including low socioeconomic status, breastfeeding for <12 months, maternal smoking during pregnancy or lactation, perinatal morbidities, and child health conditions known to affect growth. In this context, while the WHO growth charts allow for growth data to be compared across countries, these are unlikely to be appropriate for detecting abnormal growth in a particular country.1,4,6

Box 1. Calculating mid-parental height to predict adult height potential

| Boys: | father’s height + mother’s height + 13cm | 2 |
| Girls: | father’s height + mother’s height – 13cm | 2 |

If both parents are of normal stature and projected height differs from the mid-parental height by >2SD, this is suggestive of a possible pathological condition.
Identifying growth-related disorders using height measurement

The most useful tests for distinguishing the short normal child from one with a pathological condition are accurate height measurements over time and calculation of growth velocity. The importance of proper technique when measuring length and/or height cannot be overstated, as the validity of distance and velocity charts depends on measurement accuracy. The two most common reasons for the misdiagnosis of growth disorders and inappropriate referrals for further evaluation are errors in height measurement or inaccurate plotting of values on a growth curve. Other common confounders are poor measurement technique, variations between instruments and observers, and diurnal variation. Ideally, infants should be measured for length in a firm box with an inflexible board and fixed headboard; in children older than two years, height should be measured using a wall-mounted stadiometer (Figure 1).1,2,4,5

Single height measurement only identifies children whose height is outside the normal range, whereas repeated height measurements over time allow for calculation of a growth rate that can be used to define abnormal growth. Growth in a normally developing child tends to follow a given centile pattern. Most apparently healthy children who are short but growing at a normal velocity are indeed healthy (Table 1). In contrast, a child whose growth velocity is declining, irrespective of their absolute height, deserves thorough evaluation. Note that there is a low correlation between length and mid-parental height at birth and during the first three years of life. Crossing over SDS lines in this age period is therefore not unusual.1,3

Evaluating growth velocity is considered a superior measure for identifying growth-related disorders because changes in actual height only become evident after altered growth rates have been sustained over a longer period; deviations in growth away from the percentile are difficult to detect over short intervals using the growth curve. Evaluating growth velocity at each routine and acute illness visit allows for the earliest identification of problems with growth. Growth velocity is best assessed using measurements of length, head circumference and weight taken and plotted at 3-4-monthly intervals in infants. For children older than two years, weight, height and BMI should be plotted.1,2

<p>| Table 1. Normal growth velocity by age |</p>
<table>
<thead>
<tr>
<th>Age</th>
<th>Growth velocity per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 12 months</td>
<td>23-27cm</td>
</tr>
<tr>
<td>12 months to 2 years</td>
<td>10-14cm</td>
</tr>
<tr>
<td>2 to 3 years</td>
<td>8cm</td>
</tr>
<tr>
<td>3 to 5 years</td>
<td>7cm</td>
</tr>
<tr>
<td>5 years to puberty</td>
<td>5-6cm</td>
</tr>
</tbody>
</table>
| Puberty | Girls: 8-12cm  
Boys: 10-14cm |

What is the role of evaluating bone age?

Assessment of skeletal maturity has both diagnostic and prognostic purposes in a child with short stature. Bone age is considered an important indicator of maturity and is the only size-independent indicator of biological maturity routinely used from birth to adulthood. Many parameters correlate better with bone age than with chronological age (e.g. height velocity, menarche, muscle mass and bone mineral mass).

Children with familial or idiopathic short stature have a bone age equivalent to their chronological age, and children with constitutional delay of growth/puberty or endocrine disorders have a bone age less than their chronological age. Bone age is also delayed in children with malnutrition and chronic illness. In pre-pubertal children with GHD, bone age is delayed by a mean of 2±1 ‘years’ at age 6-10 years. Because the bone age of a child with endocrine diseases will progressively fall behind chronological age, calculating bone age every 12 months might be useful to differentiate constitutional delay of growth from endocrine diseases.2,7
Evaluating growth velocity at each routine and acute illness visit allows for the earliest identification of problems with growth.

The child’s shoes and any hats or hair ornaments are removed. The child faces away from the wall with the heels together and the back as straight as possible. The head, shoulders, buttocks, and heels should be in contact with the vertical surface. With the child looking straight ahead, the head projection is placed at the crown of the head. The child steps away from the wall, and the height measurement is recorded to the nearest 0.1 cm.

Figure 1. Infant length and child height measurement techniques

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**A**

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**B**

Movable head projection at right angle to board

Hat/hair ornaments removed. Head in line with the head plate. Horizontal axis of vision.

Measurer applies gentle traction beneath the jaw to maintain this position.

Fixed measuring device attached to a wall (stadiometer)

Head, shoulders, buttocks, and heels in contact with the vertical surface.

Shoes off; heels together
When and how to refer a child because of short stature

When individual growth slows and crosses the height centiles, termed ‘falling off the curve’, a pathological aetiology is more likely even if growth remains within the normal reference range on the chart. Growth velocity that is below the fifth percentile for age and gender (e.g. <5cm/year after the age of five years) or a height drop across two or more centiles on the growth chart are indications for further investigation. It is important to remember that:1,5

• During periods of illness, starvation or social deprivation, height velocity tends to decelerate but usually increases again and compensates for the previous losses (catch-up growth) when the unfavourable situation has been overcome
• Short stature with decreased weight-for-height ratio is suggestive of a chronic systemic disease attenuating growth to a degree dependent on the severity and treatment of the underlying disease
• Children who are undernourished or malnourished also present with decreased weight-for-height ratio. In children with a nutritional deficiency despite access to food (e.g. anorexia nervosa or poorly controlled type 1 diabetes), weight loss is more pronounced than the decline in linear growth, and there may also be delayed sexual maturity and bone age
• Deceleration of linear growth in a well-nourished or obese child may be an indication of an endocrine cause of short stature such as GHD, hypothyroidism or glucocorticoid excess.

A change in the rate of growth during early childhood must always be investigated. For some children, growth may be normal until the age of 10-12 years, after which the rate is markedly slowed. If constitutional delay of growth and puberty is the cause of this growth deceleration, it will be followed by a spontaneous acceleration closely associated with the eventual pubertal growth spurt. Unfortunately, this same pattern of growth deceleration after the age of 10-12 years can be associated with a pathological growth delay.1

What is best practice for differential diagnosis?

In evaluating short stature (Figure 2), a thorough medical and family history (Table 2) should complement the physical examination to determine signs, symptoms and clues that may indicate a specific disease. Relevant points in the history include birth characteristics, symptoms suggestive of chronic organic diseases, psychiatric diseases and/or severe emotional disturbances. It is also important to determine whether a slow pattern of growth occurred in either parent.

The physical examination should include a systematic examination of all body systems including a careful search for dysmorphic features and disproportionate shortening of the limbs. After a thorough medical history and physical examination has been undertaken, analysis of the growth curve and weight-for-height measurements should be undertaken. Accurate serial measurements, determination of growth velocity and mid-parental height, along with radiography to evaluate bone age, are required.1,4

If the initial evaluation suggests a genetic, endocrine, or gastrointestinal disorder, laboratory testing should be performed (Table 3). A complete laboratory evaluation of an asymptomatic child with idiopathic short stature has a low yield and is expensive. Children with short stature of no identified cause and children with certain other identifiable causes of short stature should be referred to a paediatric endocrinologist (Box 2).2

Clinicians are also faced with questions regarding the appropriate use of magnetic resonance imaging (MRI) of the brain and genetic testing. Pituitary MRI is warranted in patients with suspected GHD (owing to the potential for underlying intracranial abnormalities), but not on a routine basis for short children with no evidence of intracranial involvement or midline defect. MRI is the gold standard radiological method of evaluating children with GHD, with marked differences in MRI pituitary gland morphology suggestive of different aetiologies of GHD with different clinical and endocrine outcomes. GHD patients with
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Box 2. Indications for referring children with short stature to a paediatric endocrinologist

- Children with intrauterine growth retardation who do not catch up to the growth curve by two years of age
- Height >3SD below the mean for the age
- Growth velocity <5cm per year
- No onset of puberty by 14 years of age in boys or 13 years of age in girls
- Projected height >2SD below the mid-parental height
- Bone age >2SD below chronological age
- Diagnosis of conditions approved for recombinant growth hormone therapy.

anterior pituitary hypoplasia, pituitary stalk agenesis and posterior pituitary ectopia are probable candidates for permanent GHD in adult life. Genetic tests can contribute to a diagnosis in children with short stature associated with genetic syndromes; medical history and physical examination findings are critical to the decision whether to undertake genetic testing.4,8

Figure 2. Algorithm for the evaluation of short stature

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### Table 2. Patient history and review of systems in children presenting with growth impairment

**Past medical history**

<table>
<thead>
<tr>
<th>Question</th>
<th>Possible Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the child had any significant medical illnesses, hospitalisations or surgeries?</td>
<td>Might suggest the possibility of a chronic disease that has not yet been identified but could interfere with growth (e.g. a history of pneumonia and/or surgery in the neonatal period or meconium ileus could suggest the possibility of cystic fibrosis)</td>
</tr>
<tr>
<td>How healthy was the pregnancy? Did the mother smoke, drink alcohol or take any medication during the pregnancy? Did the mother have gestational diabetes? Was the child small, normal, or large for gestational age?</td>
<td>Excesses or constraints in the intrauterine environment can affect the child's size at birth and subsequent growth after birth</td>
</tr>
</tbody>
</table>

**Family history**

<table>
<thead>
<tr>
<th>Question</th>
<th>Possible Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>How tall are the child’s mother and father, and how tall are the parents in the context of their own families?</td>
<td>May suggest the possibility of familial short stature or significant short stature for the genetic potential (target mid-parental height)</td>
</tr>
<tr>
<td>When did the parents experience puberty (early vs late bloomer)?</td>
<td>May suggest the possibility of constitutional delay of growth and puberty</td>
</tr>
<tr>
<td>Are there any diseases that run in the parents’ families?</td>
<td>May suggest the possibility of a disease (e.g. coeliac disease) that has a genetic component and could interfere with growth</td>
</tr>
</tbody>
</table>

**Social history**

<table>
<thead>
<tr>
<th>Question</th>
<th>Possible Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is there enough food and money to get through the month?</td>
<td>Might suggest the possibility of food insecurity and malnutrition as a cause of poor growth</td>
</tr>
<tr>
<td>Has the child developed normally? How does the child do in school?</td>
<td>Might suggest the possibility of a genetic or behavioural syndrome that could affect growth</td>
</tr>
</tbody>
</table>

**Review of symptoms**

<table>
<thead>
<tr>
<th>Question</th>
<th>Possible Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questions to evaluate all systems might include: Has the child had chronic cough, shortness of breath, diarrhoea and/or malabsorption?</td>
<td>An as-yet unidentified chronic disease could interfere with growth (e.g. cystic fibrosis, other gastrointestinal disease)</td>
</tr>
</tbody>
</table>

### Table 3. Suggested laboratory tests for children with short stature

<table>
<thead>
<tr>
<th>Test</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count</td>
<td>Anaemia</td>
</tr>
<tr>
<td>Comprehensive metabolic panel</td>
<td>Hepatic and renal diseases</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate, C-reactive protein</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Follicle-stimulating hormone, karyotyping</td>
<td>Turner syndrome</td>
</tr>
<tr>
<td>Insulin-like growth factor-1</td>
<td>GHD</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone, free thyroxine (T4)</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Tissue transglutaminase and total IgA</td>
<td>Coeliac disease</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Renal disease</td>
</tr>
</tbody>
</table>
What is the role of growth hormone therapy (somatropin) in children with short stature?

Recombinant growth hormone (somatropin) is approved for a variety of conditions that cause short stature and GHD, including Turner syndrome, chronic renal failure, Prader-Willi syndrome, being small for gestational age, Noonan syndrome, short stature homeobox-containing gene deficiency, and idiopathic short stature. It is administered through daily injections over several years. The injections are generally well tolerated, but rare adverse reactions have been reported. For children with idiopathic short stature, four years of treatment results in an increased height of 3.7cm. Somatropin treatment of children with GHD leads to a catch-up in bone age that is usually appropriate for the height of the child. Response to somatropin is dependent on bone age delay in young children, and dosage appears to affect bone age acceleration.2,7

The Pediatric Endocrine Society (PES) guidelines for the use of recombinant growth hormone9 are as follows:

• To normalise adult height and avoid extreme shortness in children and adolescents with GHD (strong recommendation)
• Weight-based or body surface area-based dosing in children with GHD (strong recommendation)
• Initial dose of 0.16-0.24mg/kg/week (22-35μg/kg/day) with individualisation of subsequent dosing (strong recommendation)
• During puberty, the PES recommends against the routine increase in GH dose to 0.7mg/kg/week in every child with GHD (strong recommendation)
• Treatment at paediatric doses does not continue beyond attainment of a growth velocity below 2-2.5cm/year. The decision to discontinue paediatric dosing prior to attainment of this growth velocity should be individualised (strong recommendation).

KEY LEARNINGS

• Recognising short stature in early childhood allows for interventions to improve health outcomes and optimise final adult height
• The further below 2SD an individual’s growth falls, the more likely it is that there is a pathological condition keeping him or her from achieving their genetically determined height potential
• When an identified pathological cause of short stature is corrected this will usually result in normalisation of growth; endocrine disorders, when present, are highly treatable
• Early identification of children with abnormal growth requires robust population-specific growth monitoring systems, and well-defined and accurate referral criteria
• The importance of using the proper technique when measuring length and/or height cannot be overstated; the validity of distance and velocity charts depends on measurement accuracy
• A change in the rate of growth during early childhood must always be investigated
• Recombinant growth hormone (somatropin) is approved for a variety of conditions that cause short stature and GHD.
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References
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