SHORT STATURE IN CHILDREN

Assessing growth in childhood is an essential component of paediatric medicine.

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During childhood, linear growth is one of the most sensitive indicators of health and is affected by disease. Assessment of growth therefore is an essential and large component of paediatric medicine and accurate measurements of growth and the analysis of growth parameters are crucial for prompt recognition of disordered growth. Parental expectation and anxiety often accompany growth issues and present a challenging task to the paediatrician.

The control of growth is multifactorial, involving a complex interaction of several factors, namely genetic, nutritional (most important factor in the first year of life), environmental, endocrine and psychosocial. This review aims to give an overview of an approach to short stature, emphasising the biochemical aspects of this condition.

DEFINITION OF SHORT STATURE

Short stature is traditionally defined as a height more than 2 standard deviations (SDs) below the mean when compared with sex-specific standards based on a population of normal, healthy children at a given age. Most recent growth charts are produced from nationally adopted standards, e.g. Tanner and Whitehouse in the UK and from data derived from the Third National Health and Nutrition Examination Survey available through the Centers for Disease Control and Prevention.

Heights in a population follow a normal distribution, i.e. Gaussian distribution. Therefore 95% of children will have heights within 2 SDs and only 5% will be outside this range, meaning that 5% of the population is, by definition, short. The percentile curves are constructed (i.e. 50th percentile is the median and the 3rd and 97th percentile lines represent the 2 SDs on either side of the median) and deviations from these curves can indicate the risk for a pathological process, depending on the position of a plotted value for a particular child.

ASSESSING GROWTH

The interpretation of growth data requires the use of the most recent (i.e. updated within the last 10 - 20 years) growth charts relevant to the population being assessed.

The growth pattern is the key to diagnosis; one height measurement does not identify the growth pattern of the child, as this is a dynamic process. A minimum period of 6 months of multiple measurements is required.

The assessment of growth involves measuring the following:
- Height plotted against standard centile charts (children < 2 years of age should be assessed in a supine position by 2 individuals and children > 2 years of age should be assessed using a stadiometer). A plotted value between the 3rd and 97th percentile usually does not reflect stature affected by disease unless there is crossing of the percentiles. However, most children with a height that falls 3 SDs below the mean have a pathological cause of short stature.
- Weight plotted against standard centile charts. The crossing of centiles commonly precedes slowed growth and indicates the possibility of a chronic illness.
- Body proportions, e.g. arm span to total height ratio is expected to be around 1.0 for all ages.
- Growth velocity plotted against growth velocity centile

charts (cm/year). Velocity centile charts are invaluable in the assessment of growth disorders. This requires 2 measurements of stature made over a period of time, preferably over 1 year, and the longer the velocity remains below the 50th percentile, the more likely it is that the short stature is due to a pathological process and requires investigation.

- Predicting adult height. The child's height potential is assessed using the height of the father and mother, together with the sex of the child, to calculate the mid-parental height (MPH) (father's height + mother's height/2 + 7 cm if a male child or – 7 cm if a female child), and the 2 SD values are 10 cm on either side of the MPH. A more precise assessment of height potential can be derived using the bone age of the child, together with chronological age and current height and determining likely height outcome using the Bayley-Pinneau tables.

The most important task after growth assessment is the interpretation of the growth data to determine whether growth failure is indeed present. Thereafter it is imperative to distinguish a normal variant of growth from growth failure due to an underlying pathological condition.

The two normal variants that may present with short stature include:
- Familial short stature. Patients have a poor height prognosis and are therefore likely to be short adults. Their bone age tends to be less than their height age.
- Constitutional delay. This group of patients have slow growth rates and delayed bone age. Growth is noted to slow at about 3 years of age and again at 12 years of age. A family history of delayed growth and pubertal development may be present. These patients have a better height prognosis than patients with familial short stature. The cause, however, is unknown.

DIAGNOSIS AND LABORATORY INVESTIGATION OF SHORT STATURE

The most important diagnostic tools for the evaluation of short stature are a thorough history (birth weight/length, family heights and maturational history, nutritional enquiry, systems review for chronic illnesses, and psychosocial history) and physical examination (specific systems looking for signs of chronic illness and endocrine abnormalities, body proportions, dentition/other midline defects, visual fields/fundi, thyroid) (see Table I). Table II suggests the initial investigations recommended for the exclusion of chronic illnesses in a patient with established short stature from auxological criteria.

Following the exclusion of the disorders listed in Table II, GHD must be investigated as the possible cause of short stature. The diagnosis of GHD in childhood requires a multidisciplinary approach. It

Table I. **Aetiology of pathological short stature in children**	
Aetiology	**Examples**
Syndromes/chromosomal abnormalities	Turner syndrome, Noonan syndrome, Kallmann syndrome, Prader-Willi syndrome, Klinefelter syndrome, Russell-Silver syndrome, Down's syndrome, Seckel syndrome
Skeletal dysplasias	Achrondroplasia or chondrodystrophies
Intrauterine growth retardation with or without inadequate catch-up growth	Fetal infections or exposures Alcohol, drugs, impaired fetal nutrition, placental insufficiency
Idiopathic short stature	
Psychosocial deprivation	
Malnutrition	Kwashiorkor, marasmus, malabsorption, coeliac disease
Chronic illnesses	
• Gastrointestinal disorders	Inflammatory bowel disease, short-bowel syndrome, coeliac disease
• Renal diseases	Polycystic kidney disease, renal tubular acidosis, nephrogenic diabetes insipidus, nephritic syndrome, Fanconi syndrome
• Cardiac disorders	Patent ductus arteriosus, ventricular septal defect, tetralogy of Fallot, aortic stenosis
• Pulmonary disorders	Cystic fibrosis, poorly controlled asthma
• Haematological disorders	
• Chronic infections	
• Metabolic disorders	
Iatrogenic	Steroids, stimulants, craniospinal irradiation
Endocrine disorders	Growth hormone deficiency (GHD), hypothyroidism, gonadal dysgenesis, glucocorticoid excess, premature epiphyseal closure (androgen or oestrogen excess)

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combines a clinical and auxological assessment with biochemical testing of the hypothalamic-pituitary-insulin-like growth factor (IGF) axis and radiological evaluation. GHD is characterised by the failure of the growth hormone (GH) secretion from the anterior pituitary gland, leading to the inadequate production of the growth factor, namely, IGF-1 and its binding protein, insulin-like growth factor binding protein-3 (IGFB-3). This deficiency results in growth failure.

GH secretion is pulsatile, with increased secretions occurring during sleep. GH secretion is stimulated by growth hormone-releasing hormone (GHRH) secreted from the hypothalamus and by ghrelin secreted from the stomach and the hypothalamus. GH acts on the liver and the epiphyseal plates. In the liver GH stimulates IGF-1 and IGFBP-3 secretion, resulting in a prolongation of the half-life of IGF-1 and facilitates its transport to the target tissues. IGF-1 and GH both have growth-promoting actions at the local tissue level and the growth plate, i.e. IGF-1 mediates the biological actions of GH. Growth hormone is essential for growth throughout childhood. Linear growth is regulated by GH, IGFs, thyroid hormone, and sex steroids, where sex steroids contribute to the growth spurt during puberty.

Although the diagnosis of GHD is difficult, accurate and prompt diagnosis has important clinical and considerable resource implications. This allows for early diagnosis and therefore intervention of other possible hormone deficiencies, e.g.

hypothyroidism. Early GH replacement therapy significantly improves height prognosis and decreases the manifestation of the associated clinical features.

The following findings on history and clinical examination are suggestive of GHD:
- hypoglycaemia, prolonged jaundice, microphallus, or traumatic delivery in a neonate
- cranial irradiation
- head trauma or central nervous system infection
- consanguinity and/or affected family member
- craniofacial midline deformities.

It must be noted that GHD may present in isolation or in combination with multiple pituitary hormone deficiency (MPHD). In the setting of isolated short stature there are stringent criteria that must be satisfied to initiate immediate investigation of the hypothalamic-pituitary IGF axis.

INVESTIGATION OF THE HYPOTHALAMIC-PITUITARY INSULIN-LIKE GROWTH FACTOR AXIS

As previously noted, the investigation of this axis should only be undertaken when other causes (see Table I) of short stature have been excluded. There are, however, instances when short stature requires immediate investigation of this axis.

Because of the pulsatile nature of GH secretion, random sampling of GH in the diagnosis of GHD is unhelpful. Historically, definitive diagnosis of GHD has been made using growth hormone stimulation testing (GHST) with various pharmacological and physiological stimuli.

A number of pharmacological agents are used to stimulate the axis after an overnight fast. The more common agents used include clonidine, arginine, glucagon, insulin and L-dopa. Generally, each centre providing this service follows a well-standardised protocol, with blood sampling for GH testing done at

Table II. **Recommended initial investigations for short stature**	
Test	**Findings**
Bone age radiography (left wrist and hand if > 1 year of age and knee/ankle if < 1 year of age)	Height prediction, genetic diagnosis, growth arrest plates
Full blood count	Anaemia associated with chronic illness
Erythrocyte sedimentation rate or CRP	Inflammatory process
Biochemical screening	Renal disease, hepatic disease, bowel disease, disorders of calcium and phosphorus, nutritional and metabolic disorders
Thyroid function	Hypothyroidism, hypopituitarism
Prolactin	Hypopituitarism, pubertal disorder
Luteinising hormone, follicle-stimulating hormone, testosterone or oestrogen	Pubertal disorder
Tissue transglutaminase or anti-endomysial antibodies	Coeliac disease
Chromosomes (karyotype) or gene studies	Turner's syndrome (females), *SHOX* gene mutations
Urine testing	Protein, glucose

regular intervals in a 2-hour time period (0, 30, 60, 90, 120 minutes). The provocation testing requires great care and constant medical supervision by experienced staff in view of the risk of hypoglycaemia associated with the insulin-induced hypoglycaemia test (not recommended in children < 5 years of age). When clonidine is used, the patient should be monitored for possible hypotension. Despite the difficulty of diagnosis of GHD in the peripubertal period (low GH levels in provocation tests often encountered), no consensus exists on sex steroid priming.

In children with clinical and auxological evidence suggestive of isolated GHD, it is recommended that two provocation tests (sequential or on separate days) be carried out. In patients with central nervous system pathology, history of cranial irradiation, MPHD or other genetic defects, one GH provocation test is sufficient.

The interpretation of the response to the GH provocation tests is fraught with discrepancies. Several serum GH concentrations have been quoted to exclude or suggest the diagnosis of GHD. These values range from 5 ng/ml to < 20 ng/ml. The GH research society quote a value of < 10 ng/ml as the traditional cut-off as suggestive of GHD, although it is recognised that this value has to be revised, particularly in view of the use of newer monoclonal-based assays (which give results 2 - 3 times lower than older GH assays) and recombinant hGH reference preparations now available.

CONTROVERSIES SURROUNDING GHST

Some investigators believe that GHST should not be used for the diagnosis of GHD due to the lack of precision and accuracy, as well as the risk to the patient. It is believed that the diagnosis be based on a combination of auxological, biochemical, i.e. IGF-1 and/or IGFBP-3 levels, high-resolution neuroimaging and genetic studies, i.e. for MPHD. Experts believe that GHST is used more to justify GH therapy

than for the diagnosis of GHD. Studies have found that different provocative agents yield discordant GH responses in the same individual. With regard to sex steroid priming, studies have found that approximately 80% of normal prepubertal children failed to demonstrate peak GH levels of greater than 10 ng/ml following stimulation.

NEWER APPROACHES FOR THE DIAGNOSIS OF GHD IN CHILDREN

Since IGF-1 and/or IGFBP-3 are GH-dependent factors and IGF-1 has a longer half-life than GH, IGF-1 can provide a useful estimate of GH function. There is virtually no variation in IGF-1 secretion during the day, therefore a single sample taken at any time during the day will provide reliable assessment of the axis. The IGF-1/IGFBP-3 levels need to be interpreted with the bone age of the patient, using age and sex-related reference ranges. A decreased level is suggestive of GHD, although normal levels can occur in GHD. It is however important to exclude other causes of a decreased IGF-1 and/or IGFBP-3 levels, such as poor nutrition, liver disease, renal disease, hypothyroidism and diabetes mellitus. In children younger than 6 years of age IGF-1 levels can be as low as those found in GHD patients.

When the performance of IGF-1/IGFBP-3 level is compared with the GHST, a very poor correlation exists. The inadequacies of the GHST have been cited as reasons for this poor concordance.

Also, to date there are a limited number of studies investigating the diagnostic utility of these biochemical markers for the diagnosis of GHD. Currently the assays for IGF-1/IGFBP-3 are not standardised and therefore results may vary between laboratories. A cut-off of the 5th centile is used by most as an indication of subnormal levels.

Despite the drawbacks, measurement of IGF-1/ IGFBP-3 levels offer a safe, convenient and cost-effective

alternative, especially in those children without profound GHD.

The imaging of the central nervous system via computerised tomography (CT) scanning and/or magnetic resonance imaging (MRI) should be carried out on any child with a diagnosis of GHD, as well as for suspected intracranial tumours, optic nerve hypoplasia/septo-optic dysplasia or other structural or developmental abnormalities.

Several transcription factors have been identified to be essential in the development of the anterior pituitary gland, and mutations in these genes result in GHD, usually in combination with other pituitary hormone deficiencies. Mutations in the genes encoding for GH and GHRH result in isolated GHD. Currently, genetic studies are not offered routinely.

GH THERAPY

GH therapy is recommended for patients with proven GHD. Recently the Food and Drug Administration (FDA) has approved GH therapy for idiopathic short stature (ISS). ISS is defined as short stature without a known cause.

The aims of treatment are the normalisation of height during childhood and the attainment of normal adult height, pubertal growth, prevention of the metabolic and body composition manifestations of GHD.

The response to therapy is monitored by assessment of the increment in height and the change in height velocity of the patient. The measurements of the IGF-1/IGFBP-3 levels do not correlate well with the growth response, but may be used to assess compliance and safety of therapy.

Significant side-effects of GH therapy in children are generally rare, e.g. benign intracranial hypertension, arthralgia, oedema, etc. There is currently no strong evidence suggesting an increased risk of leukaemia or tumour recurrence in

patients treated with GH, although close monitoring of these patients is recommended. Management of side-effects involves either a reduction in dosage or a temporary discontinuation of therapy.

Further reading

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IN A NUTSHELL

Linear growth in childhood is one the most sensitive indicators of health and is controlled by multiple factors, i.e. genetic, nutritional, environmental, endocrine, and psychosocial.

Short stature is defined as a height more than 2 SDs below the mean when compared with age and sex-specific standards based on a population of normal healthy children.

The assessment of growth is central to the diagnosis of short stature and this involves height, weight, body proportion, growth velocity, and prediction of adult height assessments.

There are 2 normal variants of growth presenting with short stature – familial short stature and constitutional delay.

The aetiology of pathological short stature includes congenital abnormalities, skeletal dysplasias, malnutrition, chronic illnesses, endocrine disorders, psychosocial deprivation, idiopathic, and iatrogenic causes.

The initial laboratory investigations performed are primarily to exclude the presence of chronic illnesses in patients with auxologically established short stature. In the absence of these causes, the hypothalamic-pituitary-IGF axis is then investigated for GHD as a cause for the short stature.

The random sampling of growth hormone is unhelpful in the diagnosis of growth deficiency, and therefore growth hormone stimulation testing is generally conducted.

Currently there are many controversies about GHST, i.e. standardisation of protocols, stimulatory agents, and interpretation of the GH response, and it is therefore suggested that insulin-like growth factor-1(IGF-1) and/or insulin-like growth factor-binding protein 3 (IGF-BP3) concentrations be used to screen for GHD.

As the diagnosis of short stature is multidisciplinary, high-resolution neuroimaging and genetic studies are recommended in these patients.

GH therapy is recommended for patients with proven GHD and idiopathic short stature, with the primary aim of treatment being normalisation of height during childhood and attainment of normal adult height.