Short stature in children

When is further evaluation and referral required?

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Short stature is a common presenting problem to GPs. This article outlines the diagnostic possibilities, presents a practical approach for the initial evaluation and management and provides guidance on when referral to a specialist is recommended in children with short stature.

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Short stature, defined as height more than two standard deviations below the mean for age, sex and population group (which equates to below the 2.3rd percentile),[1] occurs in many healthy children. In most cases, short stature represents a normal variant of growth. However, careful evaluation and investigation may reveal an undiagnosed pathological condition in up to 10% of cases.[2]

Causes of short stature

The diagnostic possibilities in a child with short stature are listed in the box on page 7. The most common situations seen in general practice are variants of normal, particularly familial short stature and maturational delay (also known as constitutional delay). Some of the diagnoses indicated in the box on page 7 can only be reached after fairly extensive evaluation.[3,4]

Key points

- Many children presenting with short stature are 'normal variants'.
- Monitoring growth velocity over a six- to 12-month period is a useful parameter in assessing growth and is often all that is required in children presenting with short stature.
- Further evaluation and referral should be considered in children with severe short stature (≥3 standard deviations below the mean or <0.1st percentile, which equates to approximately >6cm below the 3rd percentile).
- Further evaluation and referral should also be considered in children with mild to moderate short stature (height below 2.3rd percentile) with any of the following:
  - low growth velocity over six to 12 months (<25th percentile for bone age)
  - clinical features suggesting a syndrome or disease
  - family history that is out of keeping with short statue
  - poor predicted adult height
  - height within normal range but falling across percentiles
  - disproportionate short stature.
- Growth hormone therapy is available on the PBS for patients with growth hormone deficiency. It is also available for some nongrowth hormone deficient indications, such as severe nongrowth hormone deficient short stature (if also growing slowly), Turner syndrome, chronic renal failure and Prader-Willi syndrome. Specialist referral of the patient is recommended if growth hormone therapy is being considered.

Causes of short stature

Normal variants
- Maturational delay (constitutional delay)
- Familial short stature
- Idiopathic short stature

Pathological conditions
- Nutritional
  - Insufficient caloric intake
  - Malabsorption
  - Chronic inflammatory bowel disease
  - Coeliac disease
- Endocrine
  - Isolated growth hormone deficiency
  - Multiple pituitary hormone deficiency
  - Hypothyroidism
  - Cushing syndrome
  - Late consequence of untreated precocious puberty
  - Late consequence of radiotherapy as treatment for childhood cancer
- Dysmorphic syndromes
  - Chromosomal (e.g. Turner and Down syndrome)
  - Other syndromes (e.g. Noonan and Russell-Silver syndrome)
  - Nonspecific syndromes associated with birth defects/mental retardation
- Intrauterine growth retardation
- Skeletal disorders
  - Achondroplasia/hypochondroplasia
  - Chondrodystrophies (e.g. Leri-Weill syndrome [short stature homeobox gene mutation])
  - Rickets and/or vitamin D deficiency
- Chronic illness or metabolic disorders
  - Renal, cardiac, hepatic, respiratory, immune disorders
  - Poorly controlled diabetes mellitus
  - Other storage disorders and inborn errors of metabolism
- Psychosocial deprivation
- Medication side effect
  - Glucocorticoids
  - High-dose oestrogen or androgen
  - Methylphenidate
  - Dexamphetamine

Importance of growth monitoring

Monitoring of growth by a child's GP is an important primary healthcare role. It is recommended that all children have their height and weight charted when they visit their GP for any reason. Such opportunistic measurements will provide valuable information if referral for a growth concern is required in the future.[5]

Evaluation of the child

History and examination

A thorough history and examination should be directed towards the diagnostic possibilities listed in the box on this page. Some specific aspects that should be explored in the history and examination are listed in the box on page 8. The age of the child at presentation will influence the approach. For example, in infants with failure to thrive it is important to focus on diet and feeding problems and to measure head circumference; for adolescents, puberty and psychosocial issues are particularly relevant. The psychological impact of short stature in the child may vary from no impact to severe. It is important to explore whether the child is concerned or only the parents because this may influence the extent of investigation and management decisions.

Guide to history and examination in children with short stature

History

- Elicit the problem
  - Duration, severity, emotional impact, psychological factors
- Perinatal history
  - Birth weight, length, gestation, drugs, alcohol, delivery, infection, jaundice, oedema, hypoglycaemia
- Family history
  - Short stature, parental heights and timing of puberty, heritable diseases
- Systemic symptoms
  - Chronic illness, neurological, detailed nutritional review
- Developmental history

Examination

- Measurement
  - Height, weight, head circumference, body proportions, waist measurement
- Body habitus
  - For example, broad chest, truncal obesity, muscle bulk
- Dysmorphism
  - Facial, midline defects, ears, eyes, palate, other
- Hands and feet
  - Short metacarpals, clinodactyly, palmar creases, lymphoedema, clubbing
- Neurological
  - Visual fields, acuity, fundi, nystagmus
- Puberty and genitalia
  - Pubertal staging, micropenis
- Signs of systemic illness
  - Check all systems

Measurement technique

A reliable reproducible measurement technique is essential and is best achieved using a wall-mounted stadiometer. Several models of wall mounted or portable devices are available and are of two basic types:

- wall-mounted backboard with measuring scale and a sliding horizontal arm
- pull down tape devices with a horizontal arm that are fixed to the wall at an appropriate height and pulled down to the child's head for measurement.

Correct installation of these devices is critical to their accuracy. Shoes and socks should be removed. The head should be positioned so that the eyes and external auditory meatus are aligned in the horizontal plane. Results are plotted on the available growth standards.

Children less than 2 years old or those who cannot stand should have their length measured in the supine position. Ideally this requires two people to ensure proper positioning. Length boards with a measuring scale and one fixed and one moveable vertical board can be used. More portable measuring mats are suitable for primary care use.

Weight of children should be measured in under garments or light clothing and similarly plotted.

The height and weight charts recommended for use in Australia[6] are derived from the Centre for Disease Control charts[7] and are shown in Figures 1a and b. Although the data is from a US population and may not be appropriate for patients of other ethnic backgrounds, growth can still be longitudinally followed on these charts by taking into account genetic height potential from the parents' heights. Growth charts specific to certain conditions, such as Down, Turner, Noonan and Prader-Willi syndromes, are also available.

Assessment for disproportion

Arm span (fingertip to fingertip) and lower segment (distance from the upper border of the pubic symphysis to floor in standing position) should be measured using a tape measure. Arm span normally approximates height (± 5 cm). Upper to lower segment ratio falls from approximately 1.6:1 in young infants to 1:1 at age 8 years and approximately 0.95 in adults. When these measurements suggest short limbs relative to the trunk, the ratio will be abnormally high and the possibility of a skeletal dysplasia should be considered. If the upper:lower segment ratio is abnormally low, then spinal abnormalities such as scoliosis or a history of spinal irradiation (causing poor spinal growth) should be considered.

Consideration of parental height

Parents' heights should be plotted at the adult end of the child's growth chart, taking into account the mean sex difference of 13 cm in adult height. For a boy, the father's height is plotted directly and 13 cm is added to the mother's height before plotting. For a girl, the mother's height is plotted directly and 13 cm is subtracted from the father's height. The midparental height (or target height) is the midpoint of these plotted percentiles. This represents the child's genetic height potential unless there is a pathological barrier to reaching it. The uncertainty of the target height, termed the target range, is ± 7.5 cm for males and ± 6 cm for females. See example of plotting and calculating the midparental height range in Figure 1a.

Interpretation of growth velocity

Growth or height velocity is one of the most useful parameters in assessing growth. This should be calculated from multiple measurements over at least six and preferably 12 months. Calculating growth velocity over shorter time periods will contribute to misleading results due to minor variations in measurement accuracy, etc. Even a growth velocity based on repeated measurements over 12 months will contain a certain amount of error and therefore must be considered together with all the other clinical information available.[8] Detailed percentile charts for growth velocity are available on the Australian growth charts.[6] Any child with a growth velocity under the 3rd percentile on any occasion, or consistently under the 25th percentile, warrants further evaluation no matter where their height lies on the growth chart. From the growth velocity standard charts

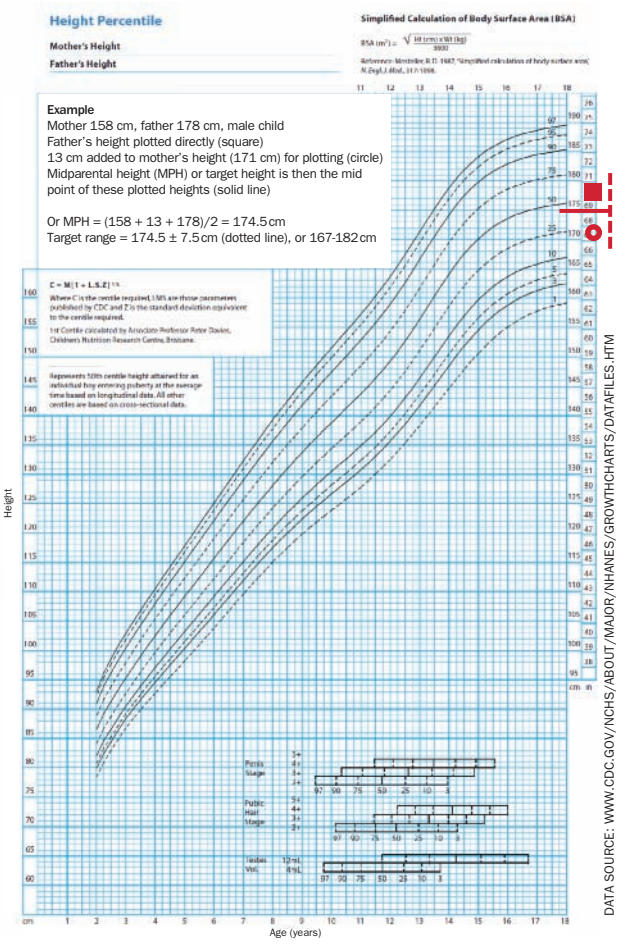

Figure 1a. Male growth chart age 2–18 years with midparental height formula and example.[6]

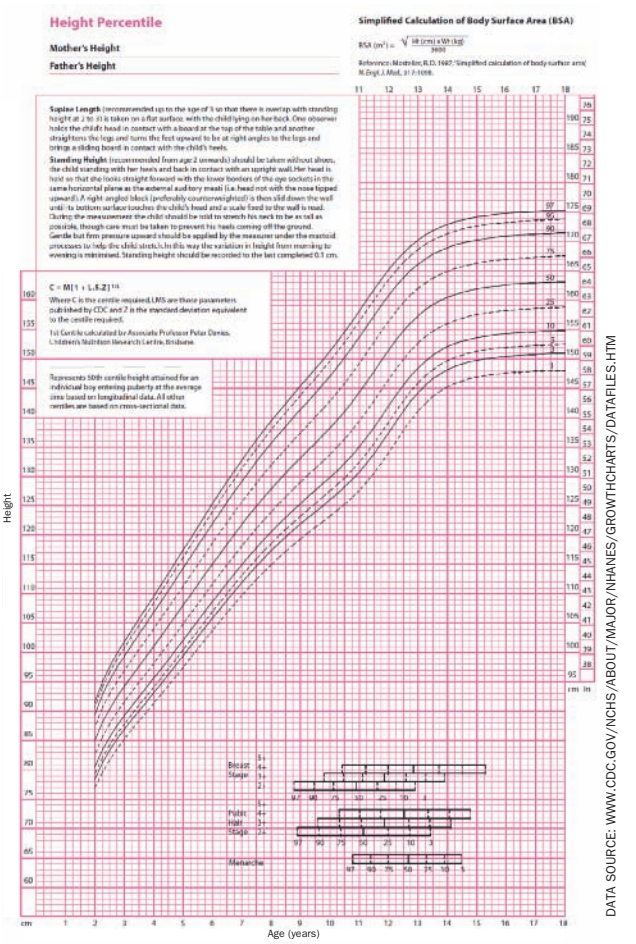

Figure 1b. Female growth chart age 2–18 years.[6]

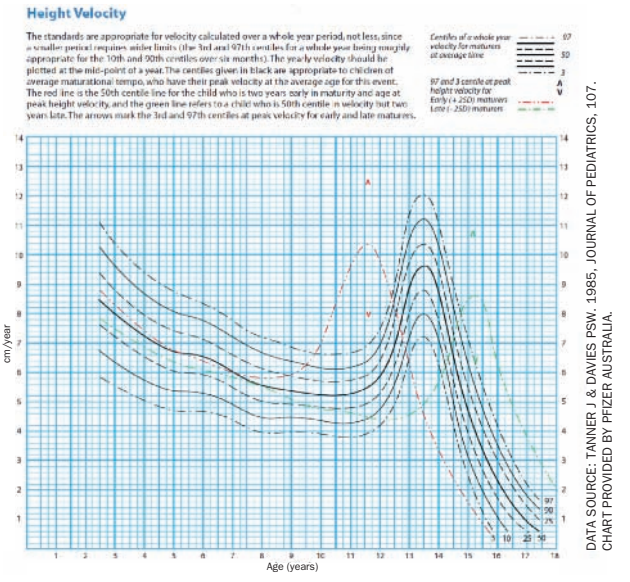

Figure 2a. Growth velocity chart for males aged 2–18 years.[6]

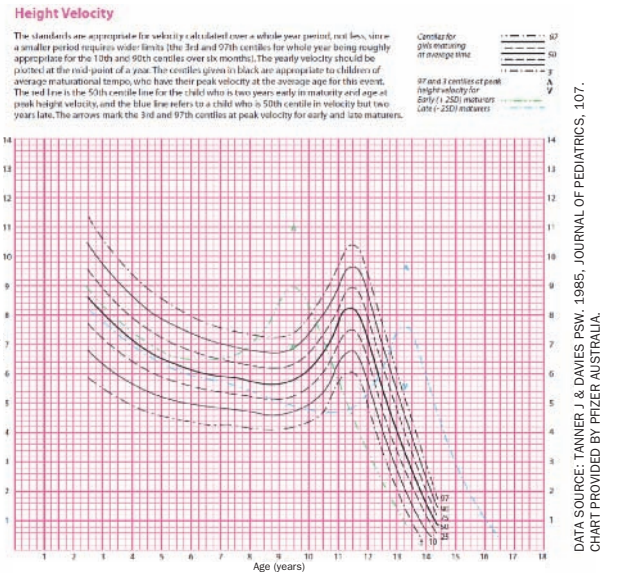

Figure 2b. Growth velocity chart for females aged 2–18 years.[6]

CASE STUDIES

Case study 1

Case scenario: A 10-year-old boy presented due to his mother's concern about short stature. His health was good. Systematic questioning and examination revealed no other concerning features. His height was 126 cm (on the 2.5th percentile) and he was prepubertal. His weight was also on the 2nd percentile. His father's height was 163 cm (3rd percentile) and his mother's height was 151 cm (3rd percentile). Thus, the calculated midparental height was 163.5 cm (3rd percentile).

Reviewing his medical records, a previous measurement by the GP, performed opportunistically when he presented with tonsillitis at the age of 6 years, was also on the 2nd percentile. This previous measurement indicated a reasonable growth velocity and was reassuring in that there was no downward crossing of the percentiles.

Diagnosis: Familial short stature.

Comment: In the absence of any worrying features, further investigations were not necessary and the family were counselled about familial short stature and the likely final height being similar to that of his father. The GP felt it was prudent to continue to monitor the boy's growth six to 12 monthly until linear growth was completed. He reached a final height of 162 cm (2nd percentile).

Case study 2

Case scenario: A 14.2-year-old boy presented with concern regarding short stature. His general health was good apart from intermittent asthma. His father's height was 173 cm (25th percentile) and mother's height 163 cm (50th percentile). Both father and paternal grandfather gave a history of slow growth in the early teenage years and delayed puberty.

At the age of 14.2 years the boy's height was 145 cm (4 cm below the 3rd percentile or 2.3 standard deviations below the mean), and growth velocity over the past six months had been 4 cm per year. Weight was on the 3rd percentile. Review of previous growth data showed that he had been on the 10th percentile for height when he was 10 years old. Testicular volumes were 4 mL on the left and 5 mL on the right, and pubic hair was early stage 2. General examination was normal. Bone age was 11.5 years and screening biochemistry was normal. Growth hormone stimulation testing revealed a normal growth hormone peak response of 25 mU/L (normal growth hormone peak is >10 mU/L).

Diagnosis: Maturational delay/constitutional delay in growth and puberty.

Comment: The strong family history and delayed bone age made a diagnosis of maturational delay very likely. The testicular volumes of 4 mL or more indicate the early stages of puberty, which is reassuring. Target height and range was 174.5 cm ± 7.5 cm. Screening investigations were undertaken because of low growth velocity and growth hormone testing was normal. A diagnosis of maturational delay (or constitutional delay in growth and puberty) was made, and when the family and patient were reassured about the situation they opted for no intervention. Alternatively, a short course of androgen therapy could have been recommended by a paediatric endocrinologist to augment his delayed puberty. Growth velocity improved spontaneously over the next 12 months and final height attained was 172 cm.

Case study 3

Case scenario: A 12-year-old girl presented with a height of 131 cm (8 cm below the 3rd percentile or three standard deviations below the mean) and she was prepubertal. Growth velocity over the past six months had been 3.8 cm per year. Family history was unremarkable with a corrected midparental height of 165 cm, and her general health was good. Bone age was 10 years and 8 months. Screening investigations were normal, but chromosomes were mosaic 46XX/45XO.

Diagnosis: Turner syndrome.

Comment: Girls with no explanation for short stature should have chromosome testing performed. Signs of Turner syndrome may be subtle or absent especially in those with mosaic chromosomes. This girl was referred immediately to a paediatric endocrinologist. The situation was discussed at length with the child and family and growth hormone therapy was commenced. Growth velocity in the first six months of treatment increased from 3.8 cm per year to 6.5 cm per year. Spontaneous puberty is unlikely and will need to be induced with oestrogen therapy, although this is often appropriately postponed a little pending response to growth hormone therapy so that height benefit is not attenuated by earlier closure of the epiphyses.

Case study 4

Case scenario: A 16-year-old girl presented with a height of 140 cm (3.3 standard deviations below the mean) and measurements at home revealed only 2 cm growth in the past 10 months. She had been experiencing headaches and was concerned that she had no pubertal development. Bone age was 12 years. Investigation was undertaken without delay and she was found to have growth hormone deficiency (peak growth hormone 1 mU/L), mild central hypothyroidism, partial adrenocorticotrophic hormone deficiency and low gonadotrophin responses. MRI scan revealed a 3 cm diameter tumour in the pituitary fossa. A craniopharyngioma was removed at surgery and postoperative endocrine studies revealed panhypopituitarism, including diabetes insipidus. Replacement therapy was commenced with thyroxine, hydrocortisone and desmopressin, and six months later growth hormone therapy was commenced. A further six months later low-dose oestrogen therapy was commenced.

Diagnosis: Undiagnosed brain tumour and resultant pituitary failure.

Comment: Short stature and delayed puberty of this degree is almost always pathological and requires immediate referral of the patient and investigation.

(Figures 2a and b) you can see that there is a prolonged phase in childhood during which both sexes grow at similar rates (decreasing from 10 cm per year in the second year of life to 6 cm per year in the seventh year). A period of prepubertal growth deceleration (decreasing to 5 to 6 cm per year) is then followed by the adolescent growth spurt, which is later and of greater magnitude in males. Thus, the net height growth during puberty is approximately 20 to 25 cm in females and 25 to 30 cm in males. Epiphyseal fusion, under the influence of oestrogen, results in the postpubertal growth slowdown and attainment of final adult height.[9]

Consideration of pubertal stage

Growth velocity should be considered in the context of the individual's pubertal status because there is a wide variation in the age of pubertal onset. In girls, the growth spurt occurs early in puberty and commences at the same time as the onset of breast development, with growth slowing down after the onset of the first period. In contrast, boys have a growth spurt that occurs later, commencing halfway through puberty.[10,11] Details of pubertal stages and the growth velocity in both early and late maturers are detailed in the Australian growth charts. Generally, pubertal stage and bone age are well correlated; thus a bone age x-ray will also help to interpret the annualised growth velocity.

Investigations

Many children presenting with short stature do not require any investigations and it may be appropriate to simply observe their growth velocity. In others, clinical features will warrant early investigation for pathological conditions (see the case studies on page 10). The box on this page includes details of suggested baseline investigations that can be performed in the primary care setting and further tests that may be arranged by the specialist.

Bone age

Bone age x-ray is a useful measurement that allows estimation of the remaining growth potential for a child or adolescent. A simple x-ray is taken of the nondominant hand and wrist and this is compared with a set of photographic standards to assess how mature the child's bones are.[12] During childhood, the growth plates gradually get smaller. By the end of puberty the growth plates are almost completely fused. In girls, when the bone age is 13.5 years, 97.4% of linear growth has occurred and the potential for further height gain is minimal. In boys, 97.6% of linear growth is achieved at a bone age of 15.5 years. The bone age may differ from the chronological age and there is a significant spread in normal children (e.g. approximately ±18 months at age 5 years; ±20 months in teenagers). The bone age can be used to estimate the final adult height. For example, a short child with a delayed bone age has a better growth potential than an equally short child in who bone age equals chronological age. However, bone age does not allow diagnostic possibilities to be distinguished because it is delayed in children with maturational delay, hormonal deficiencies and systemic illnesses.

Suggested investigations for short stature

Baseline tests (can be performed in primary care setting)

- **Blood tests**
  - Full blood count and film, C-reactive protein and erythrocyte sedimentation rate
  - Blood chemistry (renal function, liver function, calcium, magnesium, phosphate, glucose)
  - Thyroid-stimulating hormone and free thyroxine
  - Coeliac screen and IgA level
  - 25-OH vitamin D (if from an ethnic group at high risk of deficiency)
  - Karyotype (in all girls and in boys with dysmorphism)
  - Insulin-like growth factor-1 (if growth hormone deficiency suspected)
- **Urine tests**
  - Urinalysis and urine culture
- **X-ray**
  - Bone age of left wrist

Further tests (generally carried out by a specialist)

- **Blood tests**
  - Insulin-like growth factor-1 and insulin-like growth factor-binding protein 3
  - Luteinising hormone, follicle-stimulating hormone, oestradiol and testosterone, prolactin (if pubertal delay)
  - Molecular testing for short stature homeobox gene disorder
  - Comparative genomic hybridisation microarray for other genetic conditions
  - Pancreatic isoamylase
- **Stimulation tests (performed in an endocrine testing unit)**
  - Growth hormone stimulation tests
  - Other dynamic tests of pituitary function
- **Medical imaging**
  - MRI of hypothalamopituitary region

When to refer?

Severe short stature

Children with severe short stature (three standard deviations below the population mean or <0.1st percentile, which equates to approximately >6 cm below the 3rd percentile) deserve immediate investigation and referral. Even if no previous growth data are available, growth velocity is almost certainly low as they would not have achieved this low chart position without an abnormally low growth velocity. Baseline investigations should be carried out as detailed in the box on this page and can be performed while waiting for specialist review. Depending on the outcome of these baseline tests and the clinical picture, further tests may be arranged by the appropriate specialist.

Mild to moderate short stature

In children with lesser degrees of short stature (height two to three standard deviations below the population mean or between the 1st and 2.3rd percentiles), which is out of keeping with the family

Table. Eligibility criteria and requirements for growth hormone therapy on the PBS

Criteria	Requirements
GH deficient criteria	
Biochemical GH deficiency	Peak serum GH <10 mU/L on two stimulation tests Height <1st percentile Growth velocity <25th percentile for bone age
Growth retardation due to intracranial lesion or cranial irradiation	Biochemical GH deficiency Growth velocity <25th percentile for bone age 12 months since completion of oncology treatment
Neonatal hypoglycaemia due to GH deficiency	Documented hypoglycaemia and GH deficiency
NonGH deficient criteria	
Short and slowly growing	Height <1st percentile Growth velocity <25th percentile for bone age Not due to maturational delay
Turner syndrome	Genetically confirmed Turner syndrome Height <95th percentile on Turner syndrome growth charts No catch up growth, growth velocity <25th percentile for bone age
Short stature homeobox gene disorder	Genetically confirmed short stature homeobox gene disorder Height <1st percentile Growth velocity <25th percentile for bone age
Chronic renal failure	Estimated glomerular filtration rate <30 mL/min/1.73 m^2 Height <25th percentile Growth velocity <25th percentile for bone age
Prader-Willi syndrome	Genetically confirmed Prader-Willi syndrome, <18 years old Sleep study/sleep disorders addressed No uncontrolled morbid obesity

ABBREVIATION: GH = growth hormone.

history, and in whom have an abnormally slow growth velocity (<25th percentile growth velocity for bone age) or clinical features suggesting a syndrome or disease, baseline screening investigations should be performed to examine for major systemic or endocrine disturbances. If these are normal yet growth velocity remains poor over a six- to 12-month period of observation, then they too should undergo further evaluation.

If criteria for growth hormone therapy is met

Growth hormone therapy is available on the PBS under Section 100 of the National Health Act. Therapy is only available to patients who meet specific criteria as defined by the Department of Health and Ageing.[13] A summary of the eligibility criteria for growth hormone therapy on the PBS is detailed in the Table. Individual patient progress and continued eligibility for growth hormone is reassessed every six months and is stringently monitored by the Department of Health and Ageing. Most growth hormone therapy in Australia is prescribed through specialist growth centres that allow optimal monitoring.

Summary

Normal growth results from a complex interplay of genetic, endocrine, nutritional and metabolic factors; therefore, it is not surprising that there are many potential factors involved in disorders of growth. In the assessment of children with short stature and abnormal growth, a careful history and examination are required. Growth should always be plotted on the appropriate chart and interpreted along with the other clinical features. Individuals with height below the 1st percentile, with low growth velocity or crossing of the percentiles should have preliminary investigations performed and referral to a paediatric endocrinologist should be considered. **ET**

References

A list of references is available on request to the editorial office.

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