Disorders of growth

Nicola Bridges

Abstract

Most children who have short or tall stature are healthy and simply at the extremes of the normal range. Plotting a child on a centile chart is a way of comparing their height with the rest of the population. Following the child over time helps to assess whether the pattern of growth is normal. Children settle onto a centile position by 2 or 3 years of age, and after this a normal child grows fast enough to stay on the same centile until puberty. During puberty, sex steroids stimulate growth directly and increase growth hormone (GH) secretion, leading to the pubertal growth spurt. Most short children are growing in a normal pattern and do not have anything wrong with them. Any short child whose pattern of growth is abnormal (reduced growth velocity) should be investigated. Endocrine causes of reduced growth velocity include GH deficiency and hypothyroidism. In Turner's syndrome and skeletal dysplasia, GH secretion is normal but the skeletal response is abnormal. GH treatment is effective in increasing height in children with GH deficiency and some other short stature disorders. Most children presenting with short stature do not benefit from GH treatment.

Keywords Growth hormone; MRCP; Prader–Willi syndrome; short stature; small for gestational age; tall stature; Turner's syndrome

Key points

- Normal children 'set out' on a centile line by 2 or 3 years old and then grow fast enough to stay on the same centile until puberty
- Pattern of growth is a more important factor than centile position – a short or tall child growing at normal velocity is unlikely to have an underlying disorder
- Assessment of short stature should include birthweight, medical history and parental height. Girls with Turner's syndrome may not have dysmorphic features so consider checking a karyotype in any girl who seems short for her family
- Growth hormone (GH) excess is a very rare cause of tall stature. Most children with tall stature are normal, but consider genetic causes such as Klinefelter's syndrome, Marfan's syndrome and syndromes of overgrowth
- Despite media and internet focus on GH treatment, most children with short stature will not show an increase in adult height with GH treatment

Introduction

Concern about growth (usually short stature) is a common reason for referral to paediatric services. A normal growth pattern indicates that the hormonal control of growth is satisfactory, but hormonal defects, chronic disease or poor nutrition can result in failure to grow normally.

Normal growth pattern – centile charts

Plotting a child on a growth centile chart is a way of demonstrating their height compared with other children of the same age. Plotting height over a period of time is the best way to determine whether a child's growth pattern is normal. Current UK charts use World Health Organization multinational data for children aged 0–4 years (with data from Brazil, Ghana, India, Norway, Oman and the USA – based on the concept that national height differences are due to environmental rather than genetic factors), as well as data for up to 20 years of age from the UK population in the 1990s.

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Phases of growth

Normal growth in childhood can be divided into phases:

- **Antenatal** – this is the most rapid phase. Maternal nutrition and placental function are important influences.
- **Infancy** (up to about 2 years of age) – nutrition remains an important factor in growth. Changes in centile position in infancy are common, but children 'settle' onto their childhood centile position by age 2–3 years.
- **Childhood** – normal children grow fast enough to remain on the same height centile until puberty. Growth hormone (GH) is the most significant endocrine factor in growth, stimulating growth directly and via the action of insulin-like growth factor 1 (IGF-1).
- **Puberty** – sex steroids stimulate growth directly and act to increase GH secretion, resulting in rapid growth (the pubertal growth spurt).
- **End of growth** – bone maturation occurs during puberty, and growth slows down and stops as the epiphyses fuse.

Figure 1 shows the hormonal control of growth via the hypothalamic pituitary axis.

Genetic influences on height

The contribution of genetic factors in determining adult height is estimated as 80%. Genome-wide association studies have found numerous genetic variants determining adult height. Many of the genes implicated are associated with growth factors and their receptors. Clinically, the height of parents and siblings is a guide to genetic height potential, and calculating the mid-parental centile is one way of representing this. Genetic variability means that children can be unexpectedly short for their parents

The hypothalamic–pituitary axis and the control of growth

- a range of central factors influence the hypothalamic secretion of growth hormone (GH)-releasing hormone (GHRH) and somatostatin. Fluctuating secretion of these hormones stimulates the pulsatile release of GH by the pituitary
- GH circulates bound to GH-binding protein
- GH has some growth-promoting actions on its own, and binding to the GH receptor stimulates insulin-like growth factor 1 (IGF-1) production.
- IGF-1 circulates bound to IGF-1 binding proteins, binds to the IGF-1 receptor to stimulate growth (cellular divison).
- IGF-1 feeds back on the hypothalamus and pituitary to regulate GH secretion.

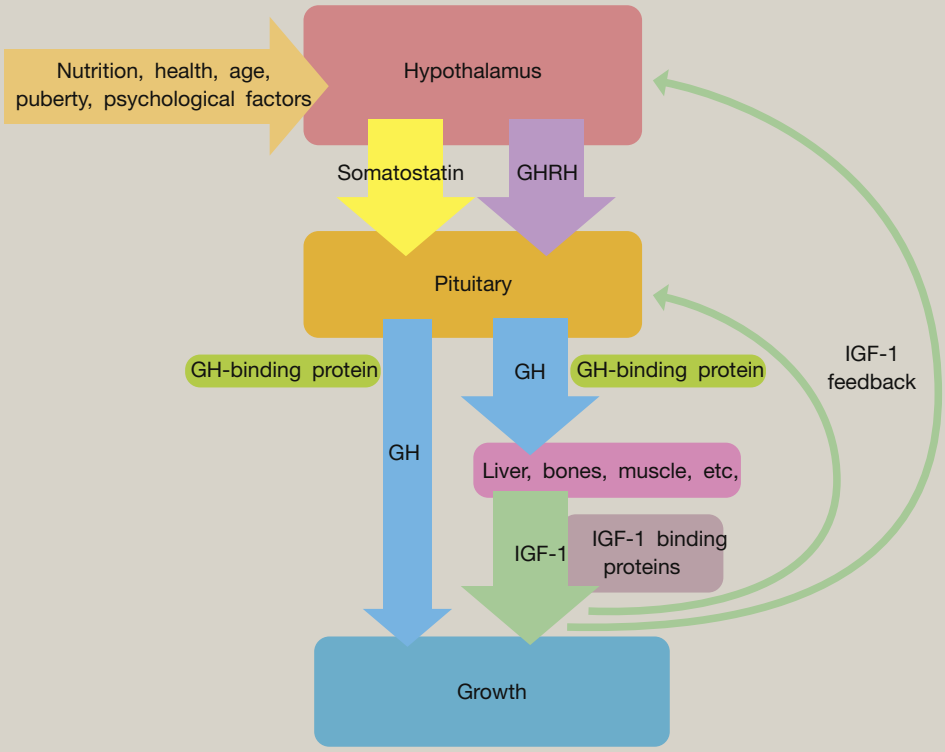

Figure 1

and still healthy. Children in this group form a large proportion of those referred for short stature.

Bone age

Bone age is assessed from an X-ray of the left hand and is an estimate of how much growth is to come. Both methods used (Tanner–Whitehouse; Greulich and Pyle) can be used to predict adult height, although the accuracy is limited, particularly when there are pathologies affecting growth.

The child referred with short stature

Table 1 shows causes of short stature. There is no definition of short stature; most children who are under the 0.4th centile are healthy, and their height is part of normal variation in the population. The terms 'familial short stature' and 'idiopathic short stature' define children who are short with no medical problem. It is sensible to assess the growth pattern of a child who is under the 0.4th centile for height, or who appears to be out of keeping with family height. Pubertal delay is a common reason for referral with short stature, and is seen mainly in boys (see Disorders of puberty on pages 575–578 of this issue).

Initial assessment should include the following:

- medical history including birthweight and neonatal history
- family history and parental heights
- requests for any previous measurements of height (look at the child's 'red book')
- examination for dysmorphic features, disproportion or features of chronic disease.

Possible baseline investigations include:

- thyroid function
- coeliac antibodies
- IGF-1 and IGF binding protein 3, although these are relatively insensitive in detecting GH deficiency
- tests looking for chronic disease (C-reactive protein, markers of malabsorption)
- bone age, useful in older children
- karyotype in girls to exclude Turner's syndrome; consider this even if there are no physical features of Turner's syndrome.

If there is disproportion or dysmorphic features, further investigations can be helpful:

- skeletal dysplasia can be diagnosed on a skeletal survey, and genetic testing is available for some forms such as achondroplasia, hypochondroplasia or *SHOX* mutations
- if the child has dysmorphic features, other medical problems or developmental delay, consider a comparative genomic hybridization array, tests for specific diagnoses such as Noonan's syndrome, or referral to a clinical geneticist.

Follow-up of a child with short stature

As mentioned above, after 2–3 years of age, normal children grow fast enough to stay on the same centile for height. There is