4 Tall stature

As tall stature becomes more prevalent and more acceptable, referrals, particularly of tall girls, appear to be decreasing. The referral of a child with tall stature is frequently the result of parental concern about actual or future final height. However, knowledge of the pathogenesis, clinical and biochemical associations and potential treatment of tall stature is clinically relevant.

Pathogenesis and differential diagnosis

Tall stature is usually associated with one of three aetiological categories. In order of frequency these are: familial advanced growth; a syndrome associated with tall stature, which has usually been present since infancy; and an abnormal increase in growth rate of endocrine origin. The differential diagnosis is shown in Table 4.1.

Assessment of the child or adolescent with tall stature

Repeated height measurements are essential for the assessment of tall stature. The combination of auxology, careful history-taking and physical examination will exclude the need for laboratory investigations in most cases. Procedures needed for the clinical assessment of a child or adolescent referred with tall stature are given in Table 4.2.

Investigations

Patients with intellectual delay may well have had previous investigations. If physical examination is completely normal and the child comes from a tall family, investigations are usually not indicated. Regular height measurements will be sufficient. If abnormalities are detected in the history or on examination, basal investigations are indicated, as shown in Table 4.3.

Further investigations will be dictated by the results of the baseline tests. If the diagnosis of excess growth hormone (GH) secretion caused by a GH secreting pituitary adenoma is considered, investigation should proceed as shown in Table 4.4.

Protocol for glucose tolerance test

Give 1.75 g carbohydrate orally (up to maximum of 75 g = two glasses of Lucozade). Serum GH at: –30, 0, 30, 60, 90, 120 and 150 minutes. Normal GH suppression is a value of <4 mU/L at some time during the test.

Causes of tall stature

Familial tall stature or constitutional advanced growth

This is the most common cause of referral of patients for tall stature. If the patient is a girl, it is frequently the mother who, having suffered herself from being tall as a child and adolescent, is concerned about her daughter. In groups of tall children, GH secretion has been shown to be statistically elevated when compared to normal or short stature children. However, in an individual child excess GH secretion is not usually apparent.

The tall stature is usually noticeable by primary school entry. Physical examination is normal. Assessment of bone age, which is likely to be advanced, and calculation

Table 4.1 Differential diagnosis of tall stature.

1 Familial tall stature
2 Syndromes associated with tall stature:
chromosomal defects
Klinefelter's syndrome
XXXY, XYY syndromes
overgrowth syndromes
Sotos' syndrome
Weaver's syndrome
Marshall–Smith syndrome
Beckwith–Wiedemann syndrome, hyperinsulinism
Marfan's syndrome
MEN 2B
ACTH resistance
Homocysteinuria
3 Tall stature of endocrine origin:
GH secreting pituitary tumour
precocious puberty
hyperthyroidism
4 Simple obesity

Abbreviations: ACTH, adrenocorticotrophic hormone; GH, growth hormone; MEN, multiple endocrine neoplasia.

Table 4.2 Procedures for the assessment of a patient with tall stature.

Height, weight, height velocity
Heights of parents, siblings
Birth weight, length, head circumference
History of previous growth, past medical history
Intellectual development
Systematic inquiry
Examination for dysmorphic features
Systematic examination
Pubertal development staging with measurement of testicular volume
Bone age and final height prediction

Table 4.3 Baseline investigations for tall stature.

Karyotype
T4, TSH
IGF-I
Bone age and final height prediction

Abbreviations: IGF-I, insulin-like growth factor; T4, thyroxine; TSH, thyroid-stimulating hormone.

Table 4.4 Investigations for suspected GH secreting pituitary adenoma.

Glucose tolerance test for GH secretion
MRI scan of pituitary
Visual fields
Cortisol (9.00 a.m.)
Prolactin
Testosterone, LH, FSH (depending on age)

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone; MRI, magnetic resonance imaging.

of final height prediction may be helpful. The likelihood of earlier than average puberty should be explained. Reassurance and growth monitoring are the principles of management.

Syndromes associated with tall stature

These disorders will not be described in detail. They are all rare; however, the principal phenotypic features of three important tall stature syndromes—Sotos', Marfan's and Beckwith–Wiedemann syndrome—are given in Table 4.5.

Endocrine causes of tall stature

The three endocrine causes of tall stature should be suspected after clinical examination. All will require hormone investigations to confirm the abnormality. Specialist referral at this stage is recommended.

GH secreting pituitary tumour

A GH-secreting tumour causes tall stature and gigantism in childhood and adolescence, and acromegaly in adult life. An association with McCune–Albright syndrome is recognized. Because of its extreme rarity in childhood, this disorder should be managed jointly with an adult endocrinologist, who will have far more experience. Suppression of GH secretion may require pituitary surgery, radiotherapy, somatostatin analogue or GH receptor antagonist therapy.

Treatment of familial (constitutional) tall stature

Occasionally, the degree of anxiety surrounding advanced growth, usually in girls, is so great that treatment is indicated to try to slow down growth and therefore reduce final height. Two forms of therapy are currently used:

Table 4.5 Principal clinical features of Sotos', Marfan's and Beckwith–Wiedemann syndromes.

Sotos' syndrome
Increased birth length
Increased birth head circumference
Recognizable facies
downslanting eyes
bossed forehead
prominent jaw
Hypotonia, clumsiness
Early puberty
50% need special education
Rare, autosomal dominant inheritance
Marfan's syndrome
Autosomal dominant
Fibrillin gene defect
One in 10 000 births
Arm span 8 cm > height
Arachnodactyly
Skeletal features
kyphoscoliosis
joint laxity
pectus excavatum
pes planus
High arched palate
Aortic dilatation, aortic, mitral valve anomalies
Myopia, lens dislocation
Beckwith–Wiedemann syndrome
Increased birth weight and length
Growth velocity and bone age advanced during first 4–6 years
Macroglossia
Hemihypertrophy
Ear signs
ear lobe creases (see Chapter 2)
pits on pinna
Hypoglycaemia
Omphalocoele
Malignancies (e.g. Wilms' tumour)
Learning difficulties

high-dose sex-steroid therapy and GH-suppressive therapy using a somatostatin analogue. In future, GH receptor antagonist therapy may be appropriate.

Sex-steroid therapy

The indication for the use of sex steroids to reduce final height is based on evidence that abnormally high circulating levels will advance skeletal maturation and eventually cause early epiphyseal fusion. De Waal from the Netherlands has published the most extensive results. In girls, ethinylestradiol 100–300 µg/day orally combined with cyclical progesterone (i.e. norethisterone 5 mg/day for days 1–14 of each calendar month), if used relatively early, reduced final height by up to 7 cm. In boys, testosterone 250–1000 mg monthly caused a similar reduction. An early age of onset of treatment (bone age 10 years in girls, 12.5 years in boys) was associated with the best results. In an extensive inquiry, 10 years after final height, no significant adverse affects were identified.

Somatostatin analogue therapy

Suppression of GH levels should theoretically slow down growth and, if continued on a long-term basis, may reduce final adult height. Hindmarsh at the Middlesex Hospital, London, has reported that the use of the somatostatin analogue octreotide in a dosage of 37.5–50 µg once or twice daily caused significant decrease in height velocity, with reduction in height prediction of up to 5 cm.

Octreotide, which is given by subcutaneous injection, may cause gastrointestinal side-effects. It is likely that to reduce final height effectively, complete suppression of GH may be necessary. This treatment would be best organized jointly with an adult endocrinologist who has had experience of its use.

Future developments

- Molecular analysis of tall stature and overgrowth syndromes is likely to identify new genetic causes of these disorders.

When to involve a specialist centre

- Dysmorphic syndromes associated with tall stature.
- Tall stature associated with excess GH secretion.
- Difficult cases of tall stature associated with hyperthyroidism or precocious puberty.
- GH receptor antagonist treatment is likely to become established as the treatment of choice for constitutional tall stature.

Controversial points

- The treatment of tall stature in girls is controversial.

High-dose oestrogen therapy is rarely practised now. Treatment with a somatostatin analogue may be effective but is invasive and associated with side-effects. New therapy using a GH receptor antagonist is promising but not yet established to be beneficial.

- As tall stature is better tolerated by society, there seems to be less indication for therapy.
- Rare conditions, such as GH secreting pituitary tumours, are very infrequently seen in paediatric practice. These patients must be managed jointly with an adult endocrine unit.

Potential pitfalls

- Failure to consider the diagnosis of or examine the patient carefully enough for dysmorphic features suggestive of Marfan's syndrome. This diagnosis may have serious consequences as these patients need life-long cardiovascular surveillance.
- Failure to appreciate that tall stature and delayed puberty are an unusual combination. An important differential diagnosis is Klinefelter syndrome, which should be considered.

CASE HISTORY

A 9-year-old girl was referred because of tall stature. She was in good health. On examination there were no dysmorphic features. Her height was just above the 97th centile and her parents' heights were on the 90th and 97th centiles. Pubertal development was: breast, stage 2; axillary hair, stage 2; pubic hair, stage 3; and no menarche.

Baseline investigations (Table 4.3) were all normal. Consequently, an endocrine cause of her advanced growth was not identified. Bone age was 12.4 years and final height prediction was 188 cm. The parents, particularly the mother who had suffered as a result of her own tall stature, enquired about treatment. The child was not particularly concerned. Treatment was not advised.

Question

Are any further investigations indicated?

Answer

Probably not. She had occasional headaches so a magnetic resonance imaging (MRI) scan of the pituitary was performed which showed a pituitary gland with a convex upper border but no suprasellar extension.

She also had a height velocity of 9.2 cm/year. She therefore had an oral glucose tolerance test for GH suppression. Her GH levels during the glucose tolerance test suppressed to 0.5 mU/L, indicating that there was no evidence of increased GH secretion.

Diagnosis: constitutional (familial) advanced growth.

References and further reading

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