The Evaluation and Management of Tall Stature

Sabine E. Hannema^a Lars Sävendahl^b

^aDepartment of Paediatrics, Leiden University Medical Centre, Leiden, The Netherlands; ^bDepartment of Paediatrics, Karolinska Institutet, Stockholm, Sweden

Key Words

Tall stature · Overgrowth · Growth reduction · High-dose oestrogen · Epiphysiodesis

Abstract

Tall stature is a common reason for consultation of a paediatric endocrinologist. It is important to always consider underlying pathology. We propose a diagnostic flowchart based on five questions. (1) Does the child have tall stature? (2) Is there evidence of a syndrome? (3) Has there been growth acceleration? (4) Are there signs of puberty? (5) Does the child grow within the target height range? Diagnostic tests can then be ordered targeted to the suspected disorder. The Bayley-Pinneau and Tanner-Whitehouse methods are reasonably accurate in predicting adult height based on bone age in girls, but neither method performs well in boys. Tall stature is not a pathological condition and generally does not need treatment. However, adolescents with a strong treatment wish and their parents should be counselled on the effectivity and safety of available treatments including surgery and high-dose sex steroids. Surgical epiphysiodesis has the advantage that a reasonable height reduction can be achieved at a more advanced bone age, allowing a more accurate adult height prediction to base any

treatment decision on. We feel that high-dose oestrogen treatment should no longer be used because of its association with reduced fecundity and imminent ovarian failure.

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Introduction

Tall stature is a fairly common reason for consultation of a paediatric endocrinologist, although not as common as short stature. This is probably at least partly due to greater social acceptance of tall stature. Children may be referred for evaluation of tall stature for a number of reasons. There may be worries about an underlying pathological cause or concerns about the adult height the child might reach and questions about possible treatment. It is important to clarify what the main concern is and who is worried, the child itself, the parents, or the referring physician.

Even when the main question is how tall the child is going to be, the paediatrician should always consider whether there may be a pathological cause of tall stature [1]. The vast majority of tall children are healthy. However, some syndromes, such as Marfan syndrome, are as-

Fig. 1. Flowchart for the diagnostic assessment of tall stature. Adapted from Visser et al. [2]. TH = Target height.

sociated with severe complications, making it essential not to miss this diagnosis. A thorough history, physical examination and evaluation of the growth chart may suffice to conclude that there is a benign cause such as familial tall stature, and these measures are otherwise essential to determine what further investigations are required [1]. Once a diagnosis has been established, it is important to critically evaluate bone age and adult height prediction, and if a child is expected to have an extremely tall adult height, one may consider treatment.

Diagnostic Process

A few key questions can be used to determine what the most likely cause of tall stature is (see flowchart, fig. 1, adapted from Visser et al. [2]) and to decide what further investigations to order (table 1).

Does the Child Have Tall Stature?

Tall stature is usually defined in relation to data from the population, with a height $>+2$ SDS being considered

tall. It is important to take into account the ethnic background and use an appropriate growth chart. Tall stature can also be defined relative to the target height, with height >2 SDS above the target height SDS being considered tall. Ideally, both parents should be measured to calculate the target height. A child may have a normal height but grow far above the target height range and this may also require further investigation. On the other hand, if a child is tall but still within the target height range, this does not mean there is no need for evaluation as the child may have a hereditary disorder associated with tall stature such as Marfan syndrome, where one of the parents may also be affected. In addition, sudden growth acceleration can be a reason for analysis even if the child is still within the target height range and height is <2 SDS.

Is There Evidence of a Syndrome?

The history should include information on birth data; increased birth weight and length are seen for example in Beckwith-Wiedemann syndrome, Simpson-Golabi-Behmel syndrome and Bannayan-Riley-Ruvalcaba syndrome, although familial tall stature may also be associ-

Table 1. Diagnostic tests that may be used to investigate various disorders associated with tall stature

Disorder	Diagnostic test
Marfan syndrome	Evaluation by ophthalmologist, cardiologist, clinical geneticist; use revised Ghent criteria [4]; FBN1 sequencing
Klinefelter syndrome/triple X syndrome	Karyotype
Fragile X syndrome	<i>FMRI</i> CGG repeat number
Homocystinuria	Plasma homocysteine level
Sotos syndrome	Use Sotos score [5]; bone age; evaluation by clinical geneticist; <i>NSDI</i> sequencing
Other syndromes	Evaluation by clinical geneticist; specific DNA tests
Precocious puberty	LH, FSH, oestradiol or testosterone; GnRH test; bone age
Pseudoprecocious puberty	Adrenal androgens, testosterone, oestradiol, AFP, hCG; bone age
Pituitary gigantism	GH, IGF-I, IGFBP3; GH suppression test (OGTT)
Hyperthyroidism	TSH, FT4
Familial glucocorticoid deficiency	ACTH, cortisol
Oestrogen deficiency/resistance	LH, FSH, oestradiol; bone age
Constitutional advancement of growth	Bone age

ated with increased birth length. In Marfan syndrome, birth length is around +1.3 SDS. Developmental or behavioural problems are associated with many syndromes such as Klinefelter syndrome, triple X syndrome, fragile X syndrome, homocystinuria, Loeys-Dietz syndrome, Lujan-Fryns syndrome, Sotos syndrome and Weaver syndrome. Previous medical history may reveal clues for a syndromic cause such as lens luxation (Marfan syndrome, homocystinuria), cardiovascular problems (Marfan syndrome, Loeys-Dietz syndrome), neonatal hypotonia and feeding problems (Sotos syndrome) or abdominal wall defects (Beckwith-Wiedemann syndrome). Family history is essential; a syndrome diagnosis may have been made in family members, but they may also have gone unrecognised so that one should specifically ask for eye, heart or musculoskeletal problems, thromboembolic events and developmental delay in tall family members.

Anthropometry should include height, weight, BMI, arm span, sitting height and head circumference. These measurements can all be plotted on charts or expressed as standard deviation scores. Syndromes can generally be classified into those with proportionate and disproportionate tall stature, although this is not an absolute division. Marfan and Klinefelter patients for example tend to have disproportionately long limbs, but a sitting height/height ratio within the normal range does not exclude these syndromes. A large head circumference is charac-

teristic of Sotos syndrome, Weaver syndrome and Bannayan-Riley-Ruvalcaba syndrome.

Physical examination should focus on dysmorphic features (typical dysmorphisms of various overgrowth syndromes are described in references [2, 3]). There are scores for systemic features of Marfan syndrome [4] and for features of Sotos syndrome [5]. Mucosa, skin and nails may reveal clues for example to MEN IIB (mucosal neuroma), Marfan syndrome (striae) or Bannayan-Riley-Ruvalcaba syndrome (pigment changes of the penis). Supernumerary nipples are often seen in Simpson-Golabi-Behmel syndrome. Macroglossia and hemihyperplasia are characteristic of Beckwith-Wiedemann syndrome. Signs of hypogonadism may be seen in Klinefelter syndrome, whereas macroorchidism is found in fragile X syndrome. Skeletal features such as pectus abnormalities, scoliosis and long legs, fingers and toes are prominent in Marfan syndrome, Loeys-Dietz syndrome and congenital contractural arachnodactyly. Scoliosis and particularly long halluces may be seen in patients with CNP overproduction or an activating NPR2 mutation.

Even if a child does not have tall stature as defined above, if the history or physical examination is suspect for a syndromic cause, this should prompt further investigation. The patient may be referred to a clinical geneticist, or if a specific syndrome is suspected, targeted (genetic) tests can be ordered. Sometimes referral to other specialties is required, for example to have a cardiac and ophthalmologic examination in suspected Marfan syndrome.

The results of these examinations are essential for the diagnosis which is made using the revised Ghent criteria [4]. Determination of bone age can also be helpful, as some syndromes such as Sotos syndrome are associated with advanced bone age.

Has There Been Growth Acceleration?

Growth acceleration after a period of steady growth may be a sign of a hormonal change such as puberty. However, in the first 2–4 years of life, growth acceleration can also be seen in children who are moving towards their own growth channel. Birth weight and birth length are not as strongly correlated to parental height as is height at the age of 2 years. Once a child has reached its growth channel, it will usually grow steadily along an SDS line.

The prepubertal child may already show a growth pattern consistent with constitutional advancement of growth. In these children, one may also see growth acceleration in the first few years, after which growth stabilises, sometimes above the target height range. Bone age may be advanced, but height for bone age usually lies within the target height range. This growth pattern is associated with early puberty and obesity in later childhood, at least in girls [6]. This is the opposite situation of constitutional delay of growth and puberty that is characterised by short stature with delayed bone age in children who will usually go on to have a late puberty.

Are There Signs of Puberty?

If puberty is early or precocious, then the pubertal growth spurt may result in growth above the target height range. Physical examination focussing on Tanner staging, the presence of acne, body odour and signs of virilisation should reveal signs of sex steroid activity. In addition, bone age will usually be advanced and adult height may be compromised. Determination of gonadotropins, gonadal steroids and adrenal steroids can help to distinguish central (gonadotropin-dependent) puberty from gonadal or adrenal disorders.

If growth acceleration is present in the absence of pubertal development, one should consider other endocrine causes. Growth hormone excess can be evaluated by determining the IGF1 level, and if this is elevated, a growth hormone suppression test may be done. Hyperthyroidism can be excluded by determining TSH and FT4. Obesity is also associated with tall stature with advanced bone age but normal adult height.

Does the Child Grow within the Target Height Range?

If the child grows within the target height range, this often indicates familial tall stature, which is the most common cause of tall stature. However, the possibility of a hereditary syndromic cause of tall stature should be considered; an affected parent may have gone undiagnosed. If one parent is very tall and the other much smaller, the child may have familial tall stature despite growth above the target height range if their growth pattern is more similar to that of the tall parent.

If a child grows outside the target height range without syndromic features and in the absence of growth acceleration, there are a few rarer disorders to consider. Individuals with late puberty due to hypogonadotropic hypogonadism may be tall due to delayed epiphyseal closure. They usually have disproportionate tall stature with a decreased sitting height/height ratio. Very rare causes of tall stature with delayed epiphyseal closure are aromatase deficiency or oestrogen resistance caused by a defect of the oestrogen receptor alpha. In tall girls with late puberty or primary amenorrhoea, 46,XY DSD should be considered. Familial glucocorticoid deficiency is another rare cause of tall stature and may be screened for by determining ACTH and early-morning cortisol.

Predicting Adult Height

The question that the child and parents find important is often, what adult height is to be expected. The Bayley-Pinneau (BP) and Tanner-Whitehouse (TW) methods are widely used to predict adult height based on carefully assessed bone age. A study in constitutionally tall children has shown that the BP method slightly overestimates adult height in girls with a mean error of prediction of 0.5 cm (± 2.7 SD), whereas TW slightly underestimated adult height with a mean error of prediction of -0.8 cm (± 3.1) [7]. In boys, neither method performed well, with a large variation in prediction error; BP overestimated adult height in boys ≤ 14 years and TW underestimated adult height in boys ≥ 15 years by as much as 4–5 cm on average [7]. These methods have also been evaluated in children with Marfan syndrome, in whom a wide variation was seen, with both over- and underestimation of adult height [8].

Growth-Reducing Therapy

Children and their parents may seek treatment to reduce growth if they find the predicted adult height unacceptable. There may be concerns about practical problems associated with tall stature such as difficulty finding appropriately sized clothing or furniture as well as social problems. However, there is little evidence that tall adults suffer from more social or emotional problems than others. One may therefore ask if and when it is ethical to treat adolescents for tall stature. What height is found acceptable will obviously differ between individuals, but generally, treatment is only considered for adolescents whose predicted adult height is more than 2.5 SD above the population mean. Various types of treatment have been used to reduce growth, either hormonal or surgical.

The most commonly used hormonal therapy uses high doses of sex steroids to accelerate growth plate maturation. Treatment with high-dose oestrogens, for example 100 µg ethinyl oestradiol, was proven effective. The achieved height reduction varies and is inversely related to the bone age at which treatment is initiated [7]. Side effects during oestrogen treatment include weight gain, nausea, headaches, hypertension and venous thromboembolism. In recent years, it has become clear that high-dose oestrogen treatment also has long-term side effects on fertility. Venn et al. [9] reported a reduced probability of conception in women who had undergone this treatment compared to untreated tall women. This was later confirmed and shown to be dose related, with lower probability of conception in those treated with 200 µg compared to 100 µg ethinyl oestradiol [10, 11]. Treated women also had an increased incidence of imminent ovarian failure [10]. There are also worries about cancer risk, especially of breast cancer. A recent study among tall women treated with very high doses of ethinyl oestradiol (250–1,000 µg) found an increased risk of melanoma compared to untreated tall women, although tumour numbers were small [12]. Treated women also had more breast tumours and malignant gynaecological tumours than untreated women, but those differences were not significant [12]. However, no very long-term follow-up studies are available yet; the mean duration of follow-up in the study by Benyi et al. [12] was 28 years, with most patients being in their forties at the time of assessment.

Treatment of boys with high-dose testosterone, such as testosterone enanthate 500 mg i.m. every 2 weeks, is less effective than oestrogen treatment in girls, and the achieved height reduction depends on the bone age at which treatment is started [7]. Side effects during treat-

ment include acne, aggressive behaviour and troublesome erections. This treatment has also been used in boys with Marfan syndrome without cardiovascular complications [8]. Fatherhood and semen quality were found to be normal in men who had undergone high-dose testosterone treatment, although treated men had slightly lower testosterone levels than untreated tall men [13]. Cancer risk has not been assessed in these men, so it is currently unclear if there is an increased risk for example of prostate cancer after this treatment.

The most commonly used surgical procedure to reduce growth is bilateral percutaneous epiphysiodesis of the distal femur and proximal tibia and fibula. As with hormonal treatment, the effect depends on the timing of the treatment. The remaining growth is reduced by approximately one third so that the surgery should generally be performed before bone age 12.5 years in girls and 14 years in boys and before a height of 170 cm in girls and 185 cm in boys to achieve a significant height reduction (at least 5 cm if predicted adult height is 185 cm in girls and 200 cm in boys) [14]. As leg growth is limited but growth of the back is not, this treatment alters body proportions. However, since most tall individuals have relatively long legs, the sitting height/height ratio after treatment is closer to the population mean than before treatment [14, 15]. Arms will also be relatively long, but this is generally not perceived as a problem. The procedure itself is short (about 60–70 min) and patients are allowed to stand on their legs directly afterwards but are advised not to engage in athletic activities for 4 weeks. The surgery leaves small scars. In experienced hands, few complications are seen. Obviously, there is the (small) risk that is associated with any anaesthesia. In a series of 21 patients, one superficial cutaneous infection was reported that did not need treatment, and pain for up to 14 days occurred in 9 patients, which was treated with oral analgesics [14]. In another series of 15 patients, one developed exostosis at the fibula and two angular deformity, but none of these complications required intervention [15]. Neurovascular damage or asymmetrical fusion are potential complications, but were not seen in these series. However, all patients should be closely followed after treatment in order to detect any such complications. Epiphysiodesis has also been performed in a few patients with Marfan syndrome without complications [14].

Tall stature by itself is not a pathological condition and generally does not need treatment. However, adolescents who have a strong wish for treatment and their parents should be counselled on the effectivity and safety of surgical and hormonal treatment as described above. Epiphysiodesis has the advantage that a reasonable height reduc-

tion can be achieved at a more advanced bone age compared to hormonal treatment, allowing a more accurate prediction of adult height to base any treatment decision on. We feel that high-dose oestrogen treatment should no

longer be offered to girls because of its association with reduced fecundity and increased risk of imminent ovarian failure.

In conclusion, any child seen because of tall stature deserves a careful evaluation to exclude underlying pa-

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