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Approach and management of constitutional delay in growth and sexual maturation

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Summary

Constitutional delay in growth and puberty is a common and benign condition for which treatment is usually not indicated. However, there is mounting evidence suggesting that adults with a history of constitutional delay in growth and puberty have a lower bone mineral content and density than the normal population. The psychological stress of being short during adolescence may also induce long lasting impact on their social and career development. Appropriate timing of hormonal treatment of such adolescents can advance the timing of height acceleration without compromising their final adult height. In this review, I will discuss the rationale of this approach.

摘要

成長期和青春期的全身性發育遲緩是一個普遍和良性的情況，毋須治療。但是越來越多的證據顯示有全身性發育遲緩病史的成年人的骨礦物含量和密度較正常人低。同時，青少年時期個子矮小所引起的心理困擾可對日後的社交和職業發展造成深遠的影響。在適當時候採用荷爾蒙治療可提前這類青少年的體高增長而不影響其成年後最終的高度。本文就這種療法做理性分析。

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Introduction

Constitutional delay in growth and puberty is a common clinical observation in childhood and 3% of children have this condition.¹ The usual presenting

feature is short stature. Constitutional delay in development is basically a benign condition and a diagnosis by exclusion. It is believed to be a normal variant of growth with slow pace of growth in infancy and early childhood, normal growth velocity during the childhood phase of growth, followed by a growth spurt at an age later than the normal population and the final attainment of normal adult height. However, there are several conditions that mimic constitutional delay in clinical presentation and very often, it is difficult to differentiate one from the other by currently available clinical tests. Confirmation of the diagnosis can only be made retrospectively by normal progression through puberty. On one hand, we must not be overzealous with our investigations of children with such a benign condition but on the other, a conservative approach in some children may result in delayed diagnosis and intervention.

Etiology

To date, the exact etiology of constitutional delay in growth and puberty remains unknown but it is thought to be related to the variation in the control of growth tempo. Investigations fail to show any endocrine abnormalities. The hypothalamic-pituitary-insulin growth factor 1 (IGF-1) axis is intact and gonadotrophin and sex hormones are appropriate for the pubertal stage.

Recently, leptin, a newly discovered protein that is secreted by adipose tissue and acts as a negative feedback on the hypothalamus to control food intake and body weight, has gained a lot of attention. An animal study on mice showed that normal prepubertal mice treated with leptin enter puberty earlier than the control mice.² Starvation of mice induces reduction in gonadotrophin secretion that can be partially reversed by leptin administration, implying that leptin may have a role in activating GnRH neurones.³ Gill, 1999, showed an association of hypoleptinaemia with delayed puberty in

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23 boys.⁴ Whether leptin acts as a primary signal involving in initiation of puberty and low level of leptin results in delayed onset of puberty warrant further study.

Some investigators attribute the delayed growth spurt to transient decrease in growth hormone secretion.⁵ These children show equivocal response to a growth hormone stimulation test. However, growth hormone and IGF-1 secretion increase when puberty occurs or when sex steroids are given. This transient decrease in growth hormone secretion is apparently the consequence of inadequate gonadal secretion. In fact, overnight growth hormone secretion was shown to be normal when this group of children was compared to a carefully matched control group.⁶

A study of 26 children with constitutional delay in growth and puberty showed that serum vitamin A levels were significantly lower than in the matched control group, although the levels of both groups were within normal range according to WHO criteria.⁷ It was concluded that vitamin A deficiency might play a role in constitutional delay in developing countries.

Clinical features and differential diagnosis of constitutional delay

Definition

The usual complaint for children with constitutional delay in growth and puberty is short stature rather than sexual immaturity. By definition, short stature is defined as body height below the third percentile which is equivalent to two standard deviation of the population mean. As different ethnic groups have different height standards, body height of an individual should only be compared to his or her own population growth chart. Delayed puberty usually refers to failure to develop secondary sexual characteristics by the age of 13 and 14 years in a female and male respectively. Constitutional delay in growth and puberty is considered as a normal variant. These subjects have short stature but normal growth rate and have a delayed pubertal growth spurt that enables them to have a longer period of prepubertal growth and finally attain an adult height. Bone age is usually delayed for chronological age by more than 2 years or 2 standard deviations, allowing them to grow to their expected height. They should be free from systemic illnesses and have normal thyroid and growth hormone function. Very often, there is a positive family history of

growth delay. Boys usually outnumber girls in seeking medical care especially at the age of early puberty. This may be explained by the difference in boys experiencing more social and peer pressure on physique than girls. Characteristics of constitutional delay in growth and sexual maturation are summarised in **Table 1**.

Differential diagnosis

As constitutional delay in growth and puberty is a diagnosis of exclusion, other conditions that can give rise to short stature in a prepubertal child have to be excluded. Short stature in a growing child can be the result of endocrine disorders like hypothyroidism, hypopituitarism, Cushing's syndrome, pseudohypoparathyroidism, pseudo-pseudohypoparathyroidism and disorders in hypothalamic-pituitary-IGF-1 axis including growth hormone deficiency, growth hormone insensitivity, i.e. Laron syndrome and defect in IGF-1 synthesis. Skeletal diseases like rickets, achondroplasia, hypochondroplasia and spondyloepiphyseal dysplasia can all result in shortness but can be easily diagnosed because of the abnormal body proportions. Systemic disorders like chronic renal disease, chronic inflammatory bowel disease, malabsorption syndrome, chronic lung disorder and thalassaemia can be excluded by a proper history and physical examination. Syndromal disorders such as Turner's syndrome, Down's syndrome, Prader-Willi syndrome, Laurence-Moon-Biedl syndrome and Russell-Silver syndrome should be looked for. Tumours in the central nervous system like craniopharyngioma, post chemotherapy and post radiotherapy of the head and neck region and septo-optic dysplasia can lead to single or multiple hormonal deficiencies resulting in short stature. Familial short stature is another differential diagnosis since stature is mostly genetically determined.

A small proportion of children, born small for gestational age, are unable to show catch up growth in

Table 1: Showing the characteristic features of constitutional delay in growth and puberty

Characteristics of constitutional delay in growth and puberty

- * Short stature, along or slightly below 3rd percentile
 - * Normal growth velocity (≥ 5 cm per year)
 - * Delayed bone age
 - * Usually has positive family history
-

early infancy, which typically occurs in the first 2 years of life. These children usually end up short.⁸ Last but not least, psychosocial deprivation can contribute to failure to thrive and short stature.

From a molecular perspective, several genes have been found to cause hypopituitarism, resulting in poor growth. These include Pit-1 gene, PROP-1 gene and HESX-1 gene.⁹ The phenotypic characteristics of mutation in the Pit-1 gene involves deficiencies of growth hormone, prolactin and thyroid stimulating hormone whereas for PROP-1 gene, deficiencies involve luteinising hormone (LH) and follicular stimulating hormone (FSH) on top of growth hormone, prolactin and thyroid stimulating hormone. A third of patients with PROP-1 mutation have ACTH deficiency as well. Expression for HESX-1 in the developing brain is more widespread and is shown to cause growth hormone and probably anti-diuretic hormone deficiency. It is worthwhile to check for these molecular defects in an individual with multiple pituitary hormonal deficiencies especially with a positive family history.

Another newly discovered gene, SHOX (short stature homeobox containing gene), located in pseudoautosomal region of sex chromosomes, is found in families with idiopathic short stature and Leri-Weill syndrome which is characterised by lateral and dorsal displacement of radius in the forearm.¹⁰

History and physical examination

A detailed history and physical examination can usually give us valuable clues in the diagnosis of short stature. Children with midline defect or micropenis may suffer from hypopituitarism. The presence of a defect in the sense of smell may point to Kallman syndrome. Mentally retarded child may have syndromal disorder or untreated hypothyroidism. A short and thin child usually indicates the presence of systemic illness or psychosocial deprivation while a short and fat child may favor diagnosis of endocrine disorder.

Among the differential diagnoses, idiopathic hypogonadotropic hypogonadism is the most difficult to be differentiated from constitutional delay of growth and puberty before the usual age of puberty. Most of the time, children are presumed to fit the diagnosis of constitutional delay. Not until they go through puberty can hypo-

gonadotropic hypogonadism be excluded. There are no reliable physical signs that allows differentiation between the two but patients with hypogonadotropic hypogonadism tend to have normal stature. Anthropometric examination of patients with constitutional delay shows a disproportion of upper segment to lower segment, with sitting height shorter than subischial leg length, implying inadequate spinal growth.¹¹ It is suggested that a large component of short stature is related to inadequate spinal growth which does not improve by the time of final height attainment. However, patients with hypogonadotropic hypogonadism typically have eunuchoid habitus which is similar to the initial presentation of patients with constitutional delay. If examination shows testicular enlargement to 4 ml in volume which is the first sign of puberty in boys or appearance of breast buds in girls, the chance of going into puberty will be high. However, this cannot rule out partial hypogonadism which may show arrest in pubertal progression later on. **Tables 2 and 3** show the differential diagnosis of short stature and delayed puberty respectively.

Basic investigations

Baseline investigations include complete blood picture, liver and renal function tests and blood gas analysis when chronic disease is suspected. X-ray of the non-dominant hand is essential to document delay in bone age as compared to chronological age. Radiological imaging of the skeleton can be done in suspected skeletal abnormalities. Chromosomal testing especially in girls can be performed if Turner syndrome cannot be confidently excluded. Hormonal work-up including thyroid function test has to be checked to exclude hypothyroidism. Growth hormone and IGF-1 testing should be considered in individual cases especially those with a height below 3 standard deviation scores and poor growth velocity.

Laboratory tests may be of limited use in the differentiation of idiopathic hypogonadotropic hypogonadism from constitutional growth delay. Baseline measurement of gonadotropin level cannot discriminate prepubertal and hypogonadotropic from early pubertal children. Onset of puberty is heralded by nocturnal luteinising hormone (LH) secretion whereas hypogonadotropic children do not have an increase in LH secretion during sleep. Measurement of LH at sleep may give us clues on diagnosis, but this method is technically

Table 2: Shows the differential diagnosis of shortness in children

Differential diagnosis of short stature

1. Familial short stature
 2. Constitutional delay in growth and sexual maturation
 3. Endocrine disorders
 - Hypothyroidism
 - Hypopituitarism
 - Cushing's syndrome
 - Pseudohypoparathyroidism, pseudo-pseudohypoparathyroidism
 - Disorders in hypothalamic-pituitary-IGF-1 axis
 4. Skeletal disorders
 - Rickets
 - Achondroplasia
 - Hypochondroplasia
 - Spondylepiphyseal dysplasia
 5. Systemic disorders
 - Chronic renal diseases
 - Chronic lung disorders
 - Haematological disorders
 - Chronic inflammatory disorders
 - Chronic malabsorption
 6. Syndromal disorders
 - Turner's syndrome
 - Down's syndrome
 - Prader-Willi syndrome
 - Laurence-Moon-Biedl syndrome
 - Russell-Silver syndrome
 7. Central nervous system disorders
 - Tumours
 - Post chemotherapy or radiotherapy to head and neck
 - Septo-optic dysplasia
 8. Genetic disorders
 - Pit-1 gene, PROP-1 gene, HESX-1 gene, SHOX gene
 9. Born small for gestational age
 10. Psychosocial deprivation
-

Table 3: Shows the differential diagnosis of delayed puberty

Differential diagnosis of delayed puberty

1. Constitutional delay in growth and sexual maturation
 2. Hypogonadotropic hypogonadism
 - Isolated gonadotropin deficiency (normal stature)
 - Kallmann syndrome (normal stature, smelling defect)
 - Prader-Willi syndrome (short, dysmorphism)
 - Hypothalamic-pituitary tumours
 - Multiple pituitary hormonal deficiencies
 3. Hypergonadotropic hypogonadism
 - Primary gonadal failure (e.g. infection, chemotherapy, radiation, ischaemia, autoimmune)
 - Turner syndrome
 - Klinefelter syndrome (chromosome 47 XXY, normal to tall stature)
-

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inconvenient. Using gonadotropin-releasing-hormone (GnRH) agonist to provide a sustained stimulation to the gonadal axis helps to improve the differentiation. Studies done by R. Rosenfield, 1990, showed that prepubertal constitutional delay and hypogonadotropic males over 14 years of age can be differentiated by serum LH rising over 12.5 IU/L at 3 hours and FSH over 6.0 IU/L at 8-12 hours after administering GnRH agonist, naferelin of 1 µg/kg.¹ A pitfall of this test is that a pubertal response cannot rule out hypogonadotropinism in delayed girls. A checklist of investigations is shown in **Table 4**.

Disadvantages of constitutional delay in growth and puberty

Finkelstein, 1992, studied 23 adult men with a history of constitutional delay in growth and puberty and found that all have decreased spinal and radial bone mineral density as measured by dual-energy x-ray absorptiometry (DEXA).¹² As peak bone mineral density is the major determinant of bone density in later life, these men may have an increased risk of osteoporotic fracture in later life. A follow up study also confirmed that these men have a decreased bone mineral density over the femoral neck when compared to the control group and the decrease in bone mineral density does not improve with time.¹³ The finding suggests that the timing of puberty

is an important determinant of peak bone density in men. However, these reports aroused a lot of criticism and controversy since bone mineral densities were measured as areal rather than volumetric bone mineral density. The former measurement can be influenced by bone and body size. Bertelloni, 1998, measured 21 young Italian men who had a history of constitutional delay and found that areal bone mineral density over lumbar spine was reduced but volumetric bone mineral density, which was calculated from DEXA measurement, was normal when compared to normal men.¹⁴ Moreira-Andres, 2000, showed that radial bone mineral density, after correction of bone and bone size, was decreased in 56 short prepubertal children having constitutional delay in growth.¹⁵ In her previous assessment, she also demonstrated that the spinal bone mineral density was decreased in children with constitutional delay.

Undoubtedly, quite a number of children with constitutional delay especially boys have experienced psychosocial stress during their development. The psychological effects may include depression, low self-esteem, psychosomatic complaints, poor school performance, violent behavior and immature social skill. Psychological assessment of 38 boys with history of constitutional delay showed that 65% of them thought their height had interfered with their success either at school, work or socially. Half of them in retrospect would have liked treatment to advance their growth spurt and half of them wanted the availability of treatment for their children faced with the same growth problem.¹⁶ Whether the Chinese population experiences the same degree of psychological stress as a result of being short in their adolescent period is still unclear. So far, no formal study has been conducted in this area.

Table 4: Shows a checklist of investigations of short stature

Baseline investigation checklist

1. Growth chart and velocity
2. Complete blood picture
3. Liver function test
4. Renal function test, electrolytes and urinalysis
5. Bone age
6. Thyroid function test

Advanced investigations

1. Chromosomal or genetic analysis for suspected syndromal disorders
 2. Growth hormone and sex hormone tests
 3. Skeletal survey for suspected skeletal disorders
 4. Neuro-imaging for suspected central nervous system disorders
-

Management

As constitutional delay is a benign condition and there is overlap with hypogonadism on clinical presentation, some physicians tend to refrain from giving treatment. Bearing in mind the disadvantages of constitutional delay, it may be worthwhile offering treatment to these children. Several articles show that the final adult height of untreated patients with constitutional delay were close to their adult height predictions, using Tanner-Whitehouse 2, Bayley-Pinneau or Roche-Wainer-Thissen methods. However, their final heights were

below the mid-parental height by 6.5 cm in one study,¹⁶ 5.1 cm in males and 5.3 cm in females in another study.¹⁷

Treatment for children with constitutional delay has been performed and tested in several studies. These children are treated with sex hormones including oral oxandrolone, depot testosterone enanthate intramuscularly for boys and ethinyl estradiol for girls. Oral testosterone is another alternative for boys but the pitfall is irregular absorption from the gastrointestinal tract. Some physicians even try using growth hormone as transient growth hormone deficiency is shown to be a feature of this condition.

Sex hormone treatment

Several randomised controlled studies have been performed to study the growth response to androgen treatment in managing boys with constitutional delay in growth and puberty.¹⁸⁻²⁹ The results consistently showed a positive effect on growth velocity during androgen treatment with sustained effect. Rosenfeld R G, 1982, recruited 16 male adolescents aged 14 to 17 years with constitutional growth delay for a prospective randomised study.¹⁸ Testosterone enanthate 200 mg was administered intramuscularly 3 weekly on 4 occasions to the treatment group. At 1 year, mean growth velocity was significantly greater in the treatment group (9.2 cm per year) than in the control group (6.0 cm per year).

Clayton P E, 1988, studied 13 boys with constitutional delay in growth aged from 7.6 to 16 years by using oral oxandrolone 2.5 mg daily for 3 months.¹⁹ The control group consisted of 14 age-matched subjects. Growth velocity increased significantly in both prepubertal and pubertal children in the treatment group while the control group did not show significant change in growth velocity.

Stanhope R, 1988, treated 10 boys of average age 14.4 years with oral oxandrolone 2.5 mg daily for 3 months, showing that growth velocity increased from the mean of 4.5 cm per year to 9.6 cm per year in three months and sustained at 8.6 cm per year after stopping treatment.²⁰

Albanese A, 1994, performed a randomised trial on 33 boys with constitutional delay in growth and puberty and a mean age of 14.6 years.²¹ Among the 33 recruited

subjects, 17 of them received oral testosterone undecanoate 40 mg per day while the remaining 16 boys received oral oxandrolone 2.5 mg per day for 3 to 7 months with a mean of 3.5 months. Significant growth acceleration was shown in 14/17 boys in the former group and 15/16 boys in the latter group. The growth acceleration was sustained when the treatment was interrupted.

Wilson DM, 1995, studied 40 boys with constitutional growth delay by a randomised block designed controlled trial.²² One group received oral oxandrolone 0.1 mg/kg daily for 1 year and the other group received placebo. Growth velocity was significantly greater in the treatment group than in the control group (9.5 cm vs 6.8 cm per year). No significant adverse effect was observed in terms of liver function and lipid profile in the treatment group.

Soliman A T, 1995, conducted a prospective randomised control trial on 198 boys aged between 14 to 18 years with constitutional delay in puberty.²³ The treatment group which consisted of 148 subjects was given testosterone enanthate 100 mg intramuscular injection monthly for 6 months. After 1 year, growth velocity increased from 4.6 ± 0.14 to 11.6 ± 0.36 cm per year in the treatment group and from 4.8 ± 0.1 to 6.1 ± 0.12 cm per year in the control group.

Crown E C, 1997, compared the height velocity in 16 boys of constitutional delay with average age of 14.3 years and testicular volume ranging from 4-6 ml.²⁴ They were divided into 3 groups. One group was the control and the other two groups were treated with 2.5 mg oxandrolone orally every day or 50 mg testosterone intramuscular injection monthly for 3 months. Growth response was assessed after 6 months and the mean height velocities were 3.8, 7.1 and 6.5 cm per year for the control, oxandrolone treated and testosterone treated groups respectively.

Brown D C, 1995, conducted a double-blind, randomised control trial on 23 prepubertal boys aged 11-14 years with constitutional growth delay, comparing the effect of low dose oral testosterone undecanoate 20 mg daily with placebo for 6 months.²⁵ A significantly greater height velocity in the treatment group than in the control group was demonstrated (5.84 cm versus 3.38 cm per year).

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In 2001, Wickman S recruited 33 boys with constitutional delay in growth and puberty and studied the use of testosterone and aromatase inhibitor in managing this condition. Twenty-three boys were randomised into 2 groups, monthly injection of testosterone enanthate for 6 months with oral placebo for 1 year or monthly injection of testosterone enanthate for 6 months with oral letrozole for 1 year.²⁶ The remaining 10 boys belonged to the non-treatment group. The group receiving letrozole, a specific aromatase inhibitor, had the slowest progression in bone age and a significant increase in predicted adult height by 5.1 cm ($p = 0.004$). The untreated and placebo groups did not show any change in predicted adult height.

Growth hormone versus sex hormone treatment

Growth hormone treatment had been used in children with constitutional delay in growth and sexual maturation as transient growth hormone insufficiency had been shown to be a feature of this condition. Buyukgebiz, 1990, compared the effect of oxandrolone with recombinant growth hormone on 26 boys with constitutional delay.²⁷ One group received oxandrolone 2.5 mg daily for 3 months and the other group received biosynthetic human growth hormone 20 units/m²/week daily given subcutaneously for 1 year. Results showed that the pre-treatment growth velocity increased significantly from 3.9 cm per year to 8.3 cm per year in oxandrolone group and 3.8 cm per year to 6.8 cm per year in growth hormone treated group. Both regimens increased growth rate twofold, with a greater extent in the oxandrolone treated group than in the growth hormone treated group.

Bierich, 1992, reported the long-term effect of growth hormone treatment in 15 children (13 boys, 2 girls) with constitutional delay. He found that there was no increase in their final adult height when they were treated with growth hormone 12-16 IU/m²/week with average duration up to 3 years.²⁸

Loche, 1991, studied the effect of short-term growth hormone or low dose oxandrolone treatment in 16 boys with constitutional delay.²⁹ They were randomly assigned to the 2 groups, one received growth hormone 0.6 unit/kg/week subcutaneously, while the other received oral oxandrolone 0.07 mg/kg daily for 6 months. Height velocity increased from 3.7 to 7.5 cm per year in the growth hormone treated group and from 4.0 to 8.1 cm per year in the oxandrolone treated group.

Although the number of study subjects was small in the studies mentioned above, it consistently showed that sex steroid is effective in bringing forward the pace of growth in children with constitutional growth delay. The use of growth hormone treatment is controversial and it is not shown to have additional benefit than sex hormone treatment. The studies are summarised in **Tables 5** and **6**.

Is final height affected by sex hormone treatment?

The final adult height is a major area of concern when using sex steroids that can enhance skeletal maturity and epiphyseal closure. Provided treatment of suitable dosage and duration was used, final height was shown to be unaffected.²⁹⁻³² The use of testosterone enanthate 50 mg intramuscularly for up to 6 months in children with constitutional delay was shown to attain a final height similar and corresponded to both predicted final height and target height.^{30,31} Using oxandrolone 1.5 mg/2.5 mg daily per oral for 3 months was also shown not to compromise final height.³² However, some boys do not have a good growth response to 3 months' oxandrolone treatment, especially for those with more quiescent profile in baseline LH-testosterone level.³³ Prolonged course of oxandrolone, which is an anabolic steroid with weak androgenic potency, of up to 1 year will be recommended and it has not been shown to alter final height.³⁴ There is no significant difference in final height in the treated groups with any form of sex hormone regimens. The earliest recommended age of starting treatment is 14 years. None of these studies reported any adverse effects or complications of using these treatment regimens. The only drawback of giving testosterone enanthate is the pain from intramuscular injection. Moreover, it has to be born in mind that inadvertent administration of androgen in large dose can induce advancement in bone age resulting in premature closure of epiphysis, liver enlargement, excessive masculinisation and priapism.

Unfortunately, studies on treatment for girls with constitutional delay are unavailable. It is generally accepted that, in girls, low dose of ethinyl estradiol of 1-2 µg daily per oral for 3-6 months or until spontaneous sexual maturation occurs, is a safe regimen.³⁵

Recommendation

Knowing that constitutional delay in growth and sexual maturation runs a relatively benign course, we all

Table 5: Studies using sex hormones as treatment for constitutional delay in growth and puberty

Author and Year	Method	Subject	Treatment	Outcome	Comment
Rosenfeld R G 1982	Randomised trial	Age: 14-17 years	Testosterone enanthate 250 mg IM 4 times every 3 weeks (n=8 boys) vs Control (n=8 boys) Duration: 3 months	After 1 year, mean growth velocity: 9.2 cm (7.2-11.6) vs 6.0 cm (2.6-10.6)	Small sample size
Clayton P E 1988	Randomised trial	Age: Prepubertal: 12.3 years (treatment) vs 12.4 years (control) Pubertal: 14.7 years (treatment) vs 14.2 years (control)	Oxandrolone 2.5 mg daily po (n=7 prepubertal + 6 pubertal boys) vs Control (n=9 prepubertal + 5 pubertal boys) Duration: 3 months	Growth velocities: 4.4 → 7.5 cm per year in prepubertal treatment group (p = 0.05), 4.7 → 8 cm per year in pubertal treatment group (p < 0.05) vs no significant change in growth velocity in control groups	Recruited non-randomised subjects into the study No allocation concealment Not double blinded
Stanhope R 1988	Randomised double blinded trial	Mean age: 14.4 years (12.9-16.3 years)	Oxandrolone 2.5 mg po daily (n=10 boys) vs Control (n=9 boys) Duration: 3 months	After 3 months, growth velocity increased from 4.5 to 9.6 cm per year (p < 0.001) vs 5.1 to 5.2 cm per year (p > 0.5)	No allocation concealment Small sample size Cross-over study, sustained effect cannot be compared
Albanese A 1994	Randomised trial	Mean age: 14.6 years (12.8-16.2 years) Testicular volume 3.8ml Bone age delayed by 3.3 years	Testosterone undecanoate 40 mg po daily (n=17 boys) vs Oxandrolone 2.5 mg po daily (n=16 boys) Duration: 3-7 months (mean:3.5 months)	Significant growth acceleration in 14/17 boys vs 15/17 boys Mean growth velocity: 4.4 → 10.1 cm per year (p < 0.0001) vs 4.1 → 9.0 cm per year (p < 0.0001)	No control group Not an intention-to-treat analysis Small sample size
Brown D C 1995	Randomised double blinded trial	11-14 years	Testosterone undecanoate 20 mg daily (n=11 boys) vs Placebo (n=12 boys) Duration: 6 months	Mean growth velocity before and during treatment: 3.18 → 5.84 cm per year vs 3.31 → 3.38 cm per year (p = 0.001) 1 year post-treatment: 5.71 cm per year vs 3.94 cm per year (p = 0.001)	No allocation concealment
Wilson D M 1995	Randomised double blinded trial	Age: 11-14.7 years	Oxandrolone 0.1 mg/kg daily po (n=21 boys) vs Placebo (n=19 boys) Duration: 1 year	Mean growth velocity: 9.5 cm per year (± 1.7) vs 6.8 cm per year (± 2.8) (p < 0.001)	
Soliman A T 1995	Randomised trial Pre-established random number table	14-18 years Height < 5th percentile	Testosterone enanthate 100 mg monthly (n=148 boys) vs Control (n=50 boys) Duration: 6 months	Mean growth velocity before and 1 year after treatment: 4.6 → 11.6 cm per year vs 4.8 → 6.1 cm per year (p < 0.05)	
Crown E C 1997	Randomised double blinded	Mean age: 14.3 years (13.0-15.7 years) Height SDS: -2.55 to -5.17 Testicular volume 4-6 ml	Control (n=5 boys) vs Oxandrolone 2.5 mg po daily (n=5 boys) vs Testosterone enanthate 50 mg IM monthly (n=6 boys) Duration: 3 months	Mean growth velocity: 3.8 cm per year vs 7.1 cm per year vs 6.5 cm per year	No allocation concealment Small sample No p-value
Wickman S 2001	Randomised double blinded trial	Mean age: 15.0 years (untreated group) vs 15.0 years (placebo group) vs 15.2 years (Letrozole group)	No treatment (n=10 boys) Randomised groups: Testosterone enanthate 1 mg/kg IM monthly × 6 months + placebo × 1 year (n=12 boys) vs Testosterone enanthate 1 mg/kg IM monthly × 6 months + Letrozole 2.5 mg daily × 1 year (n=10 boys)	Bone age advanced by 1.1 years (SD0.8) in untreated group 1.7 years (SD 0.9) vs 0.9 years (SD0.6) in the treated groups (p = 0.03) Predicted adult height: No change in the untreated and in the placebo groups Increase 5.1 cm (SD3.7 cm) in letrozole group	

Table 6: Studies comparing the use of sex hormone and growth hormone as treatment for constitutional delay in growth and puberty

Author and Year	Method	Subject	Treatment	Outcome
Buyukgebiz A 1990	Randomised trial	Mean age: 13.8 years (12.1-15.9 years)	Oxandrolone 2.5 mg daily (n=15 boys) vs RhGH 20 units/m ² /week daily s.c. (n = 11) Duration: 3 months vs 1 year	Growth velocity increased from 3.9 to 8.3 cm per year vs 3.8 to 6.8 cm per year (Difference: p=0.02)
Bierich J R 1992	Prospective	8.0-14.2 years (13 boys, 2 girls)	Growth hormone 12-16 I.U. /m ² /week Mean duration: 3 years	No increase in final adult height
Loche S 1991	Randomised trial	13.7 years vs 12.8 years	Growth hormone 0.6 units/kg/week s.c. (n = 8 boys) vs Oxandrolone 0.07 mg/kg po daily (n = 8 boys) Duration: 6 months	Growth velocity increased from 3.7 cm to 7.5 cm per year vs 4.0 to 8.1 cm per year Predicted adult height not affected in either groups

agree that medical treatment is unnecessary in most situations. However, children with the condition suffering from significant psychosocial stress and disadvantage should be identified and informed of the availability of different treatment options. Referral to a paediatric endocrinologist for a detailed assessment before the commencement of medical intervention is recommended. In boys, testosterone enanthate 50 mg monthly intramuscular injection can be offered for 3 to 6 months or oral oxandrolone 2.5 mg daily for 3 months, depending on the treatment response. The age of starting treatment should be around 14 years. Since there is not enough data to suggest the appropriate dosage and duration of sex steroids in girls with constitutional delay, treatment cannot be recommended at present. Monitoring of response in terms of height gain, pubertal progression and any possible side effects should be made before, during and after treatment.

Conclusion

It is essential to evaluate growth, pubertal development, bone age, sex hormone profile and review diagnosis during treatment. In summary, an appropriate dose of sex steroids for a short treatment course is safe and effective in treating children with constitutional delay in growth and puberty. This is beneficial in bringing forward the onset of growth spurt during a period of emotional, social and educational development without compromising the final adult height. Moreover, it has been shown that peak bone mass and bone mineral density are adversely affected in men with a history of

constitutional delay in growth and puberty. Normalising the hormonal profile with sex hormones may have an additional benefit on bone mass, though further study is required to document this phenomenon. ■

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Key messages

1. Constitutional delay in growth and sexual maturation is a benign condition and has to be differentiated from other endocrine or systemic disorders. Treatment is unnecessary in most situations.
 2. Children with constitutional delay in growth and sexual maturation suffering from significant psychosocial stress and disadvantages have to be identified for possible medical intervention.
 3. Several randomised controlled studies have consistently shown that the use of testosterone or oxandrolone is safe and effective in bringing forward the onset of growth spurt, provided appropriate dosage and duration of treatment are used.
 4. Some studies have shown that the peak bone mass and bone mineral density are adversely affected in men with a history of constitutional delay in growth and puberty.
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