

## An approach to constitutional delay of growth and puberty

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### ABSTRACT

Constitutional delay of growth and puberty is a transient state of hypogonadotropic hypogonadism associated with prolongation of childhood phase of growth, delayed skeletal maturation, delayed and attenuated pubertal growth spurt, and relatively low insulin-like growth factor-1 secretion. In a considerable number of cases, the final adult height (Ht) does not reach the mid-parental or the predicted adult Ht for the individual, with some degree of disproportionately short trunk. In the pre-pubertal male, testosterone (T) replacement therapy can be used to induce pubertal development, accelerate growth and relieve the psychosocial complaints of the adolescents. However, some issues in the management are still unresolved. These include type, optimal timing, dose and duration of sex steroid treatment and the possible use of adjunctive or alternate therapy including: oxandrolone, aromatase inhibitors and human growth hormone.

**Key words:** Constitutional delay of growth and puberty, growth hormone, human chorionic gonadotropin, hypogonadotropic hypogonadism, oxandrolone, testosterone

### INTRODUCTION

Although the commonest disorders of delayed puberty are idiopathic, concerns raised by delayed puberty are many and variably appreciated by different persons. These include possibility of underlying pathology, fear that puberty will never occur and emotional and psychosocial upset of immaturity, especially the associated short stature. In addition, concerns about long-term sequels comprising reduced final adult height (Ht), bone-mineralization and fertility may also be raised.<sup>[1-4]</sup>

Most specialists would not consider any treatment unless the boy is at least 14 years old and his bone age is at least

12 years old. However, many important questions are raised and their answers are briefly attempted in this review for better management of this condition.

### THE NATURAL HISTORY OF CONSTITUTIONAL DELAY OF GROWTH AND PUBERTY

Inheritance pattern of constitutional delay of growth and puberty (CDGP) is consistent with autosomal dominant inheritance. It occurs twice as frequently in boys versus girls. The Ht and weight deficit and the short sitting Ht are usually evident at presentation and continue up to final adult Ht. The age of onset of puberty is delayed by an average of 2.5 years in girls and 3 years in boys. Ht deficit at onset of puberty correlates with final Ht. The time between onset of puberty and pubertal growth spurt is shorter than in normal children and the peak growth velocity is attenuated. Therefore, the mean final Ht is usually shorter than both target Ht and predicted adult Ht. The final Ht lies on average 1.85 SD below the mean of healthy adults, with large individual variations. Better final Ht appears to occur in children who had their slow growth during their late childhood, while those with

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early and progressive reduction of relative Ht in the early childhood have compromised final Ht. In addition, CDGP is combined with familial short stature in around 40% of short children with Ht < 3<sup>rd</sup> centile for age and gender.<sup>[5-9]</sup>

## EARLY DIFFERENTIATION BETWEEN CONSTITUTIONAL DELAY OF GROWTH AND PUBERTY FROM PERMANENT HYPOGONADOTROPIC HYPOGONADISM

The question can be answered in many cases by following these steps:

A. Clinical assessment: This includes full physical and genital examination, studying the pattern of growth and skeletal maturation of the person as well as family history of puberty and measuring the Ht of parents. Analysis of these data can further divide these children into the following four categories:

- a. According to family history and measurements of parents' Ht into:
  1. CDGP with familial short stature ( $\approx$  40% of patients)
  2. CDGP with normal parental stature ( $\approx$  60% of patients)<sup>[10]</sup>
- b. According to the pattern of Ht deficit will further divide these patients into:
  1. Those who have Ht deficit early in their childhood (less favorable prognosis for final Ht).
  2. Those who have Ht deficit late in childhood (better prognosis for final Ht).<sup>[11]</sup>
- c. According to the size of the testes can further divide patients into two groups
  1. Those with a testicular volume = or > 4 mL (95% or more have CDGP)
  2. Those with testicular volume below 4 mL (40% of CDGP and all patients with hypogonadotropic hypogonadism (HH) have testicular volume < 4 mL)<sup>[12]</sup>
- d. According to their predicted final adult Ht into:
  1. Those with predicted Ht near to mid-parental Ht with normal Ht standard deviation score (HtSDS).
  2. Those with predicted Ht below mid-parental Ht especially those with HtSDS < 2

Unfortunately, the prediction of final adult Ht in these patients proves to be inaccurate in many studies, which increase the difficulty of taking the decision for treatment.

### B. Endocrine Assessment

This includes the measurements of:

- a. Basal serum concentrations of morning testosterone (T). Again, this can separate boys with HH into two groups.<sup>[12]</sup>

1. Those with basal T = or > 1.7 nmol/L (almost all of them have CDGP)
  2. Those with basal T < 1.7 nmol/L (all patients with HH and 45% of those with CDGP).<sup>[12]</sup>
- b. Patients who have small testicular volume (<4 mL) and low T level (< 1.7 nmol/L) need further studies: including human chorionic gonadotropin (hCG) and/or GnRH/GnRHa tests.

Table 1 presents different useful studies using these tests and their cut-point to differentiate CDGP and HH.

C. Response to a short therapeutic course of androgen  
Increased testicular length during or over the following 4 months after stopping androgen treatment indicates normal gonadotropin secretion and pubertal progression.<sup>[17]</sup>

## SHALL WE TREAT OR NOT?

The challenging question is always shall we treat or not? This question becomes easier to answer if we consider some facts in the natural history of the condition.

1. Although in majority of cases spontaneous pubertal development will "kick in," the pubertal onset is unpredictable and the average delay is around 3 years (i.e., a state of HH for a long time)
2. Many boys do not attain their mid-parental nor their predicted adult Ht and a good percentage of them end short for their parents and population
3. Many of them have combined CDGP and familial short stature
4. Methods for prediction of the final Ht are not reliable in CDGP
5. There is some evidence that this prolonged, although

**Table 1: Different endocrine tests to differentiate constitutional delay of growth and puberty from hypogonadotropic hypogonadism [modified from 12-16]**

Test	CDGP	HH
Testicular volume	> 4 mL	< 4 mL
Basal T	>1.7 nmol/L	< 1.7 nmol/L
T response to hCG (1500 U EODIMX3) <sup>[13]</sup>	> 8 nmol/L	< 3 nmol/L
LH after GnRH test (Nafarelin 0.1 mg/m <sup>2</sup> ) <sup>[14]</sup>	Increment > 4.6 U/L	Increment < 2 U/L
LH (3 h) after triptorelin (0.1 mg/m <sup>2</sup> ) <sup>[12]</sup>	LH > 14	LH < 14
T after hCG $\times$ 3 days <sup>[12]</sup>	T > 9 nmol/L	T < 9 nmol/L
LH (4 h) after decapeptyl (0.1 mg/m <sup>2</sup> ) <sup>[13]</sup>	LH > 8 U/L	LH < 8 U/L
T (7 <sup>th</sup> day) after hCG $\times$ 3 (EOD) <sup>[13]</sup>	T > 8 nmol/L	T < 8 nmol/L
T after 24 h of IM low-dose hCG (15 U/kg-once) <sup>[15]</sup>	T > 6 nmol/L	T < 6 nmol/L
LH after low-dose GnRH (10 mcg IV) <sup>[16]</sup>	++ Response	No response

CDGP: Constitutional delay of growth and puberty, HH: Hypogonadotropic hypogonadism, LH: Luteinizing hormone

transient, state of hypogonadism might affect the bone mineral content or the total bone mass of adults who had CDGP, although this is not universally accepted

- In addition; the effect of this state of hypogonadism on the onset and progression of spermatogenesis, follicle stimulating hormone (FSH and T are both required for initiation and maintenance of spermatogenesis in animal and human studies) and future fertility is still not studied
- The association of CDGP associated with incompetence and vulnerability, impaired self-esteem, reluctance to participate in athletic activities, social isolation, impaired academic performance, substance abuse and disruptive and suicide behavior have been shown in many, but not all, studies to be significant. In fact, until now the most common reason behind treating these adolescents is psychological stress experienced by the child or his parents.<sup>[6,18-23]</sup>

## ANDROGEN THERAPY, WHAT IS THE OPTIMAL TIMING, DOSE AND DURATION OF TREATMENT?

The most common drug used to treat this condition is depot T injections. Compared with other regimens, short- course low-dose depot T IM is an effective, practical, safe, well-tolerated and inexpensive regimen [Table 2]. However, some unresolved issues in the management include: the effect of androgen on inducing maturation of hypothalamic-pituitary axis, and the type, optimal timing, dose and duration of androgen treatment.<sup>[24]</sup>

Are we using androgens to sensitize/stimulate the hypothalamic-pituitary-gonadal axis to accelerate the onset of puberty? Or are we only replacing this transient, although long (2–3 years), hypogonadal state?

In fact, some good evidence of acceleration of the onset of central puberty in some boys with CDGP are proved with enlargement of the testes, during or in the 3–4 months following short course of T therapy

(3–4 months) documenting the start of normal spontaneous gonadotropins secretion by the pituitary. Stimulation of true early puberty by excessive androgen in undertreated congenital adrenal hyperplasia is another example of T stimulation of puberty in boys and girls. However, some patients with CDGP require longer and/or repeated courses of T to induce onset of true puberty (18 months). It appears that some patients need prolonged replacement until maturation of their hypothalamic-pituitary-gonadal axis evolves.<sup>[25-30]</sup>

## MONITORING ISSUES AND TAILORING TESTOSTERONE THERAPY TO SIMULATE PHYSIOLOGIC MATURATION

T, a natural androgen, is an acceptable physiologic replacement in this transient hypogonadal state. Short-term results of variable doses and duration of T therapy seem to be satisfactory [Table 2]. However, studying the pattern of normal T secretion in boys during normal puberty shall be our reference for the proper use of T therapy.

During normal puberty, normal T secretion has the following characteristics:

- Gradual increase of circulating T levels with progression of puberty from Tanner II to Tanner V stages, correlated with testicular volume
- The intra-testicular T, under the effect of luteinizing hormone (LH), is 50–100 times more than circulating T concentration
- Episodic secretion of testicular T with a higher early morning circulating level 4. T secretion is associated with increasing secretion of FSH through puberty; both appear critical for the beginning of spermatogenesis.<sup>[31-35]</sup>

The clinical challenge is to tailor T replacement to induce puberty and optimize total skeletal growth without inducing premature fusion of the growth plate and to avoid any harmful effect on spermatogenesis. In other words, T therapy should be adjusted to simulate the gradually increasing circulating levels of T from Tanner II (average 60–150ng/dL) to Tanner III (150–250ng/dL) to

**Table 2: Androgen therapy in constitutional delay of growth and puberty used in different studies [modified from 16-24]**

Dose/route	Duration (mon)	Growth	HtSDS during treatment	Final Ht/Bone age during treatment	Puberty
T 200 mg IM	Q 3 weeks × 4 months	Increased	Increased	Not affected	Accelerated
T 100 mg IM	Q month × 4 months	Increased	Increased	Not affected	Accelerated
T 100 mg IM	Q month × 6 months	Increased	Increased	Not affected	Accelerated
T 50 mg IM	Q month × 4 months	Increased	Increased	Not affected	Accelerated
T 1 mg/kg IM	Q month × 20 months	Increased	Increased	Not affected	Accelerated
T 40 mg PO	Daily × 6 months	Increased	Increased	Not affected	Accelerated
Oxandrolone 2.5 mg PO	Daily × 3–7 months	Increased	Increased	Not affected	Accelerated

T: Testosterone, Ht: Height, HTSDS: Height standard deviation score

Tanner IV (250–500 ng/dL) to Tanner V (500–750 ng/dL). In order to do that it is advisable to start with lower dose (e.g., 15 mg every 2 weeks monthly) of one of the long-acting esters (enanthate or cypionate) and gradually increasing the dose by 5 mg every 2 months.

Different T doses have been used by many authors with apparently satisfactory results.<sup>[17,36-42]</sup> The question is: can we achieve these levels of circulating T with the above used doses? Measurement of serum T levels is the most cost-effective way of monitoring T replacement therapy. In patients being treated with T enanthate or cypionate, serum T levels should be in the mid-normal range (as required) 1 week after the injection. If nadir levels 14 days after the injection are low, the interval between injections may be shortened.<sup>[36]</sup>

Monitoring T level at the end of the month or before injecting the next dose will help to decide when to stop the injection. Serum T = or > 100 ng/dL at that time points out to enough endogenous production of T and maturation of the hypothalamic-pituitary-gonadal axis. Most adolescents with CDGP need between 6 and 18 months of T therapy before maturation of their hypothalamic-pituitary-gonadal axis.<sup>[43-47]</sup>

Average circulating T concentrations after different doses of IM T doses are summarized in Table 3. It is clear that even with the low dose of T (50 mg per month), T blood level may exceed the physiological required dose (for 10–15 days per month). Although most drug delivery devices may be appropriate for full adult androgen replacement, these doses are too large for the induction of puberty. Oral T (undecanoate), because of its short half-life and wide fluctuation of serum T level is not an ideal for androgen replacement. At present, the injectable form is the only one that is easily adaptable for the increasing amounts of androgen necessary for the various stages of pubertal development.

It appears that a protocol of twice monthly injections of low doses of T with a gradual and periodic increase in the dose would approach the physiological level of serum T appropriate for the early and middle stages of puberty in

males with CDGP. A suggested protocol is as following: T enanthate IM 15 mg Q 2 weeks for 2 months; then T enanthate IM 20 mg Q 2 weeks for 2 months; then T enanthate IM 25 mg Q 2 weeks for 2 months; then T enanthate IM 30 mg Q 2 weeks for 2 months; then T enanthate IM 35 mg Q 2 weeks for 2 months; then T enanthate IM 40 mg Q 2 weeks for 2 months; then T enanthate IM 45 mg Q 2 weeks for 2 months; then T enanthate IM 50 mg Q 2 weeks for 2 months; then T enanthate IM 60 mg Q 2 weeks for 2 months.

## CONSTITUTIONAL DELAY OF GROWTH AND PUBERTY AND SPERMATOGENESIS

Normal spermatogenesis occurs early in puberty before the peak growth spurt. It may occur with the early appearance or even before the appearance of pubic hair and testes growth. For spermatogenesis to be initiated, concentrations of T well in excess of those are needed to maintain androgen effects in other regions of the body. LH-induced T secretion is associated with age-appropriate gonadotropin production. In the normal testis, LH stimulates Leydig cells and this provides the testis with high local T to act directly on the androgen receptor AR to maintain sperm production. In the T-suppressed testis (using exogenous T), the low intratesticular T may not be able to initiate or maintain spermatogenesis. FSH is important for Sertoli cell function necessary for beginning of spermatogenesis. In rat, monkey, and human models, FSH and androgens act both separately and synergistically to support a range of key events in spermatogenesis, from spermatogonial stem cell division through to final sperm release. In addition, gonadotropins regulate germ cell survival in normal adult men.<sup>[48-55]</sup> Information about the effect of delayed puberty and/or androgen therapy on future (adult) spermatogenesis and fertility are lacking and need to be studied.

## HUMAN CHORIONIC GONADOTROPIN VERSUS T THERAPY, ADVANTAGES AND DISADVANTAGES

Human chorionic gonadotropin (hCG), mainly with LH activity, can be used to induce puberty in CDGP. The half-life in serum is biphasic at 11 and 23 h with renal elimination; 10–12% within 24 h. In idiopathic hypogonadism, treatment with hCG 1500 U twice weekly, either SC or IM, for 6 months, keeps T level (and testicular size) in the normal level range similar to normal early puberty. In fact, hCG doses can be easily tailored (because of frequent injections) to give the required level of circulating T. During hCG therapy, there is diurnal variation in T, with peak serum levels in the morning falling to a nadir in the evening. In

**Table 3: Average serum concentrations of T after T depot injection**

Testosterone dose IM/month	Serum T 7 <sup>th</sup> day	Serum T 15 <sup>th</sup> day	Serum T 30 <sup>th</sup> day
50 mg	540 ng/dL	140 ng/dL	67 ng/dL
100 mg	586 ng/mL	156 ng/dL	54 ng/dL
200 mg	1500 ng/dL	350 ng/dL	125 ng/dL



adult males with HH, hCG (5000 IU IM twice/week) can maintain normal adult level of serum T and may be sufficient to induce spermatogenesis without FSH. The use of hCG therefore appears to be more physiologic and potentially safer than T in the timely initiation of spermatogenesis and testicular growth in boys with CDGP. Short-term results of hCG and T therapy in CDGP revealed comparable results. However, HCG is more expensive and requires multiple injections.<sup>[33,48,56-62]</sup>

## OTHER FORMS OF TREATMENT

### Low-dose oxandrolone

Low-dose Oxandrolone (0.1 mg/kg/day, 2.5 mg/day for 3–12 months) is associated with mean increment of Ht growth velocity during treatment, which is maintained after treatment, with no significant change in Ht for bone age standard deviation scores and no change in final Ht. The possible use of oxandrolone earlier in the course of CDGP may be an advantage of this therapy and allows the use of other form of therapy later on if puberty is delayed.<sup>[63,64]</sup>

### Addition of aromatase inhibitor

An aromatase inhibitor, e.g., letrozole (2.5 mg/PO) in addition to T (1 mg/kg/month for 6 months) appears to improve (increase) the final Ht to approach mid-parental Ht versus T + Placebo.<sup>[65,66]</sup> In fact, these results indirectly point out to a negative effect of using even low dose of T therapy on the final Ht of these patients.<sup>[65,66]</sup>

### The use of dihydrotestosterone

Dihydrotestosterone (DHT) (50 mg IM every 2 weeks, for 4 months) is associated with appearance of secondary sex characteristics (Tanner II), increased lean body mass and decreased % body fat with no change in IGF-I, mean nocturnal GH, and estradiol (E2) concentrations.<sup>[67]</sup> In theory, lack of E2 effect may increase the potential for final Ht, as with adding aromatase inhibitor; however, these long-term studies about the effect on final adult Ht are lacking.

### Growth hormone treatment for constitutional delay of growth and puberty

According to FDA-approved guidelines, boys whose Ht predictions fall to 160 cm or less are considered for treatment with recombinant growth hormone (rechGH). However, none of the available methods of prediction are sufficiently sensitive to reliably recruit 14 to 16-year-old boys with CDGP whose final Ht will fall at or below 160 cm.<sup>[68-70]</sup> Before the onset of puberty, many boys with CDGP are short (HtSDS < -2) and have delayed bone age versus their chronological age. GH treatment for boys ( $n = 36$ ) with non-familial short children with delayed

bone age, started at an average age of 9.3 years (using 0.6 U/ kg/ week divided on daily doses) resulted in a Ht gain of 1.4 SD at the final Ht. In one study, oxandrolone (2.5 mg/day for 3 months) was compared to GH therapy (20 U/m<sup>2</sup>/week for 12 months). Although both treated groups had accelerated growth velocity, the growth rate was better in the oxandrolone group. In this study, the older age of the boys (mean age = 13.9 years) and the short duration of therapy (12 months) could have affected the response to GH in these boys. Other short-term studies did not find significant effect of GH on final Ht in these boys. These data demonstrate the potential benefit of GH therapy if started early and used for longer duration in markedly short patients with CDGP. It may be an early useful adjunct to later androgen therapy in those children with poor prognosis for final Ht (i.e., those who had decelerated growth rate in early childhood, and those with short predicted adult Ht).<sup>[11]</sup>

Moreover, in a good number of boys, CDGP is associated with familial short stature.<sup>[10]</sup> The latter showed fairly good response to GH therapy. A meta-analysis of GH treatment for idiopathic short stature showed favorable response on the short-term growth rate as well as on the final Ht; this effect appears to be dose dependent.<sup>[71-74]</sup> The safety of GH treatment in pre-pubertal short boys on testicular size and T secretion was assessed and it appears that GH has no negative effect on both.<sup>[75]</sup>

Recently, it has been shown that boys with CDGP have increased total energy expenditure associated with relative deficiencies in T and lower IGF-I concentrations. Whether added nutritional supplements, alone or in combination with GH, which proved useful in many hypermetabolic states, could improve the growth pattern and final Ht of these children deserves further study.<sup>[76]</sup>

## CONCLUSION AND MAIN POINTS

The differential diagnosis of delayed puberty in boys is essentially that of HH. The most common form of this is CDGP, which entails delayed onset of puberty but normal progression to normal adult. However, this diagnosis can only be reached after excluding other causes that lead to permanent HH, which cannot be diagnosed until late.

Diagnostic evaluation of an adolescent with delayed puberty includes detailed history and physical examination, including previous and present auxological parameters and bone maturation. Familial history is useful to support the diagnosis of CDGP. General hematological and biochemical parameters are useful to rule out some chronic systemic conditions that may present only by delayed growth and puberty. Basal hormonal study includes measurement of

serum concentrations of gonadotropins (LH, FSH), T, prolactin, and thyroid hormones. Evaluation of GH-IGF-I axis may be indicated in some cases keeping in mind that IGF-I and IGFBP-3 levels are sex and age specific; they should be interpreted using skeletal age rather than chronologic age. Moreover, GH provocative testing may also yield falsely low values in some peri-pubertal individuals with CDGP unless they are primed with sex steroids.

An MRI of the hypothalamic-pituitary area may be necessary in subjects with rapid deceleration of growth rate, those with symptoms and/or signs suggesting increased intracranial pressure, or history of head trauma, and those with abnormal GH response to provocation. A karyotype is indicated in short girls with delayed puberty and in males with hypergonadotropic hypogonadism.<sup>[1-4]</sup>

HH is a lack of T in male patients secondary to hypothalamic or pituitary (low LH and FSH secretion), which may be transient (CDGP) or permanent. Boys aged 14 years or older should be suspected of being hypogonadal if they have underdeveloped testes and lack of secondary sexual characteristics. The benefits of T replacement therapy may include accelerating growth rate and inducing pubertal onset, but it shortens pubertal duration with apparently no adverse effect on final adult Ht. Androgen therapy appears to improve psychosocial function and assures normal bone mineral accretion during the critical period of adolescence and improves muscle mass and strength. Injection of low-dose of T enanthate or cypionate every 2–4 weeks or hCG twice weekly and gradual increase of doses to simulate physiological progression of puberty and maintain serum T levels in the mid-normal range (as required) 1 week after the injection appears to be a good goal. The use of low dose of oxandrolone between 12 and 14 years may offer an advantage of increasing growth rate without compromising adult Ht. The wise and early use of GH treatment with nutritional supplementation in some of these boys may be useful but remains to be proven.<sup>[69-76]</sup>

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