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Constitutional Delay of Growth and Puberty

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Abstract: Constitutional delay of growth and puberty (CDGP) is one of the most frequent reasons for referral of short children to pediatric endocrinologists. The cardinal features of CDGP are generally short stature with delayed skeletal maturation (usually in keeping with the height-age) and delayed sexual maturation (in keeping with the bone-age rather than chronologic age). Predicted adult heights are generally within the normal range for family, and no hormonal or biochemical evidence of disease is present. Many of these children are identified before the pubertal years and are referred to as having constitutional growth delay. Although CDGP has been considered a normal variant of growth and development, it is not without physical and psychosocial consequences. A relatively short sitting height is a consistent finding and contributes to a modest diminution of final adult stature. Although reduced bone mineral density has also been described, recent studies in adults with a history of CDGP suggests minimal impact on bone mineralization if skeletal size is factored into the measurement. Timely therapy in selected cases might have a beneficial affect by minimizing the negative psychosocial impact that frequently accompanies this condition.

Key Words: constitutional delay of growth and puberty, constitutional growth delay, delayed puberty

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Learning Objectives:

- Identify the characteristic features and pathophysiology of constitutional delay of growth and puberty (CDGP).
- Explain the approach to diagnosis of CDGP, including differential diagnosis.
- Describe available treatments and when treatment is appropriate.

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Constitutional delay of growth and puberty (CDGP) is one of the most frequent reasons for referral of short children to pediatric endocrinologists. In general, children with CDGP have 1) short stature with a height standard deviation score (SDS) that is ≤ -2 standard deviations (SD) for chronologic age or target height; 2) height velocity below 25th percentile for chronologic age; 3) delayed bone age; 4) no evidence of systemic illness, genetic syndrome, or endocrine disorder; and 5) pubertal onset at an age greater than +2 SD of average maturers (>14 years in boys and >13 years in girls).

Although the majority of children are identified during peripuberty with slowing of linear growth and pubertal delay, these children have a characteristic pattern of growth from early infancy and may be identified at varying ages. Children identified before the pubertal years are generally referred to as having constitutional growth delay.

GROWTH PATTERN

Characteristically, there is retarded linear growth that occurs during infancy.[1] Growth deceleration might first become apparent as early as 3–6 months of age. The retarded linear growth is greatest in the first 2 years of life, and these children frequently fall more than 2 SDs below the mean for height by 3 years of age. During this period of subnormal growth, the skeletal maturation is delayed with the result that by age 3–4 years, the child is not only short, but also has a delayed bone-age. The pattern of weight gain generally mirrors the pattern of linear growth. As a result of the weight and height percentiles falling at similar rates, the "weight for height" generally remains normal.

A similar pattern of growth deceleration is seen in infants with familial short stature. However, the pattern of weight gain might differ between these 2 conditions with constitutional growth delay manifesting slower weight gain than children with familial short stature.[2]

After 3–4 years of age, the growth rate of children with constitutional growth delay is within normal limits, and their height percentile remains relatively constant, with linear

growth parallel to, although frequently below, the 5th percentile.[1]

The onset of sexual maturation and the pubertal growth spurt is delayed. Beginning at approximately age 12 years in males and approximately 10 years in females, the patient's peers increase their height as a result of their own growth spurt, whereas the child with CDGP does not. The increasing height discrepancy between the patient and his or her peers is evident on the growth chart, particularly those derived from cross-sectional data [National Center for Health Statistics (NCHS) growth charts]. The apparent growth failure during peripuberty on such charts frequently prompts referral to a pediatric endocrinologist.

PATHOGENESIS

There is a continuum of normal growth hormone secretion that contributes to the population variance in growth and maturation.[3] There is some suggestion that those with the lowest growth hormone secretion manifest CDGP. Many children with CDGP have been found to have subnormal spontaneous GH release[4] or response to provocative stimuli.[5] In addition, GH therapy has been shown to result in an acceleration of the growth rate in constitutional growth delay.[6] However, Lanes et al. did not find decreased GH secretion in prepubertal children with constitutional growth delay.[7] In addition, when spontaneous puberty does occur in CDGP, GH secretion and IGF-I levels increase normally.

FREQUENCY

CDGP is estimated to be 5 times more common in boys as in girls. The male sex predominance might be the result of an ascertainment bias. Girls begin puberty earlier than boys and the growth spurt in girls is an early pubertal event, in contrast to boys in whom the growth spurt is a late pubertal event. Therefore, even if there is pubertal delay in a girl, she will not have to wait as long as a boy for pubertal growth acceleration. In addition, social attitudes might result in more psychosocial problems in boys with short stature than girls and therefore prompt more growth consultations in boys. However, it is also possible that the frequency distribution of timing of onset of puberty is skewed to the right in males (CDGP more common) and skewed to the left in females (idiopathic precocious puberty more common), consistent with the general experience of pediatric endocrinologists. This would suggest a sexually dimorphic pattern in the reactivity of the hypothalamic-pituitary-gonadal axis. Such a sex difference in the pituitary response to GnRH has been described by Stanhope and colleagues who demonstrated that girls release gonadotropins more readily in response to a given GnRH stimulus than do boys.[8] This might also explain the earlier onset of puberty in females.

APPROACH TO DIAGNOSIS

Infancy

In a child with subnormal growth and weight gain in the first 3 years of life, close attention should be placed on the "weight for height." As long as the weight for height percentile remains in the normal range, the major differential diagnoses include constitutional growth delay and genetic short stature. A family history of CDGP would be supportive of the former, whereas short family members make the diagnosis of genetic short stature more likely. If the "weight for height" percentile falls progressively, a more detailed evaluation is warranted focusing on caloric intake, bowel movements, pattern of drinking and urination with testing of electrolytes and thyroid function. Careful longitudinal monitoring of growth is important to ensure that the linear growth beyond 3–4 years is parallel to the 3rd percentile and that weight gain is normal.

Childhood (3–12 Years in Males, 3–10 Years in Females)

It is important to note that the shorter children grow more slowly than taller children, and that both males and females, growing along the 3rd percentile, have a growth velocity of <5 cm per year beyond age 8 years.

Evaluation of such a child will depend on the index of suspicion. With a family history of CDGP, a delayed bone-age, and otherwise healthy child, careful longitudinal follow up without any laboratory testing might be adequate. With limited prior growth data and the absence of a family history of CDGP, exclusion of an occult cause of growth failure is important and initial investigations should include blood count, sedimentation rate, blood chemistries, urinalysis, thyroid function, and measurement of the growth hormone-dependent protein (IGF-I and/or IGFBP3).

A very short boy with constitutional growth delay might be considered for anticipatory therapy (see "Therapy") at approximately age 12 years.

Peripubertal Region and Beyond

When linear growth is followed on the NCHS growth charts, children with CDGP will appear to have significant growth failure beyond age 12 in males and age 10 in females. This is primarily the result of the child being compared (on the growth chart) with a group of children, most of whom are entering puberty and experiencing pubertal growth acceleration. Many conditions such as asthma, celiac disease, inflammatory bowel disease, chronic glucocorticoid use, and renal disease can mimic CDGP and should not be overlooked.[9] Careful physical examination should be performed to look for stigmata of Turner syndrome, signs of thyroid disease, visual field defects, funduscopic abnormalities, and skeletal disproportion. Pubertal status should be assessed and growth velocity calculated over a 4- to 6-month period.

The history, physical examination, and growth velocity should enable the diagnosis to be made in the majority of cases without recourse to extensive biochemical investigations. Assessment of skeletal maturation by bone-age provides an indication of residual growth potential. The presence of other symptoms such as headaches, a borderline growth velocity, or incongruity in the pattern of pubertal development should raise suspicion and warrant biochemical investigation.

DIFFERENTIAL DIAGNOSIS

When evaluating a 14- to 15-year-old boy with short stature, pubertal delay, and low gonadotropins, the most likely diagnosis is CDGP. However, 2 alternate conditions should be considered. First, hypogonadotropic hypogonadism might present with delayed or arrested puberty. It is extremely difficult to distinguish between CDGP and hypogonadotropic hypogonadism, and there is no single practical test that can adequately differentiate patients with these 2 conditions.[10] A history of micropenis, cryptorchidism, or anosmia would make the diagnosis of hypogonadotropic hypogonadism more probable. Fortunately, the initial androgen therapy in both these conditions is the same. Only in CDGP will enlargement of testicular volume and pubertal progression occur.

The second diagnostic consideration in the differential diagnosis in a short child with delayed puberty is isolated growth hormone deficiency. Although identification of growth hormone deficiency before starting androgen therapy would be ideal, it appears that growth hormone deficiency, in the setting of CDGP, is frequently overdiagnosed. Adan and colleagues, for example, demonstrated that 21 boys with CDGP studied at ≥14 years of age who had an initial peak growth hormone in response to arginine-insulin testing of <10 ng/mL increased their peak growth hormone levels to >10 ng/mL after 2 months of long-acting testosterone therapy.[11] Therefore, non-sex steroid primed growth hormone testing should be interpreted with caution in children with delayed puberty. This is especially true in obese subjects in whom GH secretion is reduced.[12] As a screening procedure, measurement of IGF-I and IGFBP3 might be adequate. If these levels are appropriate for Tanner stage, one might consider a short course of androgen therapy (low-dose intramuscular testosterone for 3–6 months). In this case scenario, androgen therapy is both diagnostic and therapeutic. Doubling of the growth rate is seen in boys with CDGP but not with GH deficiency, because much of the growth response to testosterone is dependent on enhanced GH secretion. Enlargement of the testicles is indicative of normal gonadotropin secretion. If the individual does not have a good growth response to testosterone or does not show testicular enlargement, this suggests GH deficiency, gonadotropin deficiency, or both.[13,14]

As puberty progresses in children with CDGP, there remains the normal relationship between the stages of puberty and the growth spurt. The absence of growth acceleration at a testicular volume of 10 mL or with breast development would necessitate further investigation.[15]

CONSEQUENCES OF CDGP

Adult Height and Body Proportions

A number of studies have looked at the effect of delayed puberty on final adult height attainment. Table 1 provides the data from 3 retrospective studies in which untreated patients with CDGP were identified from clinic records and subjects were contacted for measurement of final adult stature. Subjects in all studies were of extremely short

TABLE 1. Anthropomorphic Data of Individuals with CDGP

Authors	Subjects	Initial Ht SDS (mean ± SD)	Target height (mean ± SD) (SDS ± SD)	Final height (mean ± SD) (SDS ± SD)	Mean height deficit (target-final height)
Crowne et al., 1990[25]	43 males	−3.4 ± 0.6	170.6 ± 4.8 −0.6 ± 0.7	164.1 ± 6.0 −1.6 ± 0.9	6.5cm ($P < 0.001$)
Crowne et al., 1991[45]	15 females	−3.4 ± 0.9	157.6 ± 4.2 −0.8 ± 0.7	153.0 ± 4.9 −1.5 ± 0.8	4.6cm ($P < 0.001$)
La Franchi et al., 1991[46]	29 males	−2 to −5 SD	174.6 ± 4.5 −0.3 ± 0.7	169.5 ± 4.5 −1.2 ± 0.7	5.1cm ($P < 0.002$)
	13 females	−2 to −5 SD	161.7 ± 5.5 −0.3 ± 0.9	156.4 ± 3.8 −1.3 ± 0.6	5.3cm ($P < 0.002$)

*Height in centimeters.
CDGP: constitutional delay of growth and puberty; SD: standard deviation; SDS: standard deviation score.

height, SDS<-2 at initial evaluation. In none of the studies did the individuals reach their target heights. The mean height deficits (target height - final height) ranged from 6.5–4.6 cm.

When the pubertal growth spurt occurs in patients with CDGP, its duration, peak height velocity, and consequently the total pubertal height gain are reduced. If this were counterbalanced by increased prepubertal height gain, final height would not be compromised. However, during late prepuberty or early puberty, height gain is mainly the result of growth in the lower segment and spinal growth is relatively stunted. As a result, if puberty is delayed, spinal growth is more compromised so that when growth acceleration occurs, body disproportion is already recognized. The more delayed the puberty, the more severe the disproportion. During the pubertal growth spurt, spinal growth does not seem to compensate for the previous deficit. At final height, eunuchoid proportions are still present in most patients.[16,17] Therefore, there appears to be a critical period during which normal spine growth can occur.

Bone Mineral Density

Bone mass increases during the adolescent growth spurt with very little gain after linear growth ceases.[18,19] Peak spinal bone density is achieved at a relatively young chronologic age (15 years in females and 17 years in males). In 1992, Finkelstein and colleagues reported that adult men with a history of CDGP had reduced bone density.[20] This report suggested that there might also be a critical window during which normal bone density can be achieved and that delayed puberty might have a deleterious effect on the achievement of peak bone mass. However, 2 observations challenged the notion that a critical window exists for optimal accretion of bone mineral. First, the studies reporting that adults with a history of CDGP had reduced bone density used areal bone density (aBMD) by dual-energy x-ray absorptiometry (DEXA) for comparison to controls.[20,21] Because aBMD is known to be influenced by bone dimensions and skeletal growth,[22,23] and CDGP affects height[24,25] and impairs spinal growth,[17] it is possible that findings of reduced BMD might be the result of uncritical use of DEXA. Bertelloni and colleagues therefore investigated apparent volumetric bone mineral density (vBMD) in men with CDGP and found that although vertebral aBMD was indeed reduced, vBMD was normal.[26] Second, the normalization of bone density in individuals with aromatase deficiency treated with estrogen as late as the 4th decade suggests the timing of bone mineral accretion might not be critical.[27,28]

Psychologic

Children with CDGP frequently are not able to compete equally in sports and tend to be regarded and treated as immature. Delayed physical development at this crucial time for adjustment and personality development might result in psychologic problems. Poor self-esteem and social withdrawal have been described.[29–31] In a study controlling for intelligence, boys with CDGP were shown to score significantly lower than early or mid maturing boys in educational achievement, aspirations, and expectations.[32] The negative impact of CDGP on self-esteem and psychosocial achievement might persist into adulthood.[29,33] It is not clear whether the psychologic impact on children with CDGP results from short stature, delayed sexual development, or both.

THERAPY

In most cases, the only treatment that is necessary is reassurance that growth and pubertal development will occur and that the final adult height will be relatively normal relative to the parental heights. Often the knowledge that one of the child's parents had the same pattern of growth is reassuring. However, in some children, CDGP can result in significant psychologic difficulties and reassurance will not be sufficient. Sex steroid therapy in these cases decreases the distress caused by growth and pubertal delay.[34] Another potentially beneficial effect of sex steroid therapy is minimizing the segmental body disproportion that might have resulted had the puberty occurred much later.[16]

Medical Therapy in CDGP

Testosterone is generally limited to boys whose bone-age is 12 years or greater.[35] Fifty to 100 mg of depot-testosterone monthly is given for 3–6 months. Because normal pubertal growth requires both androgen and an increase in GH production,[36] a rapid increase in growth velocity essentially excludes the possibility of GH deficiency and obviates the need for GH stimulation testing. Most of the testosterone administered will have been cleared by approximately 15 days after the injection, allowing adequate time for the hypothalamic-pituitary axis to recover from any suppression induced by testosterone.[37] If during this course of therapy, signs of puberty (testicular enlargement) are noted and progress after discontinuation of sex steroids, the diagnosis of CDGP is confirmed.

Oxandrolone is a non-aromatizable androgen with predominantly anabolic activity and weak androgenic activity. Because of the weak androgenic activity, oxandrolone has been used to promote growth in both females as well as males with CDGP. It should not be used in very young boys because this could result in both acceleration of bone-age and onset of precocious puberty.[38] Adult height is not affected by oxandrolone.[39–41]

Because of the rarity of CDGP in females, there are no studies that address the issue of estrogen therapy in girls with CDGP. As a result, there is little consensus about the optimal treatment of CDGP in females.[42] Low doses of oxandrolone (0.1 mg per day) have been used successfully in girls with CDGP.[40] Low-dose ethinyl estradiol (0.05–0.1 μg/kg per

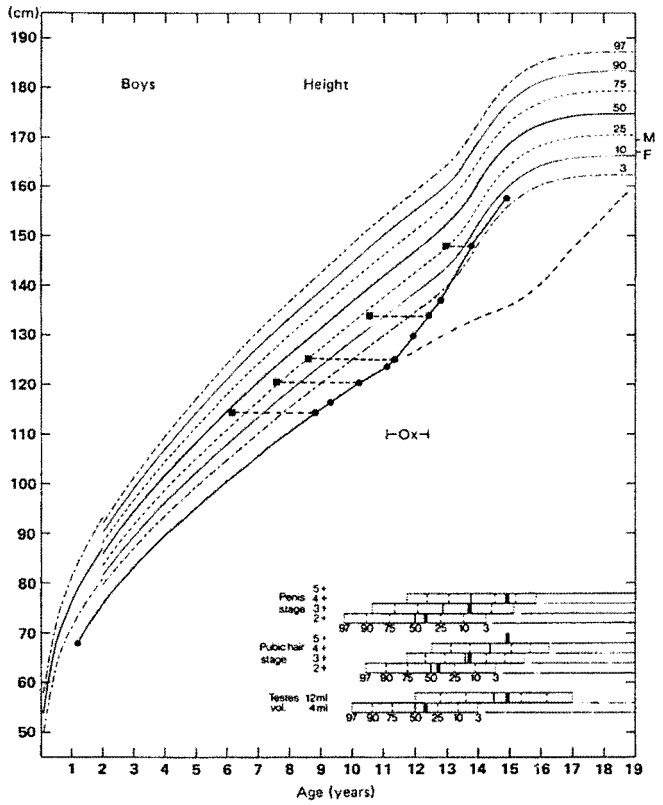

FIGURE 1. Growth data from a prepubertal boy with growth delay who was treated with low-dose oxandrolone (1.25 mg per day) from age 11.1 years for 1.3 years. The dotted line represents predicted pattern of growth if he had been untreated. By age 13.8 years, his testicular volume was 8 mL (genital stage 3), and he would not have been expected to have achieved the spontaneous growth spurt of puberty. By this age, he was 16 cm taller than he would have been without treatment. By 14.9 years, he had attained genital stage 4 and 12 mL testicular volumes so that his induced growth spurt from anabolic steroid treatment had become indistinguishable from the spontaneous growth acceleration of puberty. Ox = oxandrolone. Solid squares represent bone-age. Parental percentiles are shown on the right-hand border. Reproduced with permission from Papadimitriou A, Wacharasindhu S, Pearl K, et al. Treatment of constitutional growth delay in prepubertal boys with a prolonged course of low dose oxandrolone. *Arch Dis Child.* 1991;66:841–843.

day) for 3–12 months has been used with variable height velocity and breast response. A dose of 0.3 mg of conjugated estrogens (Premarin; Wyeth-Ayerst Laboratories, Philadelphia, PA) on alternate days or daily for several months is another option. If after temporary discontinuation of sex steroid, the estradiol level remains in the pubertal range and puberty progresses, the diagnosis of CDGP is confirmed.

It is not surprising that growth hormone therapy improves the short-term growth in children with CDGP.[43] However, long-term growth hormone treatment has not been found to improve adult height. Growth hormone offers little advantage when compared with the simple, cheap, and effective androgen therapies.

ANTICIPATORY TREATMENT

Children with CDGP are frequently identified well before they have delayed puberty. Because both growth deceleration and late spontaneous growth spurt are anticipated, some have advocated oxandrolone therapy at an earlier age to prevent the psychologic difficulties associated with CDGP in the pubertal years.[44] A prolonged (approximately 1 year) course of oxandrolone given to a boy with constitutional growth delay starting at approximately age 12 years allows earlier growth acceleration (normal boys only begin their growth spurt at a testicular volume of 10 mL) and, hopefully, the achievement of a height in the normal range at such a critical time for emotional, educational, as well as physical development (Fig. 1).

CONCLUSION

Although CDGP is considered a normal variation of growth and development, there are both psychologic and physical consequences. A relatively short-sitting height is a consistent finding in CDGP, suggesting that normal vertebral growth occurs at a relatively early age and might not be achievable in children with delayed puberty. Although reduced bone mineral density has also been described, recent studies in adults with a history of CDGP suggests minimal impact on bone mineralization if skeletal size is factored into the measurement.[26]

Although final adult height is not increased with androgen therapy in boys with CDGP, it is possible that bringing forward the timing of puberty into the normal range might permit a greater final stature than would have occurred if spontaneous puberty had been extremely delayed. However, therapy in constitutional growth delay and CDGP should not be based on auxology, but rather on the emotional and psychologic impact the condition is making on the child. In selected cases, relatively early treatment might be warranted, not only for psychologic reasons, but also to potentially minimize segmental body disproportion that accompanies significant pubertal delay.

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