

“Constitutional delay of growth and puberty in boys: a literature review”

Summary

In this article, the authors reviewed the literature covering 10 years of constitutional growth retardation and pubertal delay in boys. They examined contemporary reviews on the etiopathogenesis, clinical presentation, diagnosis, and treatment of constitutional growth retardation and pubertal delay.

Therefore, this review focuses on the diagnosis, clinical, and general therapeutic approach to constitutional growth and delayed puberty and hypogonadotropic hypogonadism in males, which are difficult to differentiate. A thorough clinical history and physical examination should be performed. Delayed puberty is caused by constitutional growth and delayed puberty in the vast majority of children. They should be distinguished from the small proportion of boys with hypogonadism, a pathological condition. A number of laboratory tests can predict the onset of puberty and its progression. However, the advent of highly sensitive immunoassay systems and radiometric immunoassays for LH, FSH, and testosterone has not completely resolved these issues, as their values can overlap between normal and pathological conditions.

Keywords: constitutional growth retardation, puberty, boys

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Abbreviations: CDGSD, constitutional delay of growth and sexual development; DSP, delayed sexual development; HH, hypogonadotropic hypogonadism; FSH, follicle-stimulating hormone; LH, luteinizing hormone; FPD, familial delayed puberty; (Gn-RH), gonadotropin-releasing hormone; (EP), Early pubertal; (HH), hypogonadotropic hypogonadism; (CeH), X-linked central hypothyroidism syndrome; (fHH), functional hypogonadotropic hypogonadism; (LH-RH), luteinizing releasing hormone; (AMH), anti-Müllerian hormone; (INHB), inhibin B; (IGF-1), Insulin-like growth factor-1 levels; (PGIF-3), protein-bound insulin-like growth factor-3; (DHEA), dehydroepiandrosterone; (Gn-RH), gonadotropin-releasing hormone; (EP), Early pubertal; (IGSF1), immunoglobulin superfamily member 1; (CeH), X-linked central hypothyroidism syndrome; (VUCS), variants of unknown clinical significance; (hCG), human chorionic gonadotropin; (PAH), predicted adult height; (TcMT), (TAPMF), transcranial magnetic therapy; to a running alternating pulsed magnetic field; UK, United Kingdom.

Background

The growth and development of children is a valuable indicator of the public health and socioeconomic well-being of a society. Therefore, the study of adolescent sexual development is a pressing issue in pediatrics, driven by the progressive deterioration of the reproductive health of the population as a whole. One type of impaired sexual development in adolescents is delayed sexual development (DSP), i.e., the absence of secondary sexual characteristics by the age

of 14 in boys and 13 in girls, which is the upper age limit of normal puberty.¹⁻⁶

It is necessary to distinguish between hypogonadism and constitutional mental retardation, which is the most common form of impaired puberty in boys and accounts for 60–80% of all forms of delayed puberty.⁷

This definition provides a definition of constitutional delay of growth and sexual development (CDGSD). While CDGSD is a hereditary variant of normal growth and development occurring in both sexes and is unrelated to familial growth, nonconstitutional delay is secondary to various underlying disorders, such as chronic diseases, malnutrition, persistent psychological problems, or hormonal abnormalities. CDGSD occurs in both boys and girls and results in a normal final height within the familial growth range.⁸⁻¹³

Disturbances of puberty can have a significant impact on physical and psychosocial well-being. CDGSD is a common cause of delayed puberty; however, functional or permanent hypogonadism should be excluded. History and physical examination should include measurements of serum follicle-stimulating hormone, luteinizing hormone, and testosterone (for boys) or estradiol (for girls); and bone age radiography. Abnormal growth velocity requires assessment of serum thyroid function, prolactin, and insulin-like growth factor I. Boys 14 years and older and girls 13 years and older may benefit from sex steroids before the onset of puberty. Referral to a pediatric endocrinologist may be warranted after the initial evaluation.^{9, 10, 13}

Distinguishing hypogonadotropic hypogonadism (HH) from CDGSD is an important clinical problem. Basal inhibin B may offer a simple, discriminatory test if the results of recent studies are replicated. However, the authors emphasize that current literature does not support the recommendation of any diagnostic test for routine clinical use, making this an important area for future research.¹¹

Frequency and prevalence

Growth retardation is one of the most common forms of growth retardation. It occurs in children of both sexes, but is more common in boys. A combination of constitutional growth retardation and sexual development with elements of familial short stature is possible, which worsens the final growth prognosis. The prevalence of this condition among males reaches 1:40.

CDGSD, as is known, it is significantly more common in boys in a ratio approaching 9:1. Whether this ratio reflects a true prevalence of this disorder in boys is a matter of debate. Some authors believe that, in fact, CDGSD occurs with equal frequency in both sexes.

There is also a pathogenetic explanation for the true prevalence of CDGSD in boys, based on differences in the hormonal regulation of gonadal function in children of both sexes. Increased LH levels are necessary and sufficient to activate androgen production in the testicles of boys. Another gonadotropic hormone, FSH, plays a specific role in the male body only in spermatogenesis. The regulator of gonadotropic secretion, hypothalamic LH-RH, is synthesized in a pulsed mode and primarily ensures an increase in LH levels. FSH levels can increase even with LH-RH pulses of low amplitude and frequency. Therefore, it becomes clear that insufficient activity of the LH-RH secretory pulse generator leads to delayed puberty, including in boys.

Etiology

Late puberty syndrome is hereditary. Often, parents and/or immediate family members share the same developmental characteristics. Children are born with normal height and weight, then their growth rate slows, becoming more pronounced at 3-4 years of age. From 5-6 years of age, the growth rate returns to 5-6 years of age. 6 cm. However, due to their initially short stature, children remain short. The bone age of these children lags behind their chronological age by an average of two years, and puberty is delayed by two to four years. This type of growth retardation has a favorable prognosis for continued growth in these patients into adulthood.

Thirty etiologies underlying delayed puberty were identified. No markers of clinical significance could be identified in girls, while a history of cryptorchidism in boys was associated with an increased risk of permanent hypogonadism (odds ratio 17.2 (95% CI; 3.4-85.4, $P < 0.001$)). Conditions causing functional hypogonadotropic hypogonadism (fHH) were more common in boys with a growth velocity below 3 cm/year than in those who grew faster (19% vs. 4%, $P < 0.05$).

In this series, the most effective markers for discriminating prepubertal boys with CRH from those with congenital hypogonadotropic hypogonadism were testicular volume (1.1 ml with a sensitivity of 100% and a specificity of 91%), GnRH-induced peak LH (4.3 IU/L; with a sensitivity of 100% and a specificity of 75%) and basal inhibin B (INHB) level (61 ng/l; with sensitivity 90%, and specificity 83%).¹⁴

Various etiologic factors lead to the development of CDGSD syndrome by affecting the key link that triggers the pubertal impulse

secretion of hypothalamic LH-RH. The pathogenetic mechanisms of the multifactorial factors that lead to late activation of hypothalamic-pituitary function remain unclear. Only a few possible pathways for these disorders are considered.

As already mentioned, CDGSD in most cases is hereditary. According to authors¹¹, 70% of patients' parents had late puberty, with delayed puberty occurring in both parents in 37% of families, the mother in 30%, and the father in 33%. However, sporadic forms of the disease also occur. In such cases, unfavorable exogenous and endogenous factors are often present: pathological pregnancy and childbirth, low height and birth weight, an unfavorable social environment surrounding the child's growth and development, and parental alcoholism. Chronic infectious and systemic diseases are typically accompanied by delayed growth and puberty.¹¹

The leading causes are gastrointestinal diseases associated with impaired intestinal absorption (celiac disease, chronic pancreatitis, hepatitis). Chronic renal failure, severe heart defects, and chronic bronchopulmonary diseases are also associated with growth and pubertal delay. Many uncompensated endocrine diseases, such as hypothyroidism, diabetes mellitus, and Cushing's disease, are also associated with growth and puberty delay.

In isolated growth hormone deficiency, spontaneous puberty begins late, after 14-15 years of age. Long-term glucocorticoid therapy for somatic diseases or inadequately increasing the dose of replacement therapy for hypocorticism and congenital adrenal dysfunction lead to significant growth retardation and delayed puberty. Delayed growth and puberty can be observed both in cases of severe weight loss due to insufficient calorie intake or unbalanced nutrition (anorexia nervosa, attempts to lose weight on low-calorie diets), and in cases of excess weight and constitutional-exogenous obesity in adolescents. Nonphysiological excess energy expenditure, such as gymnastics, professional ballet, and others, is also often accompanied by delayed growth and puberty.

As the UK (United Kingdom).¹⁵ authors point out, CDGSD is an inherited condition that often segregates in an autosomal dominant pattern (with or without complete penetrance) in most families. However, the underlying neuroendocrine pathophysiology and genetic regulation are largely unknown. More recently, new discoveries in next-generation gene sequencing have provided insight into the genetic mutations that lead to familial delayed puberty (FPD). Further insight has come from the sequencing of genes known to cause GnRH deficiency, next-generation sequencing studies in patients with early puberty, and large-scale genome-wide association studies in the general population. The results of these studies suggest that the genetic basis salary is likely to be highly heterogeneous. Abnormalities in the development of GnRH neurons, function and its descending pathways, metabolic and energy homeostatic disturbances, and transcriptional regulation of the hypothalamic-pituitary-gonadal axis may lead to the salary. This diversity of different pathogenic mechanisms influencing the release of the pubertal "brake" may occur in several age windows between fetal life and puberty.¹⁵

Pathogenesis

The pathogenesis of constitutional pubertal delay is based on disturbances in the gonadotropin-releasing hormone (Gn-RH) secretion regulation system, which is controlled by various hormonal and non-hormonal factors interacting with Gn-RH-secreting neurons. These include monoamines of the adrenergic and dopaminergic systems, melatonin, neuropeptide Y, estrogens, insulin-like growth factor-1 (IGF-1), and leptin.³ Pathological development and maturation of

diencephalic structures, as a cause of constitutional pubertal delay, is a frequent consequence of antenatal and perinatal pathology, traumatic brain injury, and microcirculatory disorders. Mental retardation is an unfavorable factor for the formation of bone density, final growth, psychological development of the adolescent personality, maturation of the reproductive system and is subject to correction.¹³

According to German authors, in prepubertal boys aged 14 years or older, differentiation between CDGSD and HG (hypogonadism) is difficult, as current diagnostic tools have limitations in sensitivity and specificity. The aim of this study was to evaluate the usefulness of markers of gonadal activity, growth axis activation, and adrenal function in differentiating between prepubertal CDGSD and HH. This retrospective study was conducted between 2006 and 2015 at an academic outpatient referral center. The clinical data of 94 boys aged 13.9 to 23.2 years, who were referred to as "pubertal delay," were reviewed. Specific diagnoses were established during the initial examination and clinical follow-up: 24 boys were diagnosed with HG, 22 boys with CDGSD, prepubertal (PP CDGSD), and 28 boys with CDGSD.

Early pubertal (EP), the latter serving as a control group. Twenty patients were excluded from the evaluation due to previous steroid treatment or associated chronic disease. Inhibin B and AMH (anti-Müllerian hormone) were measured in all (n = 74); IGF-1, BS-IGF-3, DHEA in a subgroup of patients (n = 45) in the serum at first presentation. Inhibin B and AMH were higher in boys with PP-CFRP than in boys with HH: inhibin B: 87.6 ± 42.5 vs. 19.8 ± 13.9 pg/mL; $p < 0.001$; AMH: 44.9 ± 27.1 vs. 15.4 ± 8.3 ng/mL; $p < 0.001$. Performance characteristics for the diagnosis of PP- CDGSD and HH (inhibin B ≥ 28.5 pg/mL): sensitivity: 95%, specificity: 75%; AUC: 0.955. When combined with a cutoff of AMH ≥ 20 ng/mL, specificity increased to 83%. Insulin-like growth factor-1 levels (IGF-1), protein-bound insulin-like growth factor-3 (PGIF-3), dehydroepiandrosterone (DHEA) in the blood did not differ. In boys with RP CPRP, inhibin B and IGF-1 levels were highest (138.7 ± 59.9 pg/mL/ 289.7 ± 117 ng/mL), while AMH levels were lowest (11.7 ± 9.1 ng/mL). Sertoli cell markers are useful in establishing a prognosis of whether a boy with delayed puberty will enter puberty spontaneously, whereas Leydig cell, growth, and adrenal markers are not.¹⁶

This review¹⁷ focuses on the diagnosis, clinical, and general therapeutic approach to constitutional growth and delayed puberty and hypogonadotropic hypogonadism (HH) in males, which are difficult to differentiate. A thorough clinical history and physical examination should be performed. Delayed puberty is caused by constitutional growth and delayed puberty in the vast majority of children. They should be distinguished from the small proportion of boys with hypogonadism, a pathological condition. A number of laboratory tests can predict the onset of puberty and its progression. However, the advent of highly sensitive immunoassay systems and radiometric immunoassays for LH, FSH, and testosterone has not completely resolved this issue, as their values can overlap between normal and pathological conditions.

Genetic variability or polymorphism Estrogen receptor may be a factor contributing to the rate of growth and puberty, according to the authors.¹⁸

The immunoglobulin superfamily member 1 (IGSF1) gene encodes a plasma membrane glycoprotein primarily expressed in the pituitary gland and testes. Loss-of-function mutations in IGSF1 cause X-linked central hypothyroidism syndrome (CeH), macroorchidism, and delayed puberty (delayed testosterone rise but normal testicular growth). Because this syndrome has been identified in patients with

CeH, it is unknown whether IGSF1 mutations can also cause delayed puberty without CeH. Therefore, we determined the prevalence of IGSF1 sequence variants in 30 patients with an overt X-linked form of CeH.

In four families, the authors identified three novel variants of unknown clinical significance (VUCS), with possible pathogenicity predicted by analysis. However, the genotype was not fully compatible with the CRPS; all three VUCSs showed normal plasma membrane expression in transfected HEK293 cells, and no other features of IGSF1 deficiency syndrome were observed in the VUCS-carrying family members. The observation of hyperprolactinemia in two carriers remains unexplained.

There is insufficient evidence to conclude that the three observed VUCS in IGSF1 are associated with CDGSD, making it unlikely that IGSF1 mutations are the primary cause of CDGSD.⁹

Clinic

A slight delay in growth compared to peers is observed from an early age. The growth rate in the prepubertal period is at least 5 cm/year, with the individual growth chart corresponding to the 3rd percentile. Bone age lags 2-4 years behind the chronological age and corresponds to the age of growth. Pubertal growth acceleration is delayed by 2-4 years (the timing depends on the degree of delay in bone age). Final height falls within the normal range for the given family. Typically, there is a family history of a similar developmental pattern (usually in the father or paternal relatives).

A combination of constitutional growth retardation and sexual development with elements of familial short stature is possible, which worsens the final growth prognosis.

The Indian authors suggested a critical age period for bone mass accumulation, consistent with these findings. Longitudinal studies will help elucidate why sufficient mineralization occurs after the onset of puberty in the CDGSD.⁴

Research data suggest that prepubertal boys with FSGR have normal bone turnover. However, their significantly higher urinary D-pyd levels compared to FSGR and control subjects may be an indicator of later development of osteoporosis. Therefore, long-term follow-up studies monitoring bone mineral status in prepubertal boys with FSGR from prepuberty to adulthood are needed to better understand bone metabolism in these patients.⁶

Diagnostics

All adolescents suspected of having constitutional delayed puberty should undergo a thorough evaluation, particularly because some children or adolescents with delayed puberty may have a serious underlying pathology that requires urgent investigation and treatment.¹⁹ The clinical and hormonal findings in constitutional delayed puberty and hypogonadism are identical, so specific tests to assess the body's capabilities are necessary.

If the examination reveals that the patient has a constitutional delay in puberty, the question arises as to whether the constitutional delay in growth and puberty should be treated, or whether it is simply a delay, meaning that puberty will occur, but somewhat later.

Some experts consider this condition normal, which is extremely difficult to accept. Constitutional delay in growth and puberty is accompanied by the following negative symptoms:

Severe growth retardation, which is extremely painful for patients and often leads to depression.

Underdevelopment of the external genitalia, which creates an inferiority complex in boys. Such boys often quit sports clubs and stop going to swimming pools and beaches due to fear of changing clothes in the presence of older teenagers.

Delayed psychosexual maturation, which often leads to sexual dysfunction later on.

Decreased bone mineral density.

In this case-control study, elevated phthalate levels were found in children with CDGSD in Shanghai, China, and phthalate levels were associated with CRPS, which appeared to be mediated by circulating testosterone levels (27).

Pathological causes of growth retardation and delayed puberty are common in adolescents, and the authors recommend a study combining the SDS for height and growth deviations to decide on further diagnostic testing.²⁰

In prepubertal boys, a stimulation test with human chorionic gonadotropin (hCG) can be used to differentiate between isolated gonadotropic hormone deficiency and constitutional delay of puberty. HG administered intramuscularly at a dose of 5000 units/m² on the 1st, 3rd, 8th and 10th days. Testosterone levels in serum is determined before the first injection and on the 15th day:

In case of delayed puberty, testosterone levels increase after a course of hCG injections, but in case of isolated gonadotropic hormone deficiency, they do not change. To exclude primary hypogonadism, study the anamnesis, conduct a physical examination and gonadotropin-releasing hormone tests And thyroliberin.³

In addition, a synthetic analogue is administered intravenously gonadotropin-releasing hormone-gonadorelin and evaluate the change LH levels And FSH. Patients with pituitary damage are characterized by low basal levels of LH and FSH and an unresponsive gonadotropin-releasing hormone (GnRH). A butterfly needle or catheter is inserted into a vein. Since LH and FSH secretion is pulsatile, blood is drawn twice before the test to determine basal concentrations of these hormones: 15 minutes before and immediately before gonadorelin administration. Basal concentrations are calculated as the average of the two measurements. Gonadorelin at a dose of 100 mcg is administered rapidly subcutaneously or intravenously by jet stream. Blood is drawn 15, 30, 45, 60, 90, and 120 minutes after gonadorelin administration. Serum LH and FSH concentrations are determined.^{1,2}

Evaluation of results

a. Norm. Typically, the increase in LH secretion is more pronounced and occurs earlier than the increase in FSH secretion. In adults, LH concentrations increase more than twofold and reach a maximum within 15-45 minutes after gonadorelin administration. FSH concentrations typically increase 1.5-2-fold, and sometimes remain unchanged. In women, the degree of increase in LH (but not FSH) secretion depends greatly on the phase of the menstrual cycle: the maximum secretory response to gonadorelin is observed in the luteal phase.

b. The test allows us to identify a deficiency of LH and FSH and disturbances in the secretory response to gonadotropin-releasing hormone.

Prognosis

The authors aimed to determine whether boys with CDGSD could achieve their target height and predicted adult height (PAH) in

adulthood. After measuring height, weight, pubertal stage, parental height, and bone age, patient data were extracted from files at the initial presentation. Their height and weight were measured at the end of the study, and a wrist X-ray was taken to determine bone age. PAU was calculated using the Bailey-Pinnot method²¹, and target height was estimated based on the average parental height. Patients final or near-final heights were measured and compared with the target height and PAU.

The mean age at the end of the study was 15.2 ± 0.95 , 20 ± 0.75 years, respectively. The mean bone age at the beginning of the study was 12.97 ± 1 year, and at the end - 17.6 ± 0.58 years. The mean age of the deposited bone was 2.2 ± 0.82 years. The mean value of the primary measured heights was 150.16 ± 7 cm (138-160 cm). The mean final or close to final height was 165.7 ± 2.89 cm (161-170.5 cm). The final or near-final heights in our subjects were lower than either their (165.7 ± 2.89 vs. 170.7 ± 5.17) (P-value < 0.005) or target height (165.7 ± 2.89 vs. 171.8 ± 4.65) (P-value < 0.0001).

Most patients with CDGSD do not achieve their target height or predicted adult height; they are typically shorter than their parents and the general population. These patients need to be monitored until they reach their final height, and in some cases, additional medical treatment may be indicated.

Based on the adult height of 68 males (mean age 22.5 years), a new height prediction model was calculated based on 105 height measurements and bone age determinations at a mean age of 14.0 years. The new model was adapted to the degree of bone age delay and validated in an independent cohort of 32 boys with CDGSD. The new model for predicting adult height in boys with CDGSD provides new metrics for predicting height at bone ages > 13 years and is adapted to different degrees of bone age delay. The new prediction model has good prediction capabilities and overcomes some of the model's limitations. Bailey-Pinneau.²¹

Treatment

The problem of therapy for CDGSD is still a subject of debate. Part Researchers adhere to an observational approach. It is believed that children with constitutional mental retardation have a favorable prognosis for final growth and sexual development. However, the obvious negative psychosocial and medical consequences of delayed maturation and slow growth are not taken into account. In recent years, hormonal therapy with sex steroids has been proposed. Testosterone during puberty is known to enhance pulsatile secretion of growth hormone. However, a number of questions remain unresolved regarding the effect of androgen therapy on the activation of the pituitary-gonadal system in adolescents and the impact of this therapy on the final height of patients.

In this regard, the search for safe and effective treatment methods is relevant. Physiotherapeutic transcranial techniques are being used, in particular, the use of transcranial magnetic therapy (TcMT). This method of exposure to a running alternating pulsed magnetic field (TAPMF), which has a high penetrating ability on the diencephalic structures of the brain with an alpha rhythm frequency. The running alternating magnetic field has a specific mechanism of action: it improves nerve impulse conduction; has a vasodilating effect, improves microcirculation; and normalizes cerebrospinal fluid dynamics. The high sensitivity of the hypothalamus to the action of a magnetic field is known).

Treatment of CDGSD is an under-researched area in adolescent medicine. The authors put forward the hypothesis that oral aromatase

inhibition with letrozole is more effective than low-dose intramuscular testosterone injection in inducing puberty in boys with CDGSD.¹¹

Finnish authors V.T.Huopio, H.Kariola, L.Tenhola, et al.²² conducted a randomized, controlled, open-label study at four pediatric centers in Finland. Boys aged at least 14 years with CDGSD who desired medical intervention and were showing early signs of puberty were randomly assigned in blocks of ten to receive either six low-dose intramuscular testosterone injections (approximately 1 mg/kg body weight) every four weeks for six months or oral letrozole 2.5 mg once daily for six months. Patients were followed for 6 months after the end of treatment. The primary outcomes were changes in testicular volume and hormonal markers of puberty at 6 months after the start of treatment, which were assessed in all participants who received the assigned treatment. All patients were included in the safety analysis. This study is registered with ClinicalTrials.gov, number NCT01797718²² Letrozole has been found to be a possible alternative to low-dose testosterone for boys with CRPS who elect medical intervention. However, the risks and benefits of manipulating the reproductive axis during early puberty should be carefully weighed.

Howard S.R.¹⁰ included four RCTs involving 207 participants (84 interventions) in the review. The study included men with KSRS, idiopathic short stature (ISS), and growth hormone deficiency (GHD). Three of these trials had an overall low or unclear risk of bias for the primary outcomes. Short-term growth outcomes, such as predicted adult height, were improved in all trials. Only one trial reported the primary outcome of final and near-final height as dilation in a non-randomized setting. None of the trials assessed health-related quality of life. One publication provides detailed information on the prevalence of adverse events. A significant proportion (45%) of prepubertal boys with MCS treated with letrozole developed mild vertebral morphological abnormalities compared with the placebo group.

Available data showed that aromatase inhibitors improve short-term growth outcomes. There was no evidence to support an increase in final adult height based on limited data, and only one of the four trials published definitive growth data under non-random conditions.

According to Giri D, Patil P, Blair J, Dharmaraj P. et al.,²³ testosterone therapy improves the growth rate in the first year of therapy for boys with CDGSD, without affecting their final projected height.²³

The first study on the use of testosterone gel for pubertal activation in the CDGSD population belongs to Chioma L, Papucci G, Fintini D, Cappa M.⁵ Their preliminary data support the effectiveness of short-term testosterone gel treatment to induce puberty.

The puberty nomogram assesses both delayed onset of puberty and delayed progression of puberty, allowing for the distinction between normal and abnormal pubertal development. Oral treatment was associated with pubertal induction and progression, as well as short-term growth without compromising final height, according to Lawaetz J.G, Hagen CP, Mieritz MG, who treated 173 boys with CRPS with oral testosterone.²⁴

CDGSD can cause significant psychological distress in adolescent boys. Although testosterone use in this group has been shown not to affect final adult height, the effect on growth velocity during the first year has not been widely reported. The authors concluded that testosterone therapy improves growth velocity during the first year in boys with CDGSD without affecting their final projected height.¹⁸

A cross-sectional and longitudinal study of Danish boys with normal pubertal development (Copenhagen Puberty Study) was performed. This retrospective observational study of 451 boys assessed for delayed puberty between 1990 and 2013. Eighty-eight (27%) of 287 boys had late pubertal onset according to classical criteria, whereas 173 (60%) of 287 boys had impaired pubertal progression according to the pubertal nomogram. Ninety-six (56%) of these 173 boys received oral testosterone for 0.8 years (0.5; 1.3) [median (25th, 75th percentiles)], resulting in positive effects on pubertal progression. Height increased from -1.9 SD (-2.5; -1.2) to -1.5 SD (-2.1; -0.7) ($P < 0.001$), and mean height increased from 172.3 cm (170.3; 182.8) to 178.1 cm (171.4; 191.7) ($P = .001$) after one year of treatment.²⁴

In addition to growth hormone, several pharmaceutical products have been studied for their efficacy and safety in promoting short-term and adult growth. Short-term treatment with testosterone esters in boys with constitutional growth retardation and pubertal delay is effective in promoting secondary sexual characteristics and accelerating growth.²⁵

Conclusion

Disorders of puberty can have profound impacts on physical and psychosocial well-being.

Delayed puberty, particularly in boys, is a common occurrence in pediatrics. Recent advances have improved our understanding of the neuroendocrine, genetic, and environmental factors that control sexual development and, therefore, inform the pathophysiology of delayed puberty. The discovery of kisspeptin signaling through its receptor has identified the neuroendocrine mechanisms that control the gonadotropin-releasing hormone (GnRH) pulse generator at the onset of puberty. Genetic mechanisms, ranging from single-gene mutations to single-nucleotide polymorphisms, have been identified associated with delayed puberty. Environmental factors, including nutritional factors and endocrine disorders, have also been implicated in changes in social trends and abnormal pubertal timing.

Despite these advances, a key clinical question remains how to distinguish delayed puberty due to underlying pathology or hypogonadism from constitutional growth retardation and puberty. This remains challenging, as biochemical tests are not always discriminatory. The diagnostic accuracy of newer tests, including 36-hour luteinizing hormone (LH) release tests, GnRH agonist assays, anti-mullerian hormone, and inhibin-B assays, requires further evaluation. Sex hormone replacement remains the primary available treatment for delayed puberty, the choice of which is largely determined by clinical practice and the availability of various sex steroid preparations. Spontaneous reversal of hypogonadism has been reported in boys with idiopathic LH after a period of sex steroid treatment, highlighting the importance of reassessment at the end of pubertal induction. Newer, more physiologically based treatments, such as gonadotropins or celepept in agonists, are being investigated for the treatment of hypogonadotrophic hypogonadism. Careful clinical evaluation and assessment of normal physiology remain key approaches for patients with delayed puberty.²⁶

Thus, CDGSD is a variation in the onset and timing of pubertal development without a specific endocrine anomaly. Published in 2010 El-Eshrawy MM, Abdel Aal IA, El Hawary AK. Studies show that leptin and ghrelin play a role in the onset and progression of puberty. They are involved in the regulation of GnRH secretion, with ghrelin having an inhibitory effect and leptin a stimulating effect. The authors suggested that increased ghrelin and leptin levels may be associated

with a change in the pace of puberty in adolescents with CDGSD. Thus, further studies are needed to assess differences in leptin and ghrelin levels in adolescent boys with CDGSD, and between hormones and reproductive hormones, including LH, FSH, and testosterone, although such studies have not yet been continued.

Therefore, this review focuses on the diagnosis, clinical, and general therapeutic approach to constitutional growth and delayed puberty and hypogonadotropic hypogonadism in males, which are difficult to differentiate. A thorough clinical history and physical examination should be performed. Delayed puberty is caused by constitutional growth and delayed puberty in the vast majority of children. They should be distinguished from the small proportion of boys with hypogonadism, a pathological condition. A number of laboratory tests can predict the onset of puberty and its progression. However, the advent of highly sensitive immunoassay systems and radiometric immunoassays for LH, FSH, and testosterone has not completely resolved these issues, as their values can overlap between normal and pathological conditions.

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Conflicts of interest

The author declare that there are no conflict of interest.

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