CLINICAL PRACTICE

Delayed Puberty

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 14-year-old boy with an unremarkable medical history presents because of lack of pubertal development. He has always been relatively short, but his growth velocity is slowing as compared with that of his peers. His height is 146 cm (57.5 in., <3rd percentile for age), and his weight is 37 kg (82 lb, 3rd percentile). His father, who is 168 cm (66.1 in.) tall, continued to grow until his second year in college; his mother is 153 cm (60.2 in.) tall and began menstruating at the age of 14.0 years. The patient's target height on the basis of the parental heights is 167 cm (65.8 in.). The physical examination reveals Tanner stage 1 pubic hair and prepubertal-sized testes. How should the boy be evaluated and treated?

THE CLINICAL PROBLEM

Puberty leads to sexual maturation and reproductive capability. It requires an intact hypothalamic–pituitary–gonadal (HPG) axis and is heralded by the reemergence of gonadotropin-releasing hormone (GnRH) secretion from its relative quiescence during childhood. GnRH stimulates the secretion of luteinizing hormone and follicle-stimulating hormone (FSH), which then stimulate gonadal maturation and sex-steroid production. Much is known about components of the HPG axis, but the factors that trigger pubertal onset remain elusive. It is not understood why one boy begins puberty at the age of 10 years and another at the age of 14 years.

Delayed puberty is defined as the absence of testicular enlargement in boys or breast development in girls at an age that is 2 to 2.5 SD later than the population mean (traditionally, the age of 14 years in boys and 13 years in girls). However, because of a downward trend in pubertal timing in the United States[1-3] and other countries[4,5] and differences in pubertal timing among racial and ethnic groups, some observers have advocated for updated definitions with younger age cutoffs for the general population or perhaps for particular countries or racial or ethnic groups. Development of pubic hair is usually not considered in the definition because pubarche may result from maturation of the adrenal glands (adrenarche), and the onset of pubic hair can be independent of HPG-axis activation.

Late puberty can affect psychosocial well-being, and patients, families, and practitioners are often concerned that it may affect adult stature. Adult height can be affected but on average is only slightly below the genetic target.[6] Many adolescents present with delayed puberty combined with relative familial short stature, compounding these concerns and leading to more subspecialty referrals than either condition alone.

Delayed puberty in boys usually represents an extreme of the normal spectrum of pubertal timing, a developmental pattern referred to as constitutional delay of growth and puberty (CDGP). In one large series, approximately 65% of boys and 30% of girls with delayed puberty had CDGP.[7] However, because the data were

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KEY CLINICAL POINTS

DELAYED PUBERTY

- Delayed puberty is diagnosed when there is no testicular enlargement in boys or breast development in girls at an age that is 2 to 2.5 SD later than the mean age at which these events occur in the population (traditionally, 14 years in boys and 13 years in girls).
- Constitutional delay of growth and puberty (CDGP) is the single most common cause of delayed puberty in both sexes, but it can be diagnosed only after underlying conditions have been ruled out.
- The cause of CDGP is unknown, but most patients with CDGP have a family history of delayed puberty.
- Management of CDGP may involve expectant observation or therapy with low-dose sex steroids.
- When treatment is given, the goals are to induce the appearance of secondary sexual characteristics or the acceleration of growth and to mitigate psychosocial difficulties associated with pubertal delay and short stature.
- The routine use of growth hormone, anabolic steroids, or aromatase inhibitors is not currently recommended.

obtained from a tertiary referral center, these percentages may underestimate the frequency of CDGP encountered by primary care providers. The evaluation and treatment of boys with CDGP is the main focus of this review, but consideration is given to other causes of delayed puberty and issues specific to girls.

Although CDGP represents the single most common cause of delayed puberty in both sexes, it can be diagnosed only after underlying conditions have been ruled out. The differential diagnosis of CDGP can be divided into three main categories[7]: hypergonadotropic hypogonadism (characterized by elevated levels of luteinizing hormone and FSH owing to the lack of negative feedback from the gonads), permanent hypogonadotropic hypogonadism (characterized by low levels of luteinizing hormone and FSH owing to hypothalamic or pituitary disorders), and transient hypogonadotropic hypogonadism (functional hypogonadotropic hypogonadism), in which pubertal delay is caused by delayed maturation of the HPG axis secondary to an underlying condition (Table 1, and Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

The cause of CDGP is unknown, but it has a strong genetic basis. It has been estimated that 50 to 80% of variation in the timing of puberty in humans is due to genetic factors,[8] and 50 to 75% of patients with CDGP have a family history of delayed puberty.[9,10] The inheritance of CDGP is variable but most often is consistent with an autosomal dominant pattern, with or without complete penetrance. CDGP is not sex-specific and is characterized by either relatively delayed development among family members (e.g., the average age at menarche among mothers is 14.3 years, as compared with a mean of 12.7 years among controls[9]) or evidence of true CDGP. The investigation of patients with the Kallmann syndrome and isolated hypogonadotropic hypogonadism has led to the identification of genes that play critical roles in the development and regulation of the HPG axis, but mutations that have been identified in such genes do not cause CDGP, except in rare instances.[11,12] However, the genes causing 60 to 70% of cases of the Kallmann syndrome and isolated hypogonadotropic hypogonadism remain unknown.[13] Loci have also been identified that are associated with the age of menarche in the general population,[14-18] but these particular loci have likewise not been associated with CDGP.[19]

STRATEGIES AND EVIDENCE

FIRST-LINE EVALUATION

Ruling Out Underlying Disorders

The aim of initial evaluation is to rule out underlying disorders causing delayed puberty (Table 2, and Table 2 in the Supplementary Appendix).[20-28] Pubertal development is assessed clinically and biochemically, providing information that is important for counseling and predicting further pubertal development. Eventual normal progression of puberty verifies the diagnosis of CDGP, whereas absent or slow development or cessation of development after onset is consistent with permanent hypogonadism.

Table 1. Frequency and Common Causes of Delayed Puberty Other Than Constitutional Delay of Growth and Puberty.*

Delayed Puberty	Hypergonadotropic Hypogonadism	Permanent Hypogonadotropic Hypogonadism	Functional Hypogonadotropic Hypogonadism
Frequency (%)			
Boys	5–10	10	20
Girls	25	20	20
Common causes	Turner's syndrome, gonadal dysgenesis, chemotherapy or radiation therapy	Tumors or infiltrative diseases of the central nervous system, GnRH deficiency (isolated hypogonadotropic hypogonadism, Kallmann's syndrome), combined pituitary-hormone deficiency, chemotherapy or radiation therapy	Systemic illness (inflammatory bowel disease, celiac disease, anorexia nervosa or bulimia), hypothyroidism, excessive exercise

* For a more comprehensive listing of causes of delayed puberty, see Table 1 in the Supplementary Appendix. GnRH denotes gonadotropin-releasing hormone.

Family History

A family history, including childhood growth patterns and age at pubertal onset of the parents, should be obtained. Delayed puberty in a parent or sibling followed by spontaneous onset of puberty suggests CDGP. However, if pubertal development was induced by sex steroids in family members, isolated hypogonadotropic hypogonadism is also possible, since reversal of hypogonadism is noted after the discontinuation of sex steroids in about 10% of patients with isolated hypogonadotropic hypogonadism.[29,30]

Patients and their parents should be questioned about a history or symptoms of chronic disease, with emphasis on specific disorders (e.g., celiac disease, thyroid disease, and anorexia) that may cause temporary delay of puberty (functional hypogonadotropic hypogonadism), as well as medication use, nutritional status, and psychosocial functioning. Delayed cognitive development associated with obesity or dysmorphic features may suggest an underlying genetic syndrome. Bilateral cryptorchidism or a small penis at birth and hyposmia or anosmia may suggest hypogonadotropic hypogonadism. A history of chemotherapy or radiotherapy may indicate primary gonadal failure (Fig. 1).

Physical Examination

Previous height and weight measurements should be obtained and plotted so that longitudinal growth can be carefully assessed (Fig. 2). Delayed puberty is often associated with short stature and slow growth for age although the height and growth rate are within the prepubertal normal range. Children who are underweight for height have an increased likelihood of having an underlying condition delaying HPG-axis activation. Conversely, in boys, unlike girls, being overweight can be associated with later pubertal development.[20,21] The most widely used pubertal rating system is Tanner staging[31,32] (Fig. 3). In boys, the presence of Tanner stage 2 genitalia marks the onset of pubertal development and is characterized by enlargement of the scrotum and testes and by a change in the texture and color of the scrotal skin. Testicular volume should be measured, with a volume of more than 3 ml indicating the initiation of central puberty. In patients with CDGP, both adrenarche and hormonal activation of the gonads often occur later than average, but in isolated hypogonadotropic hypogonadism, adrenarche usually occurs at a normal age.[7,33]

Bone-Age Radiography

The bone age should be reviewed by a practitioner who is experienced in interpreting such radiographs. A delay in bone age is characteristic but not diagnostic of CDGP and also may occur in patients with chronic illness, hypogonadotropic hypogonadism, or gonadal failure. Adult height prediction is an important part of counseling if short stature is a component of the presentation, and practitioners should be aware that the Bayley–Pinneau tables overestimate adult height in patients with CDGP if bone age is delayed by more than 2 years (Table 2, and Table 2 in the Supplementary Appendix).

Hormone Measurements and Brain Imaging

Pubertal onset is characterized by the accentuation of diurnal secretion of gonadotropin and

testosterone (in boys) and estrogen (in girls) before apparent phenotypic changes. Basal levels of luteinizing hormone and FSH are low in patients with CDGP or hypogonadotropic hypogonadism, whereas such levels are usually elevated in those with gonadal failure. Serum levels of insulin-like growth factor 1 (IGF-1) can be helpful in the evaluation of growth hormone deficiency but must be interpreted carefully because levels are often low for chronologic age but within the normal range for bone age. Thyroid-function tests are routinely obtained. Brain magnetic resonance imaging (MRI) is indicated when there are signs or symptoms to suggest a lesion in the central nervous system. Otherwise, although some clinicians routinely perform brain imaging, a reasonable strategy is to defer such evaluation until the age of 15 years, at which point many patients with CDGP will have spontaneously begun puberty and will require no further evaluation. Full neuroendocrine testing is warranted in patients with hypothalamic–pituitary tumors causing hypogonadotropic hypogonadism, since they may have additional pituitary-hormone deficiencies.

SECOND-LINE EVALUATION

Most patients will not have an apparent alternative cause for delayed puberty on initial evaluation, suggesting CDGP as the likely diagnosis. However, no test can reliably distinguish CDGP

Table 2. Investigations for Delayed Puberty.*

Variable	Interpretation
First-line	
Growth rate	In early adolescence in both sexes, an annual growth rate of less than 3 cm is suggestive of a disease specifically inhibiting growth (e.g., growth hormone deficiency, hypercortisolism, and hypothyroidism), but such rates can also be seen in CDGP. Boys with delayed puberty who are overweight tend to have height and predicted adult height consistent with their genetic height potential.[20,21]
Tanner stages	In girls, Tanner stage 2 breast development is usually the first physical marker of puberty. In boys, a testicular volume of >3 ml is a more reliable indicator of the onset of puberty than Tanner stage 2 genital development.
Testis volume in boys	A testicular volume of >3 ml (≥2.5 cm in length) indicates central puberty. Most healthy boys with a testicular volume of ³3 ml will have a further increase in testicular volume or pubic-hair stage, or both, at repeated examination 6 mo later.[22]
Bone age	A bone-age delay of >2 yr has arbitrarily been used as a criterion for CDGP but is nonspecific. A bone-age delay of 4 years has been associated with a mean overprediction of adult height of 8 cm. In children with short stature who have no bone-age delay, adult height is usually underestimated by the Bayley–Pinneau tables.[23]
Biochemical analyses	To rule out chronic disorders, common tests include complete blood count, erythrocyte sedimentation rate, creatinine, electrolytes, bicarbonate, alkaline phosphatase, albumin, thyrotropin, and free thyroxine. Additional testing may be necessary on the basis of family history and symptoms and signs, including screening for celiac disease and inflammatory bowel disease.
Serum luteinizing hormone	At low levels, values obtained on immunochemiluminometric (ICMA) assays are at least 50% lower than those obtained on immunofluorometric (IFMA) assays.[24] Values of <0.1 IU per liter are not specific for hypogonadotropic hypogonadism. Values of >0.2 IU per liter on ICMA or >0.6 IU per liter on IFMA are specific but not sensitive for the initiation of central puberty; some adolescents in early puberty have lower values.[24] In delayed puberty, elevated values suggest primary hypogonadism. In general, luteinizing hormone is a better marker of pubertal initiation than follicle-stimulating hormone.
Serum follicle-stimulating hormone	At low levels, values obtained on ICMA are approximately 50% lower than those obtained on IFMA. Values of <0.2 IU per liter on ICMA or <1.0 IU per liter on IFMA suggest hypogonadotropic hypogonadism but are not diagnostic.[24,25] In delayed puberty, a value above the upper limit of the normal range for the assay is a sensitive and specific marker of primary gonadal failure.
Serum insulin-like growth factor 1	Measurement is used to screen for growth hormone deficiency. An increase in the level during follow-up or during or after treatment with sex steroids makes the diagnosis of growth hormone deficiency less likely. Growth hormone provocation tests are needed to diagnose growth hormone deficiency.
Serum testosterone in boys	A morning value of 20 ng per deciliter (0.7 nmol per liter) often predicts the appearance of pubertal signs within 12 to 15 mo.[26]

Table 2. (Continued.)

Variable	Interpretation
Second-line	
Gonadotropin-releasing hormone test†	A predominant response of luteinizing hormone over follicle-stimulating hormone after stimulation or peak luteinizing hormone levels of 5 to 8 IU per liter (depending on the assay) suggests the onset of central puberty. However, patients with CDGP or hypogonadotropic hypogonadism may have a prepubertal response.
Human chorionic gonadotropin test†	Peak testosterone levels are lower in patients with hypogonadotropic hypogonadism than in those with CDGP.[27]
Serum inhibin B†	Prepubertal boys with a baseline inhibin B level of >35 pg per milliliter have a higher likelihood of CDGP.[28] In boys, unmeasurable inhibin B indicates primary germinal failure.
Serum prolactin	Elevated levels may indicate hypothalamic–pituitary tumors causing hypogonadotropic hypogonadism. In such cases, additional pituitary-hormone deficiencies may be present. Measurement of macroprolactin (a physiologically inactive form of prolactin) is recommended in patients with unexplained hyperprolactinemia.
Brain magnetic resonance imaging	Imaging is performed to rule out underlying disorders of the central nervous system. Imaging in patients with the Kallmann syndrome commonly shows olfactory-bulb and sulcus aplasia or hypoplasia and thus may help differentiate the Kallmann syndrome from hypogonadotropic hypogonadism in patients with an apparently normal or difficult-to-evaluate sense of smell.
Genetic testing	Genotyping for known monogenic causes is currently a research procedure and not warranted in routine clinical practice.

* For a more comprehensive listing of investigations, see Table 2 in the Supplementary Appendix. CDGP denotes constitutional delay of growth and puberty.

† These tests are used to try to differentiate CDGP from isolated hypogonadotropic hypogonadism. However, validation in larger, independent studies is needed before the use of such tests can be fully endorsed. Often, clinical follow-up is needed to confirm the diagnosis; no endogenous puberty by the age of 18 years is diagnostic of isolated hypogonadotropic hypogonadism.

from isolated hypogonadotropic hypogonadism, so the diagnosis of CDGP cannot be made with certitude. Observation usually resolves this conundrum; isolated hypogonadotropic hypogonadism is diagnosed if endogenous puberty has not begun by the age of 18 years. Several tests have been proposed to distinguish CDGP from isolated hypogonadotropic hypogonadism (Table 2, and Table 2 in the Supplementary Appendix). If basal gonadotropin levels are inconclusive, stimulation by GnRH or a GnRH agonist may be helpful.[24,25] Stimulated levels of luteinizing hormone in the pubertal range indicate that the HPG axis has been reactivated and that secondary sexual development is likely to occur within 1 year. However, the GnRH test alone often cannot differentiate CDGP from isolated hypogonadotropic hypogonadism because prepubertal values may be observed in isolated hypogonadotropic hypogonadism or in patients with CDGP in whom the HPG axis has not yet been activated. Recent data suggest that baseline levels of inhibin B may facilitate discrimination between these conditions,[28] but replication is needed before this or other tests can be routinely adopted.

Growth hormone secretion in the basal state, as well as after provocative testing, may be decreased in patients with CDGP. If concern about growth is sufficient to warrant stimulation testing of growth hormone, sex-steroid priming with estrogen or testosterone is necessary for reliable results in patients with delayed puberty; estrogen stimulates endogenous growth-hormone secretion, and sex-steroid priming facilitates separation of true growth hormone deficiency from the physiologic low growth hormone secretion that stems from low estrogen levels. If a patient has a normal growth rate, growth hormone provocation testing is not necessary, whereas low IGF-1 levels together with reduced growth velocity warrant testing.

TREATMENT

Patients with CDGP

The options for management of CDGP include expectant observation or therapy with low-dose testosterone (in boys) or estrogen (in girls) (Table 3, and Table 3 in the Supplementary Appendix). If puberty has started, clinically or biochemically, and stature is not a major concern, reassur-

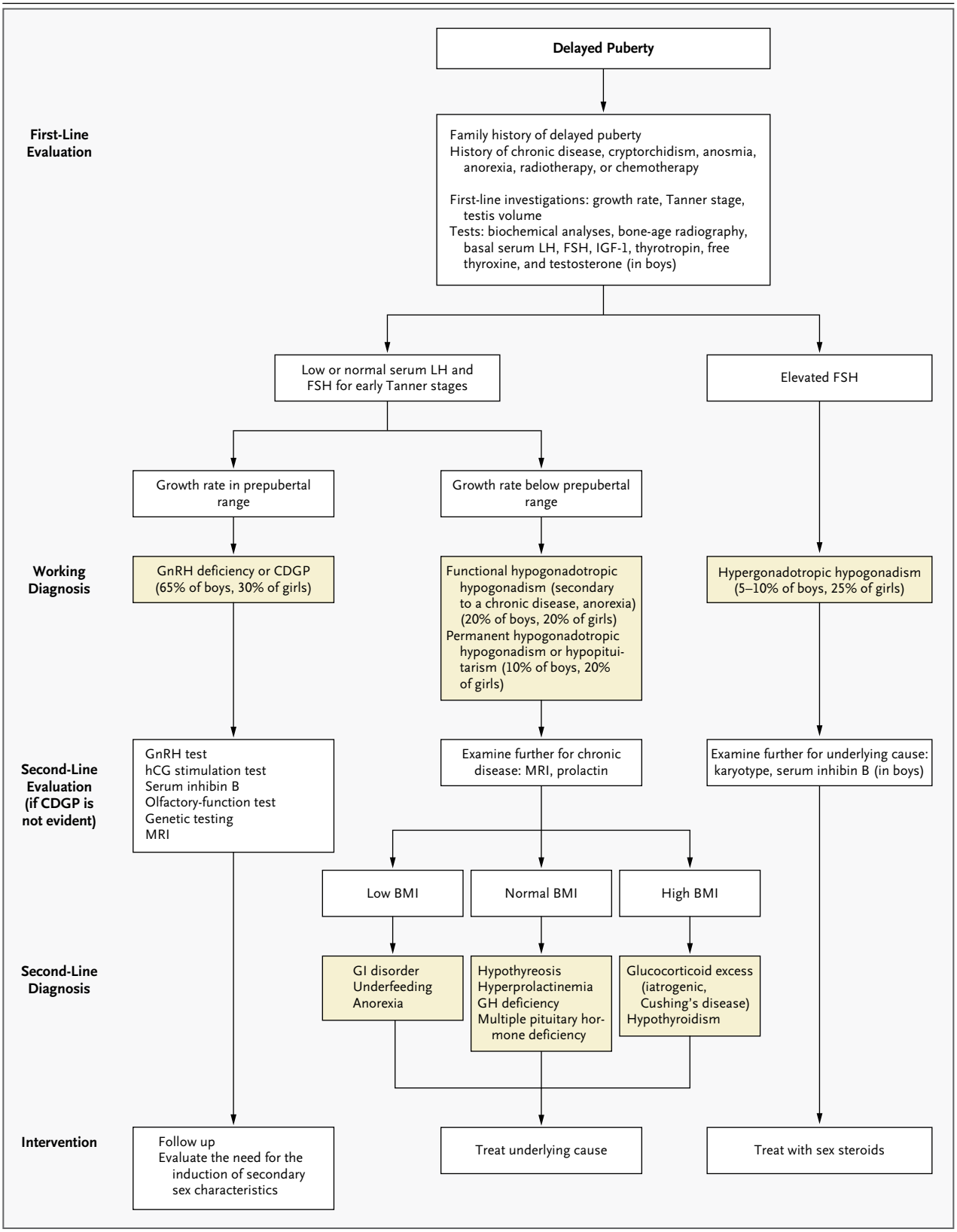

Figure 1 (facing page). Algorithm for the Evaluation of a Patient with Delayed Puberty.

Percentages of patients with delayed puberty with various conditions are from Sedlmeyer and Palmert.[7] Percentages do not add up to 100% because of rounding and because a small percentage of patients have disorders that cannot be classified with the use of this algorithm. BMI denotes body-mass index, CDGP constitutional delay of growth and puberty, FSH follicle-stimulating hormone, GH growth hormone, GI gastrointestinal, GnRH gonadotropin-releasing hormone, hCG human chorionic gonadotropin, IGF-1 insulin-like growth factor 1, LH luteinizing hormone, and MRI magnetic resonance imaging.

ance with realistic adult height prediction is frequently sufficient. If therapy is initiated, it is usually to assuage psychosocial difficulties that may derive from negative interactions with peers, decreased self-esteem, and anxiety about growth rate or body habitus.

Numerous studies of treatment of CDGP in boys have been reported. Although some randomized, controlled trials have been performed with small numbers of subjects, studies have been largely observational and have involved treatment with short courses of low-dose androgens.[34-36] The data suggest that treatment leads to increased growth velocity and sexual maturation and positively affects psychosocial well-being, without significant side effects, rapid advancement of bone age, or reduced adult height. Similar data are not available for girls, but similar outcomes are likely as long as therapy is initiated with appropriately low doses of estrogen.

For a subset of patients with CDGP, short stature can be more worrisome than delayed puberty, and indeed CDGP is considered by some observers to be a subgroup of idiopathic short stature. Although the Food and Drug Administration has approved the use of growth hormone for the treatment of idiopathic short stature and height that is 2.25 SD below average for age, this therapy has at best a modest effect on adult height in adolescents with CDGP, and its use in CDGP is not recommended.

In boys with CDGP and short stature, another potential therapeutic approach is aromatase inhibition, but this treatment requires further study before it should be incorporated into routine practice.[37,38] Aromatase inhibitors block the conversion of androgens to estrogens; because estrogen is the predominant hormone needed for epiphyseal closure, the use of aromatase inhibitors could prolong linear growth and potentially increase adult height. In controlled trials in boys with short stature or delayed puberty, aromatase inhibitors delayed bone maturation and appeared to increase adult height.[37,38] However, the amount of height gained as well as the optimal timing, dose, and duration of therapy with aromatase inhibitors remain uncertain.[39] Moreover, potentially adverse effects, especially impaired development of trabecular bone and vertebral-body deformities, which were observed in boys with idiopathic short stature who were treated with letrozole,[40] must be considered.

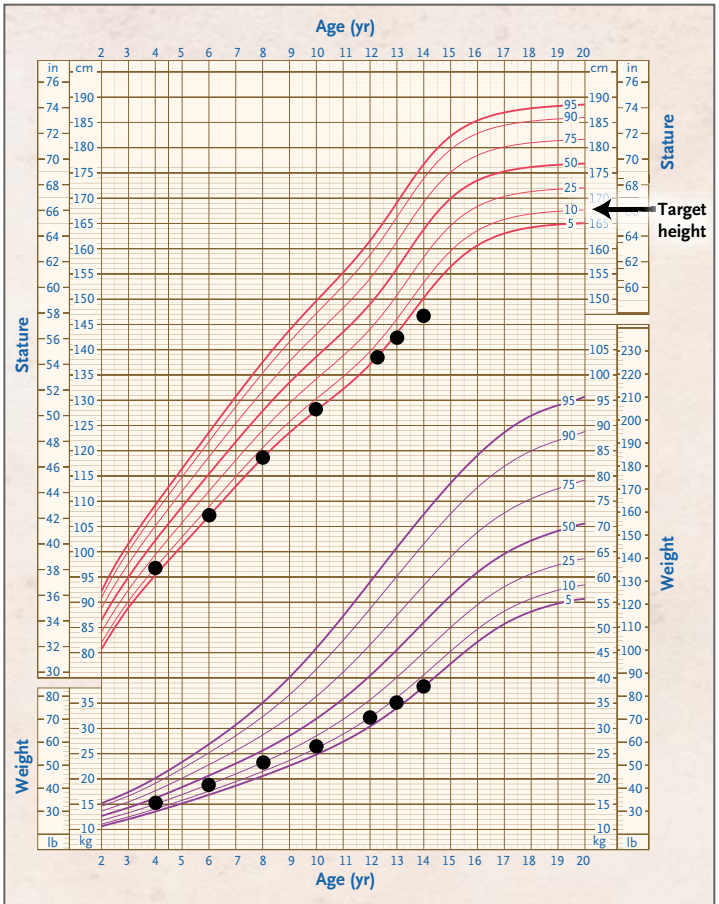

Figure 2. Linear Growth in Delayed Puberty.

In children with delayed puberty (data points), linear growth progresses with a normal preadolescent height velocity (>3 cm per year). Height relative to that of peers (height percentile) may decrease slightly before the usual adolescent age range, but this effect is accentuated when the child with delayed puberty does not undergo a growth spurt in concert with his or her peers. Consequently, the height percentile decreases in the early teenage years. In children with constitutional delay of growth and puberty, a late growth spurt will facilitate subsequent catch-up growth, but adult heights are often slightly shorter than expected on the basis of parental heights.

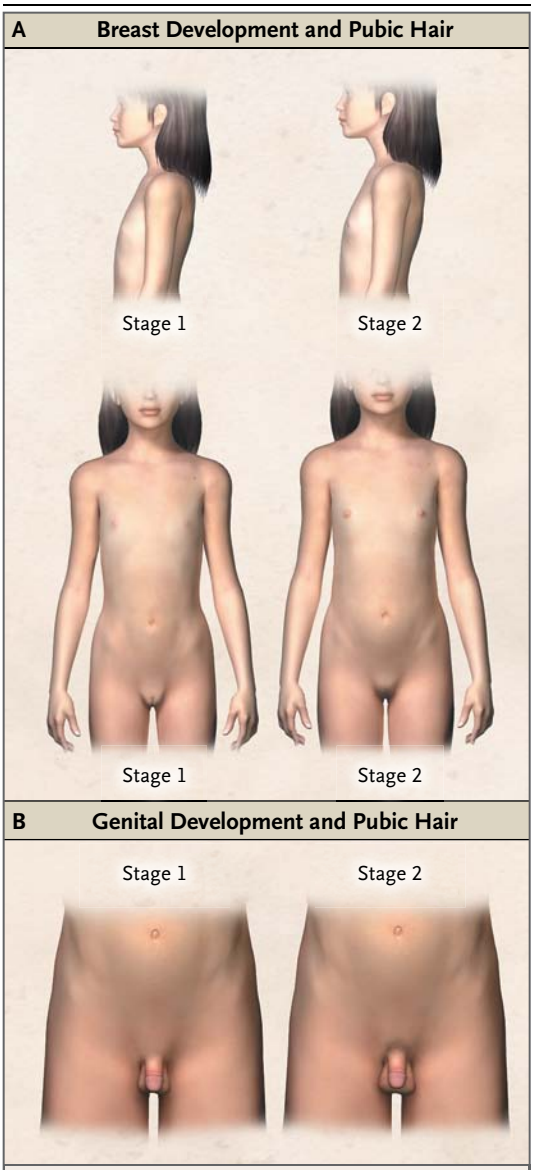

Figure 3. Tanner Stages in the Assessment of Delayed Puberty.

Delayed puberty is often associated with short stature and slow growth for age although the growth rate is within the prepubertal normal range. Physical markers of puberty can also be delayed. In girls (Panel A), breast development from Tanner stage 1 (preadolescent) to stage 2 (appearance of the breast bud) should traditionally take place between 8 and 13 years of age, and in boys the development of genital Tanner stage 1 (preadolescent) to stage 2 (enlargement of the testes and scrotum and change in the texture and reddening of the scrotal skin) should take place between 9 and 14 years. Recent data regarding earlier timing of puberty suggest that these traditional age cutoffs should be adjusted downward, but new age ranges have not yet been defined.

Permanent Hypogonadism

In boys and girls with hypogonadotropic hypogonadism, initial sex-steroid therapy is the same as that for CDGP, but doses are gradually increased to full adult replacement levels during a period of approximately 3 years (Table 3). In hypogonadotropic hypogonadism, exogenous testosterone does not induce testicular growth or spermatogenesis and exogenous estrogen does not induce ovulation, and the induction of fertility in both sexes requires treatment with pulsatile GnRH[42-45] or exogenous gonadotropins.[44] In girls with hypogonadotropic hypogonadism, treatment with estrogen needs to be combined with progestin for endometrial cycling.

AREAS OF UNCERTAINTY

Further research is needed to establish appropriate age cutoffs for delayed puberty in different racial and ethnic groups and to better understand the physiological basis of CDGP. Suggested causes of CDGP include increased total energy expenditure[46] and increased insulin sensitivity,[47] but no definitive cause has been identified. Studies should carefully assess the psychosocial distress among children with delayed puberty, whether this distress has long-term sequelae, and what effect sex-steroid supplementation has on these outcomes. It remains unclear whether adult bone mass is adversely affected by pubertal delay[48] and whether this represents a medical reason to initiate sex-steroid replacement. Distinguishing between CDGP and isolated hypogonadotropic hypogonadism remains difficult in many cases, and further assessment of the role of inhibin B or other markers for this purpose is needed. Randomized trials are needed to compare different estrogen formulations, routes of administration (oral vs. transdermal), and drug regimens to determine optimal therapy for girls with delayed puberty. Studies are needed to identify genes that cause CDGP, which would also elucidate factors that regulate the timing of puberty.

GUIDELINES

To our knowledge, there are no recent guidelines regarding the evaluation and treatment of CDGP.

Table 3. Medications for the Treatment of Constitutional Delay of Growth and Puberty (CDGP).*

Drug and Formulation	In Children with CDGP	Side Effects and Cautions
Boys		
Testosterone		Erythrocytosis, weight gain, prostate hyperplasia; high doses can cause premature epiphyseal closure; not for use in boys with a bone age of <10 yr
Enanthate, cypionate, and propionate	Not recommended before 14 yr of age; initial dose, 50–100 mg every 4 wk for 3 to 6 mo; repeated treatment with 25-to-50-mg increment in dose (not exceeding 100 mg)	All administered by intramuscular injection; local side effects: pain, erythema, inflammatory reaction, and sterile abscess; priapism can occur in patients with sickle cell disease; longer duration of effect for testosterone enanthate than propionate
Undecanoate†	No data available on intramuscular injection	
Transdermal preparations	No data available	Local irritation; applied topically at bedtime; after application, must avoid close skin contact with others
Aromatase inhibitors		Not yet approved for this indication; after onset of puberty, may increase gonadotropin secretion and circulating testosterone levels[41]
Oral letrozole	2.5 mg daily	Decreased level of high-density lipoprotein cholesterol, erythrocytosis, vertebral deformities[40]
Oral anastozole	1.0 mg daily	Less potent than letrozole
Girls		
Estrogen		
Ethinyl estradiol (component of contraceptive pills)	Initial dose, 2 μg daily; increase to 5 μg daily after 6–12 mo; lower-dose pills available in Europe	Liver toxicity, increased levels of some plasma-binding proteins, potentially greater risk of thromboembolism and arterial hypertension than with natural estrogens
17β-Estradiol		
Oral	Initial dose, 5 μg per kilogram of body weight daily; increase to 10 μg per kilogram daily after 6–12 mo	Natural estrogen, may be preferable to synthetic estrogens; transdermal route may have advantages over oral administration
Transdermal patch	Overnight patch: initial dose, 3.1–6.2 μg per 24 hr (one-eighth to one-fourth of 25-μg 24-hr patch); increase by 3.1–6.2 μg per 24 hr every 6 mo	No data on dose equivalent between estradiol patches and gel available in younger patients
Conjugated equine estrogens	Initial dose, 0.1625 mg daily for 6–12 mo with subsequent adjustment to 0.325 mg daily; dose depends on formulation	Not estradiol precursors; use is questioned as not being physiological and because of reports of increased cardiovascular risks in postmenopausal women
Progestin		
Various options (usually oral)	Usually necessary only if estrogen treatment continues longer than 12 mo	Added to induce endometrial cycling after 12–18 mo of estrogen therapy (later if estrogen dose is increased slowly, sooner if breakthrough bleeding occurs)

* For further discussion of these agents and of treatment of permanent hypogonadism, see Table 3 in the Supplementary Appendix.
† Testosterone undecanoate tablets or anabolic steroids are not recommended for the induction of secondary sexual characteristics.

CONCLUSIONS AND RECOMMENDATIONS

The patient in the vignette has delayed puberty. Given that he is male and has a family history of late pubertal development, CDGP is the most likely diagnosis. Before making this diagnosis, a careful evaluation is required to rule out other causes; this is especially true among young women, in whom underlying disorders are more common.

In CDGP, in which pubertal delay is transient, the decision regarding whether to treat should be made by the patient; the goal of therapy, when used, is to induce the acceleration of secondary sexual characteristics or growth and to mitigate psychosocial difficulties. For boys who elect to be treated, we initiate monthly intramuscular injections of 50 mg of testosterone ester for 3 to 6 months; this regimen can be repeated for another 3 to 6 months with dose escalation (Table 3). If spontaneous puberty has not occurred after 1 year, other diagnoses, such as permanent hypogonadotropic hypogonadism, should be reconsidered, and MRI of the brain is indicated. We believe that when CDGP is treated, therapy should be with testosterone alone, even if stature is a prominent concern. We do not use growth hormone or anabolic steroids for delayed puberty, nor do we recommend aromatase inhibitors for this indication, pending more data from randomized trials.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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