Delayed Puberty

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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 and other countries 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. 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. However, because the data were...
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: 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, and 50 to 75% of 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.

**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). 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.
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.\textsuperscript{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.\textsuperscript{20,21} The most widely used pubertal rating system is Tanner staging\textsuperscript{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.\textsuperscript{7,33}

Table 1. Frequency and Common Causes of Delayed Puberty Other Than Constitutional Delay of Growth and Puberty.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Delayed Puberty</th>
<th>Hypergonadotropic Hypogonadism</th>
<th>Permanent Hypogonadotropic Hypogonadism</th>
<th>Functional Hypogonadotropic Hypogonadism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>5–10</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Girls</td>
<td>25</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Common causes</td>
<td>Turner’s syndrome, gonadal dysgenesis, chemotherapy or radiation therapy</td>
<td>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</td>
<td>Systemic illness (inflammatory bowel disease, celiac disease, anorexia nervosa or bulimia, hypothyroidism, excessive exercise)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} For a more comprehensive listing of causes of delayed puberty, see Table 1 in the Supplementary Appendix. GnRH denotes gonadotropin-releasing hormone.
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 <3 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 |
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.† 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.‡

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second-line</td>
<td></td>
</tr>
<tr>
<td>Gonadotropin-releasing hormone test†</td>
<td>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.</td>
</tr>
<tr>
<td>Human chorionic gonadotropin test†</td>
<td>Peak testosterone levels are lower in patients with hypogonadotropic hypogonadism than in those with CDGP.‡</td>
</tr>
<tr>
<td>Serum inhibin B†</td>
<td>Prepubertal boys with a baseline inhibin B level of &gt;35 pg per milliliter have a higher likelihood of CDGP.§</td>
</tr>
<tr>
<td>Serum prolactin</td>
<td>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.</td>
</tr>
<tr>
<td>Brain magnetic resonance imaging</td>
<td>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.</td>
</tr>
<tr>
<td>Genetic testing</td>
<td>Genotyping for known monogenic causes is currently a research procedure and not warranted in routine clinical practice.</td>
</tr>
</tbody>
</table>

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-
Delayed Puberty

First-Line Evaluation

- Family history of delayed puberty
- History of chronic disease, cryptorchidism, anosmia, anorexia, radiotherapy, or chemotherapy
- First-line investigations: growth rate, Tanner stage, testis volume
- Tests: biochemical analyses, bone-age radiography, basal serum LH, FSH, IGF-1, thyrotropin, free thyroxine, and testosterone (in boys)

Low or normal serum LH and FSH for early Tanner stages

- Growth rate in prepubertal range

GnRH deficiency or CDGP (65% of boys, 30% of girls)

Functional hypogonadotropic hypogonadism (secondary to a chronic disease, anorexia) (20% of boys, 20% of girls)
- Permanent hypogonadotropic hypogonadism or hypopituitarism (10% of boys, 20% of girls)

Examining further for chronic disease: MRI, prolactin

- Examine further for underlying cause: karyotype, serum inhibin B (in boys)

Second-Line Evaluation (if CDGP is not evident)

- GnRH test
- hCG stimulation test
- Serum inhibin B
- Olfactory-function test
- Genetic testing
- MRI

Second-Line Diagnosis

Low BMI
- GI disorder
- Underfeeding
- Anorexia

Normal BMI
- Hypothyroidism
- Hyperprolactinemia
- GH deficiency
- Multiple pituitary hormone deficiency

High BMI
- Glucocorticoid excess (iatrogenic, Cushing’s disease)
- Hypothyroidism

Intervention

Follow up
- Evaluate the need for the induction of secondary sex characteristics

Treat underlying cause

Treat with sex steroids
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.79:38 However, the amount of height gained as well as the optimal timing, dose, and duration of therapy with aromatase inhibitors remain uncertain.79 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.
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 or exogenous gonadotropins. 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 and increased insulin sensitivity, 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 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).*

<table>
<thead>
<tr>
<th>Drug and Formulation</th>
<th>In Children with CDGP</th>
<th>Side Effects and Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boys</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enanthate, cyionate, and propionate</td>
<td>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)</td>
<td>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</td>
</tr>
<tr>
<td>Undecanoate†</td>
<td>No data available on intramuscular injection</td>
<td>Local irritation; applied topically at bedtime; after application, must avoid close skin contact with others</td>
</tr>
<tr>
<td>Oral letrozole</td>
<td>2.5 mg daily</td>
<td>Decreased level of high-density lipoprotein cholesterol, erythrocytosis, vertebral deformities††</td>
</tr>
<tr>
<td>Oral anastrozole</td>
<td>1.0 mg daily</td>
<td>Less potent than letrozole</td>
</tr>
<tr>
<td><strong>Girls</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethinyl estradiol (component of contraceptive pills)</td>
<td>Initial dose, 2 μg daily; increase to 5 μg daily after 6–12 mo; lower-dose pills available in Europe</td>
<td>Liver toxicity, increased levels of some plasma-binding proteins, potentially greater risk of thromboembolism and arterial hypertension than with natural estrogens</td>
</tr>
<tr>
<td>17β-Estradiol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>Initial dose, 5 μg per kilogram of body weight daily; increase to 10 μg per kilogram daily after 6–12 mo</td>
<td>Natural estrogen, may be preferable to synthetic estrogens; transdermal route may have advantages over oral administration</td>
</tr>
<tr>
<td>Transdermal patch</td>
<td>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</td>
<td>No data on dose equivalent between estradiol patches and gel available in younger patients</td>
</tr>
<tr>
<td>Conjugated equine estrogens</td>
<td>Initial dose, 0.1625 mg daily for 6–12 mo with subsequent adjustment to 0.325 mg daily; dose depends on formulation</td>
<td>Not estradiol precursors; use is questioned as not being physiological and because of reports of increased cardiovascular risks in postmenopausal women</td>
</tr>
<tr>
<td>Progestin</td>
<td>Various options (usually oral)</td>
<td>Added to induce endometrial cycling after 12–18 mo of estrogen therapy (later if estrogen dose is increased slowly, sooner if breakthrough bleeding occurs)</td>
</tr>
</tbody>
</table>

* 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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