Klinefelter Syndrome

Cynthia M. Smyth, MD; William J. Bremner, MD, PhD

Klinefelter syndrome is the most common sex chromosome disorder. Affected males carry an additional X chromosome, which results in male hypogonadism, androgen deficiency, and impaired spermatogenesis. Some patients may exhibit all of the classic signs of this disorder, including gynecomastia, small testes, sparse body hair, tallness, and infertility, whereas others, because of the wide variability in clinical expression, lack many of these features. Treatment consists of testosterone replacement therapy to correct the androgen deficiency and to provide patients with appropriate virilization. This therapy also has positive effects on mood and self-esteem and has been shown to protect against osteoporosis, although it will not reverse infertility. Although the diagnosis of Klinefelter syndrome is now made definitively using chromosomal karyotyping, revealing in most instances a 47,XXY genotype, the diagnosis also can be made using a careful history and results of a physical examination, with the hallmark being small, firm testes. As it affects 1 in 500 male patients and presents with a variety of clinical features, primary care physicians should be familiar with this condition.

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be the normal XY type, whereas the extra X chromosomes may be detectable only in the testes or peripheral blood cells.11

The presence of an extra X chromosome is considered the fundamental etiologic factor of KS. The constant components of the disorder remain as Kleneifelter et al described, but in contrast to their hypothesis, Leydig cells are hypofunctional, although the testosterone levels may be in the normal range, and patients exhibit diverse degrees of virilization.1,11,12 Their hypothalamic-pituitary-gonadal axis11,15,23 is the classic 47,XXY.25 The prevalence may be greater, however, in certain groups such as patients seen for endocrine, psychiatric, or infertility problems.30,32

### Clinical Manifestations

When Leydig cell failure occurs before puberty, testosterone levels are low, the normal changes of puberty do not develop, and the obvious features of eunuchoidism are present. Features of androgen deficiency include eunuchoidal proportions with abnormally long legs (hips to soles, 2 inches greater than hips to head) and arm span greater than height; sparse or absent facial, axillary, pubic, or body hair; decreased muscle mass, with a feminine distribution of adipose tissue, including gynecomastia; and small testes and penis.20 In many patients, even with classic KS, testosterone levels may be in the normal or low-normal range (Figure 1).1,11 Total testosterone levels may be falsely high as serum hormone-binding globulin levels in patients with KS are elevated, and free testosterone levels, which may be a more accurate assessment of the androgen status in KS, are low.11,23 Serum levels of gonadotropins (particularly FSH) are uniformly elevated in KS.1,11 There is a wide variability in clinical expression, related to the timing and amount of androgen deficiency. The distribution of clinical and laboratory values in classic KS1,11 are shown in the following tabulation:

<table>
<thead>
<tr>
<th>Pathologic Feature</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infertility</td>
<td>99-100</td>
</tr>
<tr>
<td>Small testes</td>
<td>99-100</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>50-75</td>
</tr>
<tr>
<td>Decreased pubic hair</td>
<td>30-60</td>
</tr>
<tr>
<td>Decreased facial hair</td>
<td>60-80</td>
</tr>
<tr>
<td>Decreased testosterone levels</td>
<td>65-85</td>
</tr>
<tr>
<td>Elevated gonadotropin levels</td>
<td>90-100</td>
</tr>
<tr>
<td>Decreased penis size</td>
<td>10-25</td>
</tr>
</tbody>
</table>

The constant features of the disorder are small testes and absent spermatogenesis, whereas the fre-
frequency of decreased facial and pubic hair, gynecomastia, and low testosterone levels varies. Testis size is uniformly reduced, usually less than 2 cm in length, 1 cm in width, and 4 mL in volume in adults, compared with the normal values of 4 cm, 2.5 cm, and at least 15 mL, respectively. In addition, the tests are typically firmer than normal due to the fibrosis of the seminiferous tubules.

Mosaic individuals have an even wider diversity of findings, especially in the histologic characteristics of testicular biopsies. Samples from male subjects with XY/XXY genotype reveal that 14% to 61% of their seminiferous tubules contain maturing spermatids, which explains the rare cases of fertility in these patients.

The eunuchoidal skeleton often present in KS consists of an increased armspan, which exceeds body length by 2 cm or more, and an above-normal height, usually greater than 184 cm and mostly attributable to abnormally long legs. This increased length of the lower body—from pelvis to soles—is present before puberty and, therefore, does not arise primarily because of delayed epiphyseal closure due to androgen deficiency, but because of a fundamental difference in the growth rate caused by the presence of the additional X chromosome. Testosterone deficiency, however, contributes to the abnormal body proportions, as similar eunuchoidal skeletal features occur in other disorders of androgen insufficiency present before puberty (Figure 2).

ASSOCIATED DISORDERS

Breast carcinoma is rare in men; its incidence in most populations is less than 1 case per 100,000 man years. However, it is at least 20 times more common in patients with KS, who account for about 4% of all cases. Although some authors have not found a relationship between KS and male breast cancer, the sample studied may have been too small, as the expected incidence of breast cancer in KS is about 1 case in 5000 men. Nearly all patients with KS and breast cancer have gynecomastia, which may be a predisposing factor. Given this low frequency, there is no evidence to support the use of screening mammography or prophylactic resection of palpably enlarged breasts in KS.

Extragonadal germ cell tumors also occur with increased frequency in KS. The typical patient is 15 to 30 years of age and has metastatic disease, usually with mediastinal involvement, at the time of presentation. These neoplasms probably arise from incomplete migration of the primordial germ cells from the endoderm of the yolk sac to the urogenital ridge. The persistently elevated gonadotropin levels in KS may contribute to the malignant transformation of these cells. Even with extensive metastases, however, these tumors are potentially curable with chemotherapy.

Intellectual and Psychiatric Disorders

The prevalence of KS among male subjects in mental and penal institutions is about 1%, 5 times higher than in the general population, which has led to the belief that patients with KS are inherently mentally subnormal and prone to criminal behavior. Large-scale screening studies have refuted these impressions, but they have demonstrated a higher frequency of learning disabilities and poor impulse control, findings that may explain the increased rate of incarceration. Although many patients with KS have above-average or superior intelligence, poor school performance is common.
performance is common, with specific reductions in verbal IQ scores, delayed speech and language acquisition, diminished short-term memory, and decreased data retrieval skills. They may also have a higher incidence of dyslexia and attention-deficit disorder. These intellectual difficulties seem to derive from the extra X chromosome and, indeed, patients with KS variants possessing more X chromosomes (e.g., 48, XXXY; 49, XXXXY) have greater incidence of mental retardation.

Psychiatric disorders ranging from anxiety and neuroses to psychosis and depression are common in KS. Compared with other boys their age, adolescents with KS consider themselves more sensitive, introspective, apprehensive, and insecure. They also have more problems with peer groups and less sexual interest in girls. The combination of feminine physical features, poor motor coordination, and difficulties in speech and memory probably impairs the attainment of adequate self-esteem, increases anxiety, and promotes insecurity. The intertwining of these factors makes it difficult to determine what influence, if any, the extra X chromosome or a low androgen state has on human behavior. Testosterone replacement therapy advances the development of secondary sexual characteristics and alters gender identification and subsequent behavior; in addition, it may have independent effects on promoting self-esteem.

Osteoporosis

Androgen deficiency is an important risk factor for osteoporosis in men, and testosterone replacement therapy improves bone mineralization and osteoid formation, in part through the conversion of testosterone to estradiol, which prevents bone breakdown. Free testosterone levels are highly correlated with bone mineral density in patients with KS. Compared with controls, 25% or more of patients with KS have decreases in bone mineral density of 12% to 15%; patients with untreated KS have deficient testosterone levels during puberty and consequently do not achieve a normal peak bone mass. Testosterone replacement treatment before the age of 20 years can improve bone mass to normal values, whereas testosterone replacement therapy begun later produces no significant increase but may help prevent further bone loss and possibly fractures in older men.

Endocrine Disorders

Diabetes mellitus, although more common in patients with KS than in the general population, is generally mild and similar to the adult-onset form. Thyroid reserve levels appear diminished, but whether hypothyroidism is more frequent remains unclear. Adrenal function is normal.

Venous Disease

Klinefelter syndrome predisposes patients to various venous diseases. In 1 study, 21 (20%) of 104 patients had varicose veins, which were often severe and appeared at an early age. There is a 10- to 20-fold increased prevalence of venous ulcers and an increased risk for deep venous thrombosis and pulmonary embolism, perhaps related to a basement membrane defect in venous valves or an underlying hypercoagulable state.

Taurodontism

Taurodontism, an uncommon condition of the teeth affecting 0.5% to 3.0% of the general population, consists of enlargement of the pulp with a thin-
TREATMENT

Testosterone replacement treatment has no effect on infertility caused by KS, but it corrects the androgen deficiency. This therapy results in an increase in facial and pubic hair, a more masculine distribution of body fat, more goal-directed thinking, improved self-esteem, less fatigue and irritability, and increased libido, strength, and bone mineral density. The optimal time to initiate testosterone replacement therapy is at the beginning of puberty, about age 11 or 12 years. This timing permits boys with KS to experience pubertal changes similar to their peers and allows testosterone to have its most marked effects on bone mineral density. When the diagnosis of KS is made in adulthood, testosterone replacement therapy is still beneficial in producing positive changes in mood and behavior, muscle mass, and bone integrity.

The increased testosterone serum levels resulting from this therapy eventually produce a decrease in serum LH and FSH levels. The effect on gonadotropin levels, however, is not so rapid or pronounced as it is in controls. Once begun, testosterone administration should continue throughout life in patients with KS. In addition to its virilizing effects, it also stimulates erythropoesis and increases the number of suppressor T lymphocytes. It has no effect on testicular size or spermatogenesis, and it usually does not reduce gynecomastia, which can be very well treated with plastic surgery.

The most widely used form of androgen replacement therapy is the intramuscular injection of testosterone enanthate and testosterone cypionate, which have similar pharmacokinetics and safety profiles. Typical doses necessary to maintain normal serum testosterone levels for an adult with KS are 200 mg of either ester every 2 weeks, when started in puberty, doses are usually 50 to 100 mg initially, with an increase of 50 to 100 mg every 2 to 4 weeks until adult doses are reached. Because of the small testes, the scrotal sac is diminished, and its surface area is insufficient for transdermal preparations of testosterone requiring administration at that site. Although convenient, newer formulations that may be applied on nonscrotal skin are more expensive than intramuscular testosterone preparations, and their use in patients younger than 18 years has not received adequate evaluation.

Weight gain may occur during testosterone replacement therapy, due to the accumulation of lean body mass and fluid. Mild acne may also occur. Sleep apnea may occasionally develop in older men and cause erythropoiesis. Androgens also lower high-density lipoprotein levels, so lipoprotein and hematocrit levels should be followed up. In general, the testosterone esters are well tolerated at replacement doses, and the benefits of increased bone density, a more masculine physique, and overall psychological well-being outweigh these side effects in patients with KS.

SCREENING

The diagnosis of KS may be made in utero when chromosomal karyotyping is performed on a sample of amniotic fluid obtained routinely from pregnant women of advanced maternal age. Parents told of the diagnosis of KS should be carefully counseled on the wide variety of clinical manifestations that may be present in their child. This information can help parents consider testosterone replacement therapy early in puberty and increase their awareness of learning disabilities and gender identification issues that may present during childhood or adolescence.

All school-age boys should have their testes palpated as part of a complete physical examination, and those with learning disabilities or trouble with their peers deserve special attention. Typical size of less than 4 mL, gynecomastia, taur-


