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## Klinefelter syndrome presenting as behavioral problems in a young adult

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### Abstract

**Background**—An 18-year-old Somali man presented to a primary care clinic to investigate a potential pathophysiological reason for behavioral problems at school that had arisen in the past 1–2 years. A previous physical examination at school revealed the patient to have small, firm testicles which prompted further testing.

**Investigation**—Thyroid function and levels of prolactin, total testosterone, follicle-stimulating hormone and luteinizing hormone were determined. Testes were measured. Chromosome analysis testing was performed to determine the patient's karyotype.

**Diagnosis**—Klinefelter syndrome with a 47,XXY karyotype.

**Management**—Testosterone replacement therapy was recommended, but the patient declined treatment.

### The case

An 18-year-old Somali man presented to a primary care clinic with concerns about behavioral problems at school. Along with his sibling and mother, he had immigrated to the US 3 years earlier, after fleeing somalia with his family at the approximate age of 3 years and living in a Kenyan refugee camp for approximately 12 years. He provided paperwork from his school stating that he would frequently leave class and wander the hallways for several minutes before returning. When confronted by school staff, he became angry. He denied boredom or restlessness and provided no explanation for his actions. The family attributed his behavior to a head injury at 4 months of age, but the behavioral issues at school had only become apparent in the past 1–2 years. His mother stated that he had always been easily distracted, would forget about commitments and lie frequently. Shortly after immigration to the us, he had been transferred to special education classes because of an

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#### Author contributions

All authors researched the data for the article, provided a substantial contribution to discussions of the content, contributed equally to writing the article and reviewed and/or edited the manuscript before submission.

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inability to stay focused in class and poor school performance. Learning disability evaluations at the time were inconclusive owing to inattentiveness and limited English proficiency of the patient. He did not meet criteria for a diagnosis of mental illness or attention deficit–hyperactivity disorder (ADHD) when evaluated by his school. The patient had no previous medical care other than a brief physical examination upon his arrival in the US at immigration. He had no other known past problems or injuries. He was taking no medications and denied use of tobacco, alcohol or other drugs. The school nurse who had completed a physical exam that is required before participation in school sports programs contacted the health-care provider at the time of the patient's initial visit regarding concern about the patient's very small testicular size. The patient had not contacted the clinic because of the testicular size discrepancy, but rather in hopes of receiving brain imaging and referral for further psychiatric evaluation. He denied any history of sexual activity with others. On review of systems at admission, he denied anosmia.

At the time of physical examination, the patient was a slim male with a height of 178 cm, weight of 53.7 kg and a BMI of 16.9 kg/m<sup>2</sup>. His long arms and legs were noted, but length of limbs was not measured. The patient had a sparse beard but showed normal hair growth in the axillary, chest and genital areas. He had no gynecomastia. The patient's stage on the Tanner scale (which defines physical measurements of development on the basis of external primary and secondary sex characteristics) was normal for his age as regards hair growth and penis size (Tanner stage 5, penis length approximately 15 cm). His testicles were firm and total testicular volume was <10 cm<sup>3</sup> as measured by a ruler. The patient showed no visual field deficits, as determined by confrontation field testing.

Thyroid function, levels of prolactin, total testosterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were normal (Table 1). Karyotype testing of peripheral blood mononuclear cells revealed a 47,XXY karyotype in 20 of 20 cells examined. Sperm count was not determined, as the patient was not concerned about his fertility at the time of examination.

The patient was informed that his testosterone levels were on the low end of the normal range and that testosterone treatment might improve cognition and concentration, but the patient declined hormone replacement therapy. He agreed to have an explanatory letter sent to his school. The patient continued to have difficulty in school and has now opted to start treatment.

## Discussion of diagnosis

Klinefelter syndrome with the classic 47,XXY karyotype is a common chromosomal abnormality affecting one in 500–1,000 males. The extra chromosome can originate from either parent as the result of a nondisjunction event during germ-cell meiosis.<sup>1</sup> In 7% of men with Klinefelter syndrome, a nondisjunction error in embryonic mitosis can result in a mosaic variant (46,XY/47,XXY) and usually confers a less severe form of the disease depending on the proportion of trisomic to normal cells.<sup>2,3</sup> By contrast, higher grade aneuploidies, such as 48,XXXY or 49,XXXXY, although rare, are associated with more severe physical and cognitive manifestations.<sup>4</sup>

Despite the availability of chromosome analysis testing in many laboratories, Klinefelter syndrome remains severely underdiagnosed. An estimated 10% of cases are detected during prenatal amniocentesis, and an additional 26% are diagnosed during childhood or adulthood.<sup>2</sup> A large Danish study reported even lower rates of diagnosis, with only one-fourth of adult men with Klinefelter syndrome being diagnosed.<sup>3</sup> The investigators also found a substantial delay in diagnosis, with only 10% of cases identified before puberty.<sup>3</sup>

Much of the difficulty in the diagnosis of Klinefelter syndrome stems from the wide variety of symptoms and signs and their emergence only at puberty. With reductions in the frequency and duration of appointments when a patient is examined in primary care, as well as the decreased frequency of testicular exams performed for screening purposes, this condition is often missed. Detection during infancy and early childhood is rare. Occasionally, small phallus or hypospadias will prompt karyotype testing, but often the genitals are normal through early childhood.<sup>5</sup> After the age of 5 years, affected boys have a marked acceleration in growth rate, primarily as a result of abnormally long leg length which may be an early indication of Klinefelter syndrome. The pathophysiology of the increased growth rate of the legs has not been determined, but as it occurs before puberty, it is thought to be related more directly to the presence of an extra X chromosome, rather than to hormonal changes.

Puberty occurs at a normal age, but primary testicular failure ensues, resulting in small firm testes with a volume of <10 cm<sup>3</sup> each side, azoospermia and a variable degree of androgen deficiency. Whereas some boys develop essentially normal secondary sexual characteristics, a greater number of affected patients will manifest the classic picture of tall stature, eunuchoid habitus, sparse body and facial hair, decreased muscle mass and a female distribution of body adipose tissue.<sup>5,6</sup> The prevalence of gynecomastia is poorly studied, with reports varying widely from 38–80%.<sup>1,4,5,7</sup> Small firm testes and infertility are nearly universal in men with Klinefelter syndrome.<sup>7</sup>

Testosterone concentrations begin to decline markedly around the time of puberty, and FSH and LH concentrations will correspondingly increase.<sup>5</sup> In general, LH and FSH levels will not be in the normal range in men with Klinefelter syndrome aged >14 years.<sup>8</sup> The case patient was 18 years of age with normal LH and FSH levels, calling into question the true age of the patient. Many refugees from somalia are uncertain as to their year of birth, and wide variance and inaccuracies in the stated age of these individuals are frequent.

Some patients, as in the described case, have normal total testosterone concentrations. One explanation may be a 'pseudonormalization' owing to a high concentration of serum hormone-binding globulin and, therefore, free testosterone concentration may be a more accurate means of assessing androgen status.

Evaluation for infertility is the most common reason adult patients seek medical attention. Additionally, more than two-thirds of patients aged >25 years will report erectile dysfunction and diminished sexual interest.<sup>1</sup> Azoospermia is found on semen analysis. Karyotype testing is usually diagnostic, but results may be falsely negative in mosaic individuals. No universally accepted diagnostic criteria exist, and some experts have

suggested that an individual with low-grade mosaicism and few manifestations should not be labeled as having Klinefelter syndrome.<sup>5</sup> Some 47,XXY/46,XY mosaic patients may even exhibit intact fertility.<sup>2</sup>

### Cognitive and behavioral manifestations

Early studies reported disproportionate numbers of individuals with Klinefelter syndrome in the prison system, which led to the perception that Klinefelter syndrome was associated with criminality.<sup>5,7</sup> This finding was later refuted in large-scale screening studies, but certain cognitive patterns such as poor impulse control and learning disabilities have been observed in patients with this disorder.<sup>7</sup> As in the case patient, behavioral problems can be the primary drive to seek medical care and may be one of the first clues to diagnosis. Long-term prospective studies have shown that patients with the classic 47,XXY karyotype have mean intelligence scores in the average to low-average range.<sup>9</sup> In general, individuals with below average scores show learning difficulties in specific areas of verbal and executive tasks.<sup>5,9</sup> Delayed speech, slower than average problem-solving abilities, impulsiveness, reduced attention span, memory problems and possibly dyslexia and autism have been reported.<sup>1,7,9–11</sup> Longitudinal studies suggest that reduced verbal skills are prominent in children with Klinefelter syndrome, but whether these difficulties persist into adulthood is less evident.<sup>9</sup> Certainly, adults with Klinefelter syndrome have attained a wide range of educational and professional accomplishments.<sup>5,10</sup> High-grade aneuploidies, such as 48,XXXY and 49,XXXXY, are associated with decreased intelligence quotient scores, with a drop of approximately 15–16 points for each additional X chromosome.<sup>4</sup> Notably, more than 1,000 genes are encoded on the X chromosomes, many of which are expressed in the brain.<sup>12</sup> However, how the interplay between these genes, X chromosome inactivation and androgen deficiency accounts for the cognitive phenotype remains undetermined.<sup>9</sup>

Patients with Klinefelter syndrome have a higher burden of psychiatric conditions, especially depression, anxiety, schizophrenia and psychosis, than the general population.<sup>4,5,13,14</sup> Adolescents are described as being sensitive, introspective and unassertive.<sup>4,7,10</sup> These characteristics may be related to feelings of insecurity about physique, speech difficulties and perceived acceptance from peers.<sup>7</sup> However, some studies have found that patients with Klinefelter syndrome tend to have more difficulty in interpreting social and emotional cues and show more distress during social interactions.<sup>11,15,16</sup> An association between autistic behavior and the X chromosome has been proposed,<sup>16</sup> but additional research is needed to confirm any relationship. Researchers of a large cohort study found that Klinefelter syndrome was associated with diagnoses of psychoses, neuroses and personality disorders.<sup>17</sup>

Previous studies of children and young adults with Klinefelter syndrome found a greatly decreased linguistic ability and increased diagnosis of ADHD, thus leading to a recommendation to screen for Klinefelter syndrome in boys with language disabilities and/or behavioral difficulties.<sup>18</sup> However, language disabilities can manifest as subtle problems with linguistic processing, and no singular phenotype exists.<sup>19</sup> In refugees, such as the described patient, behavioral and cognitive problems can be common, arising from the physical and psychological trauma of experiencing a childhood in war-torn countries and

refugee camps. Keeping in mind lack of previous medical care among many immigrants and refugees, the practitioner has a duty to screen for Klinefelter syndrome and other potential endocrinologic or medical diagnoses in these individuals.

## Treatment and management

### Cognitive abilities

Provided that Klinefelter syndrome is identified early on in childhood, speech therapy and attention to learning problems can minimize or prevent speech and language difficulties later in life.<sup>5,10</sup> Parents and teachers can modify the patient's school curriculum with a focus on vocabulary, syntax and auditory memory skills.<sup>10</sup> These changes were suggested to the case patient's school, and he received additional support.

### Testosterone replacement therapy

No consensus on the best timing of starting testosterone therapy in adolescents has been reached to date. However, if pubertal development is not evident by age 14, initiation of testosterone replacement therapy should be recommended. Testosterone replacement therapy can aid in normal pubertal development, including an increase in muscle mass, masculine distribution of body adipose tissue, body and facial hair and libido. This normalization, in turn, may help preserve the self-confidence of the affected individual. Testosterone replacement therapy may also improve mood, concentration, energy and social interactions with peers.<sup>5</sup> Once initiated, life-long testosterone replacement is recommended to maintain virilization, energy and libido, as well as to minimize a decline in BmD.<sup>7,20</sup> Although population-based studies have found that Klinefelter syndrome is associated with a 40% increased risk in mortality, primarily owing to neurologic, circulatory, respiratory and genitourinary diseases, whether testosterone replacement therapy mitigates this risk is unknown.

Timely initiation of testosterone replacement can prevent the development of gynecomastia, but it rarely reverses this complication once it has occurred. At this point, surgery is the only option. Moreover, testosterone replacement does not restore infertility which affects over 99% of men with Klinefelter syndrome.<sup>12</sup>

Testosterone replacement can be accomplished by several routes (Table 2). Intramuscular injections of testosterone enantate every 2–3 weeks is the simplest and most common means of testosterone administration. A new injectable form, testosterone undecanoate, is available in many countries and can be administered every 10–12 weeks to treat testosterone deficiency. The intramuscular injections have several disadvantages. First, patients may not tolerate the serial injections owing to localized pain, bleeding and bruising. Also, testosterone concentrations tend to fluctuate from high levels immediately after administration to low levels before the next scheduled dose.

Transdermal patches and gels have become quite popular, and their daily administration may mimic the body's physiologic circadian pattern. Drawbacks to transdermal approaches include skin rashes and a substantially greater cost than injectable testosterone. Topical gel

products unfortunately carry the risk of inadvertent transmission to individuals in close contact with the patient.

Oral formulations are generally used as a last resort because of widely variable pharmacokinetics and the so-called 'first-pass effect' that results from metabolism of testosterone in the liver.<sup>21</sup> Oral alkylated androgens such as methyltestosterone are formulated to minimize the first-pass effect, but carry a risk of hepatotoxicity and are, therefore, not widely used.<sup>22</sup> Buccal testosterone, which also avoids the first-pass metabolism, has limited use owing to its wide variations in absorption.<sup>21</sup>

Regardless of the mode of administration, the dose is titrated with a goal of reducing symptoms and normalizing LH and serum testosterone concentrations.<sup>4,5,7</sup> Adolescents are usually started at low doses initially, which are gradually increased to adult doses over a period of several years.<sup>10</sup>

## Fertility

For those patients who want children, the only options used to be *in vitro* fertilization using donor sperm or adoption. The finding that viable testicular sperm can be surgically retrieved from testes of adult men with Klinefelter syndrome challenged the previous notion of complete azoospermia. Indeed, spontaneous pregnancy in nonmosaic individuals has been reported in the literature.<sup>23</sup> When combined with medications such as aromatase inhibitors and human chorionic gonadotropin to increase endogenous testosterone production, microsurgical testicular sperm extraction (TESE) can recover viable sperm in almost three-quarters of cases. Although the quantity of sperm is insufficient for intrauterine insemination, intracytoplasmic injection (ICSI) results in pregnancy in over 50% of couples.<sup>5,24</sup> TESE can also be used to retrieve sperm for cryopreservation for couples who desire multiple future pregnancies but want to avoid repeat TESE surgery. Reproductive technologies such as TESE and ICSI offer promise for men with Klinefelter syndrome, but health insurance companies frequently do not cover the costs, which are substantial.<sup>6,12</sup>

## Issues of long-term care

Most of the considerations for screening in Klinefelter syndrome are related to alterations in the hormonal milieu, which increase the risk of comorbid conditions, such as osteoporosis and venous disease (Table 3).

Androgen deficiency increases the risk of osteoporosis. Untreated Klinefelter syndrome during puberty prevents achievement of normal bone mass. Individuals with Klinefelter syndrome who have been treated with testosterone have a decreased risk of osteoporosis, in part because testosterone is converted to estradiol which helps prevent the breakdown of bone.<sup>7</sup> Testosterone treatment started >20 years of age will not achieve normal BMD goals in individuals with Klinefelter syndrome but can prevent further bone loss; no studies have examined its effect on the reduction of fractures.<sup>20,22</sup>

Gynecomastia may be a predisposing factor for the development of breast cancer; however, the evidence is weak.<sup>7</sup> A Danish register study did not demonstrate an increased risk of mortality from breast cancer.<sup>25</sup> Even in the studies which did show a relative increased risk

of breast cancer in individuals with Klinefelter syndrome, the overall risk was still vastly lower than that of women.<sup>4,5,26</sup> Therefore, screening tests such as mammograms are not recommended.<sup>7,26</sup>

Men with Klinefelter syndrome have a 10-fold increased risk of varicose veins and venous ulcers. They also have a fivefold increased risk of deep vein thrombosis and pulmonary embolism.<sup>27</sup> Cases of Klinefelter syndrome have been reported that first presented with leg ulcers and deep vein thrombosis.<sup>28</sup> The etiology of this increased risk remains unclear.

Taurodontism, a dental problem caused by a larger pulp to enamel ratio that leads to early tooth decay,<sup>29</sup> is present in 40–75% of individuals with Klinefelter syndrome, compared with <3% in the general population. This association between Klinefelter syndrome and taurodontism has led to efforts to increase awareness among dentists, so that they may counsel patients, parents or physicians to seek karyotype testing if taurodontism is found on dental radiography.<sup>30</sup> Patients diagnosed with Klinefelter syndrome should be counseled about their increased risk of tooth decay and referred to dental care.

Increased risk of diabetes mellitus and the metabolic syndrome has also been noted in patients with Klinefelter syndrome. The reasons for this association remain elusive. Prospective studies in other populations have shown that low levels of testosterone changes the distribution of body adipose tissue, favoring abdominal obesity. This truncal obesity has been proposed to increase insulin resistance and is the cause for increased incidence of the metabolic syndrome in this patient population.<sup>5</sup>

Overall, men with Klinefelter syndrome exhibit a decreased life expectancy, with a significantly reduced median survival of 2.1 years.<sup>25</sup> No single cause has been identified as the main reason for this reduced survival; rather excess mortality was the result of a wide variety of diseases, including infectious, neurological, circulatory, pulmonary and genitourinary diseases.

## Conclusions

Klinefelter syndrome is common, as it affects one in 500–1,000 men, but it remains undiagnosed in the majority of patients suffering from the disease. Behavioral problems or learning delays may be the first presenting symptom, as illustrated by the described case. Poor and immigrant populations may be particularly vulnerable to missed diagnoses, given the limited access of these individuals to amniocentesis, pediatric care or infertility evaluations, which are the most common avenues that lead to a diagnosis of Klinefelter syndrome. Physicians should consider the possibility of Klinefelter syndrome when caring for adolescent boys with difficulties at school, given that the diagnosis may help to tailor educational resources. Furthermore, treatment with testosterone can lessen the stigma of appearing different from peers and may improve mood and cognition. Compared with the general population, individuals with Klinefelter syndrome have an increased risk of developing osteoporosis, breast cancer, venous disease and tooth decay. Increased awareness among physicians and patients can help to detect and treat these problems as they arise.

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#### Learning Objectives

Upon completion of this activity, participants should be able to:

1. Describe the epidemiology and prognosis of Klinefelter syndrome.
2. Examine effective diagnostic strategies for Klinefelter syndrome.
3. Apply results from the current review to development of effective management plans for the long-term care of patients with Klinefelter syndrome.

**Table 1**

Investigations performed in the case patient

<b>Parameters</b>	<b>Result</b>	<b>Reference range</b>
TSH (mIU/l)	0.821	0.4–5.0
Free T <sub>4</sub> (pmol/l)	10.3	7.7–15.4
Total T <sub>3</sub> (nmol/l)	2.3	1.1–2.7
Prolactin (pmol)	304	0–608
Total testosterone (nmol/l)	12.5	8.7–34.7
Follicle-stimulating hormone (IU/l)	8	0–14
Luteinizing hormone (IU/l)	8	0–14

**Table 2**

## Options for testosterone replacement therapy

<b>Formulation</b>	<b>Dose</b>	<b>Advantages</b>	<b>Disadvantages</b>
<i>Intramuscular</i>			
Testosterone cypionate or testosterone enantate	50–200 mg every 2–3 weeks	No clear advantages over other options but possibly less expensive, if self-administered	Peak and trough effects (that is, symptoms disappear after an injection, but gradually return as testosterone levels decline) Frequent injections may not be tolerated owing to localized pain, bleeding and bruising
Testosterone undecanoate	1 g every 10–12 weeks	Less frequent injection than with testosterone cypionate	Large (4 ml) injection volume Rare postinjection cough
<i>Oral</i>			
Buccal	30 mg twice per day	No injection	Variable absorption Frequent dosing per day
Testosterone undecanoate	40–120 mg two to three times daily	No injection	Frequent dosing per day
<i>Topical</i>			
Gel	5–10 g per day 1% gel	No injection Mimics physiologic circadian patterns	Expensive Occasional skin irritation Risk of person-to-person spread
Transdermal patch	5 mg per day (nonscrotal patch) 5–15 mg per day (scrotal patch)	No injection Mimics physiologic circadian patterns	Expensive Frequent skin irritation Adhesion problems

**Table 3**

Screening considerations for long-term complications of Klinefelter syndrome

<b>Complication</b>	<b>Prevention</b>	<b>Screening</b>
Osteopenia and osteoporosis	Can be prevented by testosterone replacement therapy started during puberty	BMD scan Measurement of vitamin D level
Breast cancer (rare)	Surgical correction of gynecomastia may reduce risk	Physical exam Screening mammogram not recommended
Varices	Avoid prolonged standing, consider compression stockings	Physical exam
Leg ulcers	Avoid prolonged standing, consider compression stockings	Physical exam
Deep venous thrombosis	Caution with prolonged air and car travel	Physical exam
Taurodontism	Good oral hygiene	Regular dentistry visits
Diabetes mellitus	Exercise and diet	Measurement of fasting glucose levels or HbA <sub>1c</sub> testing
Metabolic syndrome	Exercise and diet	Measurement of waist circumference and fasting lipid levels