Klinefelter Syndrome

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Key Points

Genetics

- Klinefelter syndrome should be considered in boys with gynecomastia or hypogonadism.
- The diagnosis of Klinefelter syndrome will lead to the initiation of testosterone replacement therapy and may help facilitate access to appropriate educational resources.

Ethics

- Primary care physicians can help affected boys and their parents understand and adjust to the diagnosis.

Learning Objectives

Participants will be able to:

- Describe clinical indicators for workup of Klinefelter syndrome in boys and adolescent males;
- Explain the concerns that could be faced by adolescents with Klinefelter syndrome;
- Describe the benefits of an early diagnosis of this syndrome.

Family History Issues

Klinefelter syndrome (47,XXY) is a sporadically occurring chromosome abnormality with a prevalence of approximately 1/500 in males. Family history does not represent a risk factor for this condition.

Red Flags 

Klinefelter syndrome is suspected in males with developmental delay, hypogonadism, gynecomastia, or infertility. It is likely that many males with 47,XXY remain undiagnosed.

Case 28. A 14-Year-Old Boy: the Clinical Utility of a Diagnosis of Klinefelter Syndrome

Your patient Ronnie P started having difficulties in school when he was eight years old. His teacher noted that he seemed to be irritable and impulsive; she raised the possibility of attention deficit disorder. In addition, Ronnie was noted to have mild difficulties with spelling and composition. Although he was requiring some additional help with these tasks, his IQ was normal (104) and he had been progressing academically with his peer group. He was tall for his age (95th percentile in height). He had no physical or medical problems. A detailed evaluation by a psychologist revealed some impulsivity, but insufficient findings to support a diagnosis of attention deficit disorder. Tutoring was arranged, and he continued to progress adequately in school.

At age 14 years, he develops gynecomastia. At this point, he is seen by an endocrinologist who raises the question of Klinefelter syndrome, because of the combination of gynecomastia and small testes. A chromosomal study reveals a 47,XXY karyotype.

Clinical Care Issues

Klinefelter syndrome

The diagnosis of Klinefelter syndrome is based on the presence of at least one extra X chromosome, in the presence of a Y chromosome. The most common form of Klinefelter syndrome is due to a 47,XXY karyotype and is found in about 80% of cases, but can also be due to variant karyotypes, such as 48,XXXY, 48,XXYY, 49,XXXXY, and 47,XXY/46,XY mosaicism [Lanfranco et al 2004]. The prognosis of individuals with variant karyotypes can be different from the prognosis of 47,XXY individuals. Some geneticists reserve the term "Klinefelter syndrome" for symptomatic adolescents and adults, and refer to fetuses, newborns, or children without symptoms as having 47,XXY.

Medical findings in Klinefelter syndrome. Individuals with Klinefelter syndrome may have characteristic clinical findings that can be treated by medical or other kinds of intervention. Most significantly, individuals with Klinefelter have small testes with azoospermia and deficient production of testosterone in adolescence and adulthood. The majority of affected males enter puberty at the expected chronological age,f but testicular size does not increase as expected. If untreated, adolescents may have gynecomastia and inadequate secondary sexual development. Individuals with Klinefelter syndrome benefit from testosterone replacement therapy to promote secondary sexual development and normal sexual function. In addition, for many people with Klinefelter syndrome, normal serum testosterone concentration is associated with improved strength, activity level, mood, concentration, libido, and sense of well-being. It also has a positive effect on bone mineral density. Once present, gynecomastia is not influenced by testosterone replacement therapy.

Gynecomastia is unlikely to resolve spontaneously in Ronnie's case. Although treatment is usually not medically indicated, surgical intervention can be performed for psychological and/or aesthetic reasons by a surgeon experienced in mammary plastic surgery.

Males with Klinefelter syndrome are usually infertile and appropriate anticipatory guidance may be helpful for Ronnie as he progresses through puberty. Some men produce a small number of sperm, allowing for the use of assisted reproductive techniques with intracytoplasmic sperm insertion (ICSI) to achieve pregnancy [Tachdjian et al 2003]. Since fertility is occasionally possible in Klinefelter syndrome, affected males should not assume they are infertile without semen analysis. Testosterone replacement therapy does not improve fertility.

Developmental issues in Klinefelter syndrome. Klinefelter syndrome is associated with an increased prevalence of learning disabilities, particularly in language-based learning skills. In the first six to 12 months, a delay is typically seen in the use of words and phrases. In school-aged children, language problems can manifest in tasks such as reading and spelling. Deficits in language development are shown in verbal IQ scores, which are significantly lower than sibling controls although performance IQ scores are not significantly different [Manning & Hoyme 2002].

Having a medical explanation may facilitate formal evaluation of learning disabilities and appropriate educational interventions. Outcome data quantifying the benefit of such interventions are not available. However,

children with medical diagnoses are eligible for testing and intervention earlier than children who do not have a specific identified cause for delay.

Because Ronnie's diagnosis was established during puberty, he may have unique concerns. Physical changes he has experienced, such as gynecomastia, can predispose to feelings of embarrassment and insecurity. School difficulties and relatively low muscle strength and agility associated with Klinefelter syndrome also may negatively affect his self-esteem. Such problems may manifest as anger, frustration, or depression.

Risk Assessment

Klinefelter syndrome occurs from non-disjunction, the failure of the X chromosomes (or X and Y chromosomes) to separate properly in the process of ovum or sperm development, resulting in the presence of an extra X chromosome. This is usually a sporadic event and is not hereditary. There are no parental behaviors or maternal exposures that are known to cause Klinefelter syndrome.

Genetic Counseling and Testing

If Ronnie's parents have more children, their risk of having another child with a chromosome imbalance is less than 1% when maternal age is less than 38 years, and rises as an age-related risk after that time. Other family members are not at increased risk of having a child with a chromosome abnormality.

Interventions

Testosterone replacement therapy is recommended to treat or prevent the following: sparse body and facial hair, breast development, and diminished libido. Hormone treatment is also helpful in stimulating energy level, muscle mass development, and general well-being, and may prevent osteoporosis. If hypogonadism is recognized early enough, testosterone replacement therapy should be offered at the time of puberty. It may help with psychological adjustment through improved body image and mood. Because the most effective methods of androgen replacement therapy are still being perfected and vary among individuals, referral to a pediatric endocrinologist is recommended for boys with Klinefelter syndrome before the start of puberty, at about age 11-12 years, or as soon as the diagnosis is made.

Due to testosterone deficiency, men with Klinefelter syndrome are at

increased risk for osteoporosis. Optimal calcium and vitamin D intake should be encouraged. Screening for osteoporosis with bone mineral density studies can help determine if osteoporosis is present before medical complications occur.

Men with Klinefelter syndrome seem to have an increased risk of breast cancer [Hultborn et al 1997, Swerdlow et al 2001] and may benefit from instruction in breast self-exam and from counseling to bring any breast abnormalities to medical attention. Screening mammography has no role in men because of the rarity of the disease and the small size of the male breast, which allows easy palpation of most masses [Giordano et al 2002].

Men with Klinefelter syndrome are also at increased risk for autoimmune disorders such as diabetes mellitus and hypothyroidism. Additionally, men with this condition are prone to varicose veins and leg ulcers due to venous stasis. Although no formal guidelines have been established, an annual physical examination should include an assessment of signs and symptoms of these disorders [Robinson et al 2001].

XXY males should be evaluated for the presence of specific learning problems and for negative self-appraisal. Such an evaluation includes academic testing, oral and written language skills, and memory and auditory processing. Identification of specific learning disabilities can lead to development of an individualized educational program (IEP) for students who meet certain criteria.

Ethical/Legal/Social/Cultural Issues

Ronnie may struggle in adjusting to his diagnosis. He may feel different from his peers, both with respect to his physical development and because of his history of learning problems. Ronnie may be struggling to hide his gynecomastia.

In talking to Ronnie and his parents, it may be helpful to point out the advantages of having the diagnosis of Klinefelter syndrome at this age. Testosterone replacement therapy will help him develop secondary sexual characteristics like other males. The diagnosis will lead to a better understanding of the reason for his developmental problems. Educating this family about Klinefelter syndrome should focus on the benefits of knowing about the diagnosis so that his treatment can be optimized.

Resources

- **American Association for Klinefelter Syndrome and Support**
- **Klinefelter Syndrome Support Group Homepage**
- **National Library of Medicine Genetics Home Reference**
  Kinefelter syndrome
- **GeneTests Online Medical Genetics Information Resource**
- ***GeneReviews*, GeneTests Online Medical Genetics Information Resource**

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