KLINEFELTER SYNDROME: A CHROMOSOME DISORDER

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Summary

Klinefelter syndrome is the most common genetic sex chromosome disorder cause of human male infertility. Affected males carry an additional X chromosome, which results in male hypogonadism, androgen deficiency, and impaired spermatogenesis. Klinefelter syndrome or XXY terms are often used interchangeably, they actually refer to two quite different, though related, conditions. Male with Klinefelter syndrome affects gynecomastia, small testes, sparse body hair, tallness whereas others, because of the wide variability in clinical expression, lack many of these features. Most men who have Klinefelter syndrome are not able to father children. However, some men with an extra X chromosome have fathered healthy offspring, sometimes with the help of infertility specialists. Most men who have Klinefelter syndrome can expect to have a normal and productive life. Early diagnosis, in conjunction with educational interventions, medical management, and strong social support will optimize each individuals potential in adulthood. Treatment consists of testosterone replacement therapy to correct the androgen deficiency and to provide patients with appropriate virilization. The XXY chromosome pattern can not be changed. But, there are a variety of ways to treat the symptoms of the XXY condition as educational treatments, therapeutic options, medical treatments. Here, we review the literature functions of Klinefelter syndrome, its symptoms, causes and treatment.

KEYWORDS: Klinefelter syndrome, XXY, Sex chromosome

Introduction

Klinefelter syndrome is the most common form of male hypogonadism with a characteristic chromosomal abnormality of 47, XXY[1], also known as the XXY condition, describes a group of chromosomal disorder in which there is at least one extra X chromosome added to a normal male karyotype, 46, XY. As more individuals suspected of having Klinefelter syndrome had chromosome studies done, other karyotypes were sometimes observed, such as 48, XXYY; 48, XXXY and 49, XXXXY[2-3]. This Klinefelter syndrome (KS) can be synonymed as XXY male – XX male – XXYY male – XXXY male – XXXXY male[4].

Klinefelter syndrome is found in about 1 out of every 500-1,000 newborn males. The additional sex chromosome results from a random error during the formation of the egg or sperm. About half of the time the error occurs in the formation of sperm, while the remainders are due to errors in egg development. Women who have pregnancies after age 35 have a slightly increased chance of having a boy with this syndrome[5].

HISTORY

Klinefelter syndrome or XXY terms are often used interchangeably, they actually refer to two quite different, though related, conditions. In 1942, Dr. Harry Klinefelter while working at the Massachusetts General Hospital in Boston published with fellow researchers a report about nine adult males who had similar features[6]:

- tall (around six feet)
- small testes or hypogonadism
- inability to produce sperm
- sparse facial and body hair
- gynecomastia

By the late 1950's researchers discovered that men with these features (Klinefelter syndrome), had an extra X sex chromosome, and were XXY instead of the typical male arrangement of XY.

It was believed to be an endocrine disorder of unknown etiology, until 1959, when Jacobs *et al*. recognized that Klinefelter syndrome was a chromosomal disorder in which there is an extra X chromosome resulting in the karyotype of 47,XXY [7].

CHROMOSOMES AND KLINEFELTER SYNDROME

Chromosomes, the spaghetti-like strands of hereditary material found in each cell of the body, determine such characteristics as the color of our eyes and hair, our height, and whether we are male or female. Women usually inherit two X chromosomes-one from each parent. Men tend to inherit an X chromosome from their mothers, and a Y chromosome from their fathers. Most males with the syndrome Dr. Klinefelter described, however, have an additional X chromosomes total of two X chromosomes and one Y chromosome. [6,8]

SYMPTOMS

Males who have Klinefelter syndrome may have the following symptoms: The most common symptom is infertility. Other symptoms may include:

- Abnormal body proportions (long legs, short trunk, shoulder equal to hip size)
- Enlarged breasts (gynecomastia)
- Sexual problems

- Less than normal amount of pubic, armpit, and facial hair
- Small, firm testicles
- Tall height

Not all males with the condition have the same symptoms or to the same degree. Symptoms depend on how many XXY cells a man has, how much testosterone is in his body, and his age when the condition is diagnosed. The XXY condition can affect three main areas of development:

- ***Physical development***: As babies, many XXY males have weak muscles and reduced strength. They may sit up, crawl, and walk later than other infants. After about age four, XXY males tend to be taller and may have less muscle control and coordination than other boys their age[9].
  As XXY males enter puberty, they often don't make as much testosterone as other boys. This can lead to a taller, less muscular body, less facial and body hair, and broader hips than other boys. As teens, XXY males may have larger breasts, weaker bones, and a lower energy level than other boys[10].
  By adulthood, XXY males look similar to males without the condition, although they are often taller. Klinefelter syndrome is associated with an increased risk for breast cancer, a rare tumor called extragonadal germ cell tumor, lung disease, varicose veins and osteoporosis[11]. Men who have Klinefelter syndrome also have an increased risk for autoimmune disorders such as lupus, rheumatoid arthritis and Sjogren's syndrome.
  XXY males can have normal sex lives, but they usually make little or no sperm. Between 95 percent and 99 percent of XXY males are infertile because their bodies don't make a lot of sperm[12].
- ***Intelligence***
  A wide range of intelligence quotient (IQ) has been noted and extends from well below average to well above average. Based on the Wechsler Intelligence Test, Verbal IQ is usually lower than Performance IQ. Most of the differences between Verbal IQ and Performance IQ appear to relate to deficits in verbal abilities and to decreased auditory memory and processing[13].
- ***Language development***: As boys, between 25 percent and 85 percent of XXY males have some kind of language problem, such as learning to talk late, trouble using language to express thoughts and needs, problems reading, and trouble processing what they hear.
  As adults, XXY males may have a harder time doing work that involves reading and writing, but most hold jobs and have successful careers[14].
- ***Social development***: As babies, XXY males tend to be quiet and undemanding. As they get older, they are usually quieter, less self-confident, less active, and more helpful and obedient than other boys.
  As teens, XXY males tend to be quiet and shy. They may struggle in school and sports, meaning they may have more trouble "fitting in" with other kids.
  However, as adults, XXY males live lives similar to men without the condition; they have friends, families, and normal social relationships.

CAUSES

Klinefelter syndrome is not inherited; it usually occurs as a random event during the formation of reproductive cells (eggs and sperm). An error in cell division called nondisjunction results in a reproductive cell with an abnormal number of chromosomes. For example, an egg or sperm cell may gain one or more extra copies of the X chromosome as a result of nondisjunction. If one of these atypical reproductive cells contributes to the genetic makeup of a child, the child will have one or more extra X chromosomes in each of the body's cells.[15]

Most often, Klinefelter syndrome is caused by a single extra copy of the X chromosome, for a total of 47 chromosomes per cell. Males normally have one X chromosome and one Y chromosome in each cell (46, XY), but males with Klinefelter syndrome have two X chromosomes and one Y chromosome (47, XXY). Some males with Klinefelter syndrome have the extra X chromosome in only some of their cells; these cases are called mosaic 46, XY/47, XXY[2,16].

About half of the time the error occurs in the formation of sperm, while the remainder are due to errors in egg development. Women who have pregnancies after age 35 have a slightly increased chance of having a boy with this syndrome.[12]

The extra copies of genes on the X chromosome interfere with male sexual development, preventing the testicles from functioning normally and reducing the levels of testosterone.

TREATMENT[17]

The XXY chromosome pattern can not be changed. But, there are a variety of ways to treat the symptoms of this condition.

- Educational interventions – As children, many individuals with Klinefelter syndrome qualify for special services to help them in school. Teachers can also help by using certain methods in the classroom, such as breaking bigger tasks into small steps.
- Therapeutic options – A variety of therapists, such as physical, speech, occupational, behavioral, mental health, and family therapists, can often help reduce or eliminate some of the symptoms of Klinefelter syndrome, such as poor muscle tone, speech or language problems, or low self-confidence.
- Medical management – Testosterone replacement therapy (TRT) can greatly help individuals with Klinefelter syndrome get their testosterone levels into the normal range. Having a more normal testosterone level can help individuals develop bigger muscles, a deeper voice, and facial and body hair. TRT often starts when a boy reaches puberty. Some XXY males can also benefit from fertility treatment to help them father children.

Conclusion

The term Klinefelter syndrome (KS) describes a group of chromosomal disorder in which there is at least one extra X chromosome to a normal male karyotype, 46,XY. Klinefelter Syndrome is a relatively common disorder with a recognized cognitive and behavioral phenotype including deficits in language and language-based learning disabilities and executive and attentional dysfunction, surprisingly little work has been done to examine the neurobiologic differences that underlie these abnormalities. It also affects male sexual development, preventing the testicles from functioning normally and reducing the levels of testosterone. Low Testosterone can lead to breast development (gynecomastia), decreased libido, incomplete masculinization with female body hair distribution (sparse facial, armpit, and pubic hair) and an inability to father children (infertility). Men with Klinefelter syndrome are infertile because they cannot make sperm.

Testosterone therapy may help to produce more normal development including more muscle mass, hair growth and increased sex drive.

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