



Klinefelter Syndrome

Klinefelter Sendromu

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Abstract

Klinefelter syndrome is the most common sex chromosome disorder in males. Variation in clinical presentation and insufficient awareness of this syndrome among clinicians lead to fifty percent of patients remain undetected. Typical clinical features of Klinefelter syndrome are various degrees of hypogonadal symptoms, atrophic testes and gynecomastia. However, these typical clinical symptoms may not be present in all patients. Even if serum testosterone levels are not markedly low, elevated serum follicle-stimulating hormone is a considerable laboratory finding. Definitive diagnosis is made by karyotype analysis of peripheral blood lymphocytes. It must be kept in mind that this analysis may be normal in rare conditions. Early recognition of patients during puberty and handling them as soon as possible is important. Testosterone replacement therapy results in increased muscle mass, bone mineral density and libido. The patient's mood and self-esteem improve significantly. In general, patients with Klinefelter syndrome are accepted as infertile, however, assisted reproductive techniques may provide fertilization. *Turk Jem 2013; 17: 63-7*

Key words: Klinefelter syndrome, sex chromosome, hypogonadism, testosterone

Özet

Klinefelter sendromu erkeklerde en sık görülen seks kromozom bozukluğudur. Klinik özelliklerinin değişiklik göstermesi ve bu sendromun hekimler tarafından farkındalığının yetersizliği neticesinde hastaların %50'sinden fazlası tanısız kalmaktadır. Klinefelter sendromunun tipik klinik özellikleri farklı seviyelerde hipogonadizm bulguları, atrofik testisler ve jinekomaastidir. Bu tipik klinik özellikleri olmayan hastalarda da Klinefelter sendromu olabileceği unutulmamalıdır. Testosteron seviyeleri çok düşük olmamasına rağmen serum folikül stimüle hormon seviyesinin normalin üzerinde olması Klinefelter sendromu için önemli bir laboratuvar bulgusudur. Kesin tanı periferik kandaki lenfositlerden yapılan kromozomal analiz ile konulur. Bu analizin nadiren normal bulunabileceği akılda tutulmalıdır. Pubertal dönemdeki hastaların tanısının mümkün olduğunca erken konması ve tedavinin başlanması önemlidir. Testosteron tedavisi kas kitlesinin, kemik mineral yoğunluğunun ve libidonun artmasını sağlar. Hastanın ruh hali, kendine güveni belirgin olarak iyileşir. Genel olarak Klinefelter sendromlu hastalar infertil kabul edilse de, son yıllarda uygulanan bazı yardımcı üreme yöntemleri ile fertilizasyon sağlanabilmektedir. *Turk Jem 2013; 17: 63-7*

Anahtar kelimeler: Klinefelter sendromu, seks kromozomu, hipogonadizm, testosteron

Introduction

The so-called Klinefelter clinical syndrome was first defined in 1942 by Harry Klinefelter and his colleagues by showing the elevated excretion of urine FSH on 9 male patients who had small testes, gynecomastia and no ability of spermatogenesis (1). It was thought to be an endocrine disease yet the etiology was not found at that time. In 1956, Plunkett and Barr, studied buccal mucosa cells of men with Klinefelter syndrome and described the pathognomonic

appearance, nowadays called Barr body (2). In 1959, Jacobs and Strong stated that Klinefelter syndrome was a chromosomal disease and they were able to identify a 47,XXY chromosome structure created by an extra X chromosome causing this clinical picture (3).

80% of patients with Klinefelter syndrome have 47,XXY karyotype which is usually referred as the classic type. And the rest (20%) has the 46,XY/47,XXY mosaic form, high-grade aneuploidies or X chromosome structural abnormalities (4). Klinefelter syndrome

is the most common sex chromosome disorder in males. Studies show that the incidence of Klinefelter syndrome in the neonatal period is 1/500-1000 and the prevalence in adults is 1/2500. As this syndrome does not cause premature mortality, the detection of low prevalence in adults shows a possible omission of the diagnosis of Klinefelter syndrome. Calculations show that more than 50% of Klinefelter syndrome patients have not been diagnosed (5). Klinefelter syndrome has been implicated in the etiology of 11% of azoospermic patients and 3% of infertile men (6).

Pathogenesis

Extra X chromosome usually occurs during gametogenesis when ovum or sperm carries an extra X chromosome along with the normal sex chromosome. Cases of Klinefelter syndrome developed due to the errors in the stage of mitosis following the formation of the zygote are rare (7). In a study using DNA probes, cases of paternal division errors constitute 53.2% of all Klinefelter syndrome patients. 43.7% of the maternal division error rate, on the other hand, might result in meiotic division errors occurred either during the first (34.4%) or the second phase (9.3%) (8). Some surveys show that the maternal error rate in the first and the second phases may vary proportionally in relation to the mother's age. In fact, it has been shown that the error rate of the first phase increases in advanced maternal age (9). Mitotic errors developed after the formation of zygote forms the remaining small proportion (3.2%) of the errors (8).

The majority of patients with Klinefelter syndrome has a 47, XXY chromosomal pattern, yet some have numerical chromosome abnormalities such as 48,XXXYY; 48,XXYY; 49,XXXYY and a mosaic-like structures like 47,XXXYY/46,XY. Actually, of all cases of Klinefelter syndrome, only 10%-20% are thought to have a different abnormality than that of 47,XXY (4). As the number of X chromosomes increases, patients show more dysmorphic features. Besides cryptorchidism, more pronounced retardation in sexual characteristics, an increase possibility of hypoplastic scrotum, symptoms of mental retardation begin to emerge in these patients (10). In addition to such numerical chromosomal abnormalities, we can rarely see structural chromosomal aberrations as well. Among them, isochromosome Xq structural chromosomal abnormalities constitute 0.3 to 0.9% of all Klinefelter syndrome patients (11).

Clinical Manifestations

The clinical manifestations of the Klinefelter syndrome may be due to hypogonadism caused by the disease, or directly due to chromosomal abnormalities. Symptoms vary depending on the period of the age of the patients. Prenatally, Klinefelter syndrome can be detected by the karyotype evaluation of the pleural fluid in amniocentesis. However, an amniocentesis on suspicion of Klinefelter is not within the perinatal routine because it does not show any significant features in ultrasound examination during pregnancy. It can only be diagnosed with karyotype analysis if the pregnant woman has amniocentesis for some other reasons (12). Studies focused on the maternal period, those examining various factors such as the maternal age, did not reveal any related factor

increasing the probability for Klinefelter syndrome (13).

During delivery, nothing specific could be observed in infants related with classic Klinefelter syndrome. In fact, studies showed that congenital malformations such as clinodactyly, cleft palate and inguinal hernia were seen more frequently in infants with Klinefelter syndrome than healthy male children (14). The rate of congenital malformations especially increases in Klinefelter syndrome patients with a high degree of chromosomal abnormalities. The rate of congenital malformations has been reported as 70-100% in cases with 48,XXYY, 48,XXXYY, 49,XXXYY. The most common malformation is clinodactyly. This is followed by cleft palate, inguinal hernia, cardiac abnormalities and radioulnar synostosis. More rarely occur genitourinary malformations, such as hypospadias and undescended testes (10,15).

Usually, physical findings and developmental characteristics of children with classic Klinefelter syndrome are not different from normal children. In fact, studies show that the size of the penis and testicular volume are smaller in children with Klinefelter syndrome than those of their peers and they are also taller (16).

Another feature that can be seen in children with Klinefelter syndrome is problems in learning and cognition. It has been shown that the degree of these problems increases in parallel with chromosomal aberrations (17). Beside the problems such as a delay in speech and movement, learning difficulties, a delay in reading, abnormalities in cognitive functions like aggressiveness and non-compliance can be seen in those patients. IQ levels are usually normal in classic form but very low levels can also be seen in patients with high malformations (10,15,17).

These features are not usually clinically detectable at prepubertal period in patients with classic Klinefelter syndrome. It has been reported that only 10% of Klinefelter syndrome patients can be diagnosed in their prepubertal period (4). The classic clinical features of patients with Klinefelter syndrome start to become recognizable during adolescence. The most noteworthy feature is the absence of testicular volume increase during adolescence. Because of the loss of germ cells and fibrosis in the seminiferous tubules, testicular becomes rigid (18). These patients, however, usually have normal development of secondary sex characteristics. Axillary / pubic hair development, increase in penis size, increase in muscle mass, beard-mustache development and sound quality changes develop in their usual way. However, due to less than expected level of testosterone and a delay to reach normal testosterone level, these patients are taller than their peers. One of the most important features of the physical examination is gynecomastia and it can be seen in 50% of the cases (15).

The most obvious and most persistent clinical feature in adulthood is small testicular volume (<4 ml). Onychoid structure and the presence of gynecomastia along with different degrees of androgen deficiency are the most typical symptoms of Klinefelter syndrome (9). Table 1 shows percentages of symptoms in adult patients. During this period, patients often present themselves with the complaint of infertility. Testicular examination should be performed in patients with infertility and if there is a clinical suspicion, a genetic analysis should be requested. In patients with Klinefelter syndrome, azoospermia is detected with a very high percentage. Onikoid body

structure seen in these cases is slightly different than those seen in prepubertal hypogonadism. Unlike the classic presentation of long arms and long legs, the lower extremity is disproportionately longer, in comparison to the upper extremity. Also, the length of the lower extremities seen in prepubertal period is more dominant and it is thought to be the result of a chromosomal aberration (19). Gynecomastia, believed to be resulted from androgen aromatization, is thought to be one of the most important symptoms in adult patients with Klinefelter syndrome and can be detected at %50 of patients. It is a permanent physical finding and does not change with treatment. In patients with Klinefelter syndrome, due to psychosocial consequences caused by androgen deficiency; character disorders, personality disorders, and behavioral problems arise. These patients usually have problems in psychological adjustment.

It should be noted that patients without the typical features might have Klinefelter syndrome as well. Especially in the majority of patients with mosaicism, there are no symptoms to be found. Only 25% of the patients can get diagnosed in adulthood. Some patients can be diagnosed at a very advanced age and some surviving patients may remain undiagnosed (4).

In mosaic forms, clinical features vary widely. Mosaic Klinefelter syndrome cases have variable and less severe phenotypic properties than the classic type. It is mostly depending on where the tissue with the extra X chromosome is. The most common mosaic form is 47,XXY/46,XY. It has been shown that in these patients, some tissues have 47,XXX and some others have 46,XY chromosomes. Mosaicism, different from 47XXY chromosome arrangement, probably occurs as a result of a division in the mitotic phase after the conception. There are patients showing clinical signs at various levels as well as patients showing no symptoms. Some cases can be diagnosed only by oligospermia or infertility problems (15). %14 to %62 of patients with the mosaic form of 47XXY/46XY have normal XY karyotype in testicular tissue, and thus spermatogenesis and fertility is preserved in these patients (21).

The bone mineral density of patients with Klinefelter syndrome has been shown to be normal in childhood until the beginning of puberty but in later periods it becomes lower compared to the healthy age/sex groups. Hypogonadism was found to be the most important cause of bone mineral deficiency. Testosterone replacement for the risk of osteoporosis should be started early and must be maintained in long term (22).

It is known that these patients have 20 to 50-fold increased risk of breast cancer than healthy men and %6 of all male breast cancer cases are among these patients.

This increased risk can be explained by several times higher ratio of estradiol / testosterone in patients with Klinefelter syndrome than normal karyotyped men. Another possibility is the existence of two X chromosomes that can increase the genetic risk of breast cancer (23). Studies have been reported that certain diseases were more prevalent in patients with Klinefelter syndrome. In studies investigating the prevalence of autoimmune diseases, type 2 diabetes mellitus, and leg ulcers; the probability of having these diseases was higher in patients with Klinefelter syndrome (9,15,16).

Laboratory - Diagnosis

The characteristics of patients suspected of Klinefelter syndrome varies according to age groups. The most typical feature is having small testes. Usually testicular volume does not exceed 3-4 ml in patients with Klinefelter syndrome (9). However, in patients at their pre-pubertal period, this feature does not contribute much to the diagnosis. It is very difficult to suspect Klinefelter syndrome at this age group in the absence of other findings.

The majority of patients are diagnosed with Klinefelter syndrome during their puberty period. Delayed puberty is often seen in these patients. In Klinefelter syndrome, the most typical clinical manifestation is testicles not getting bigger despite the development of secondary sex characteristics. And if gynecomastia is present as well, then Klinefelter syndrome is most likely the expected diagnosis.

In adult males with complaint of infertility, the possibility of Klinefelter syndrome must be considered as a fact. When consulting a physician, the small size of testicular volume may not be the patients' complaint. Secondary sex characteristics and the primary sex functions such as erection and ejaculation are often normal in patients with Klinefelter syndrome. Especially in patients with azoospermia, Klinefelter syndrome should be investigated after reviewing other easily excludable causes.

In patients with Klinefelter syndrome, serum testosterone levels usually begin to rise with puberty. Sometimes an increase in testosterone during puberty may happen a little late than peers. Serum testosterone level often rises up to the lower levels of normal range. Normal levels can be seen in patients with mosaic form, while much lower levels is seen in patients with high-chromosomal defects. In classic cases, serum testosterone levels gradually decrease in time.

One of the most typical laboratory findings in patients is an increase in serum gonadotropin levels in puberty. Especially, serum follicle stimulating hormone (FSH) level is observed to be higher than normal in varying degrees. The increase in serum luteinizing hormone (LH) levels, on the other hand, is lesser. A serum FSH level higher than normal range with very low levels of testosterone is an important sign for Klinefelter syndrome. In almost all patients with Klinefelter syndrome, an elevation of serum FSH is seen in lab findings (6,9,20). In patients with mosaic form, serum FSH level

Table 1. Findings and the percentages seen in adult patients with Klinefelter syndrome

Findings	Percentages (%)
Infertility	99-100
Small testicles	99-100
Increased levels of gonadotropin	90-100
Decreased testosterone levels	65-85
Decreased facial hair	60-80
Gynecomastia	50-75
Decreased pubic hair	30-60
Decreased penile length	10-25

is seen to be slightly higher, while serum testosterone levels are usually normal.

In patients with Klinefelter syndrome, it has been shown that there is a mild increase in serum estradiol levels. The cause of this increase is thought to be as a result of an increased testosterone aromatization (20). Yet the increase amount in the level of estrogen does not support the diagnosis. In fact, estrogen levels can be normal in most patients. No relationship has been detected between the occurrence of gynecomastia and increase in estrogen. Gynecomastia patients might have high levels of estrogen, while no gynecomastia could be detected in patients with significantly higher estrogen serum levels.

Another common laboratory finding in almost all of the patients with Klinefelter syndrome is serious reduction in the number of sperm. Although the majority of patients have normal ejaculation function, sperm is rarely seen in the ejaculate. The ejaculate of patients with mosaic form is more likely to contain sperm. Although rare cases of spontaneous fertilization are published in the literature, spontaneous fertilization is not possible in patients with Klinefelter syndrome. Fibrosis of seminiferous tubules is seen in the histology of testes (18).

The definitive diagnosis is made by chromosome analysis of lymphocytes from peripheral blood. However, it should be kept in mind that this analysis can rarely be found normal. Chromosomal analysis from skin fibroblasts or testicular biopsy specimens may show mosaic chromosomal structure.

Klinefelter syndrome can easily, quickly and reliably be diagnosed by Barr body analysis of the buccal mucosa biopsy specimen. In studies, its sensitivity and specificity are found as 82% and 95%, respectively.

Treatment

The primary item in treatment is the therapy for hypogonadism. Especially in patients with low levels of testosterone, testosterone replacement should be performed. For patients in pubertal period, early diagnosis and immediate initiation of treatment is important. Testosterone therapy provides an increase in muscle mass, strength-toughness, hair growth, bone mineral density and libido. The patient's mood and his self-confidence improve significantly. Untreated patients show a significant increase of fatigue and reluctance as well as increased irritability and aggressiveness (25). In patients with normal levels of testosterone, no replacement therapy is necessary. However, it should be noted that testosterone level in these patients is usually in the lower region of normal range. In addition, in these patients, free testosterone levels are generally lower due to increased sex hormone binding globulin. In patients with no treatment plan, free fractions should be evaluated carefully and a detailed clinical evaluation is needed as well. Depending on the seminiferous tubule fibrosis in patients with Klinefelter syndrome, testosterone level decreases over the years. Therefore, patients without treatment must be followed-up periodically. Intramuscular injections of testosterone enanthate or testosterone cypionate are the most commonly used testosterone replacement therapy agents. These injections are usually done within 3-week intervals. Without delay, treatment should start with low doses

during puberty and dose should be increased in parallel with pubertal development. Depending on the requirements of the patient, the frequency of injection can be made in 2 to 4 week intervals (9). In recent years, depo-testosterone preparations have been developed, which can be applied with 3-month intervals.

As an alternative to injection, there are testosterone preparations orally or percutaneously administered. Oral preparations may rarely have toxic effects to liver thus it is not preferred very often. Also preparations applied to the skin in a patch or gel form have been developed. Studies have shown no significant difference in efficacy between injected preparations and these other types (26). However, when using gel preparations, a special attention should be paid against a contamination of the female partner.

It has been shown that testosterone treatment has no effect on gynecomastia (27). In adult patients gynecomastia does not regress with testosterone therapy. Actually it may even develop despite the treatment in pubertal patients. If necessary, resection of breast tissue should be performed with cosmetic surgery.

Testosterone replacement therapy eliminates all negative effects related to androgen deficiency but it has no effect on fertility (6). This therapy does not ensure spermatogenesis. There is no spermatogenesis in patients with Klinefelter syndrome, thus the possibility of fertility is considered to be very low in general. Seldom in Klinefelter syndrome patients, who had spermatozoa in their ejaculate, pregnancies were reported with the help of human chorionic gonadotropin therapy. However, as the majority of patients are azoospermic, fertilization is not possible spontaneously or with gonadotropin treatment.

In recent years, however, fertilization can be achieved with some assisted reproductive methods in patients with Klinefelter syndrome. For this purpose, the sperm detected in testicular is isolated with the so-called testicular sperm extraction (TESE) method and then spermatozoa gets ejaculated into the ovum with the so-called intracytoplasmic sperm injection (ICSI). In Klinefelter syndrome patients, publications have demonstrated a 40%-50% chance of sperm extraction with TESE method, and a 20%-25% possibility of pregnancy after ISCI (28).

Infants, whose fathers have Klinefelter syndrome, mostly have normal karyotype. However, studies have found that these infants have higher rates of chromosomal hyperploidy (29). Hence in centers with the necessary equipments, genetic analysis is highly recommended before the implantation.

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