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Klinefelter's syndrome and social handicaps in Southeast of Turkey.

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Abstract

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. XXY aneuploidy is the most common disorder of sex chromosomes in humans, with prevalence of one in 500 males. Other sex chromosomal aneuploidies have also been described, although they are much less frequent, with 48,XXYY and 48,XXXY being present in 1 per 17,000 to 1 per 50,000 male births

In this study we aimed to evaluate the postnatally screened karyotype results in man who were referred diagnosis of Klinefelter syndrome between 1998 and 2010 in the city of Diyarbakir, Southeast Turkey.High resolution Giemsa banding chromosome analysis and/or fluorescence in situ hybridization were done males diagnosis of Klinefelter syndrome . A total of 552 cases were evaluated retrospectively.One hundred twenty out of 552 (21.74%) cases showed of Klinefelter syndrome.Genetic counseling was provided for the cases that received Klinefelter syndrome results. The rate of gonosomal chromosomal abnormalities was social problem in our region. Chromosomal analysis is strongly suggested particularly in those who suffer fertility problems.

Keywords: *Chromosomal abnormality, Male infertility, Klinefelter syndrome*

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Introduction

In 1942, Dr Harry Klinefelter published a report on nine men with a constellation of features: testicular dysgenesis, elevated urinary gonadotropins, microorchidism, eunuchoidism, azoospermia, and gynecomastia (1). 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(2). During the early 1970's, a number of centers began screening newborns for sex chromosomal abnormalities, because there was a need to obtain accurate information about childhood development in this condition (3). Previous studies of XXY individuals were extremely biased toward more severely affected individuals, since these patients were drawn largely from mental or penal settings where large numbers of men could be screened. These earlier studies implied a risk for mental deficiency and behavioral problems. As prospective, unbiased studied have reported their results in recent years, it has become clear that most XXY boys demonstrate reductions in speech and language abilities which are correlated with decreased reading and spelling achievement (4) .Infertility, azoospermia, or both may result from atrophy of the seminiferous tubules. Practically all individuals with a 47,XXY karyotype are infertile. Patients with Klinefelter syndrome mosaicism (46,XY/47,XXY) can be fertile

Most, but not all XXY males, are infertile with small testicles, increased numbers of Leydig cells, tubular sclerosis, and interstitial fibrosis of varying degrees (5). Their ejaculate is usually azoospermic, and levels of testosterone are typically low to low-normal.

Men with Klinefelter Syndrome (KS) have one extra X chromosome (XXY) and vary considerably in their cognitive and behavioral phenotype (2). The cells with at least one extra X chromosome are believed to create deficiencies in male sexual characteristics (5). It is for this

reason that XXY individuals frequently are undetected until adolescence until they present to a physician for lack of normal male sexual growth (5). It is at this time that they are often prescribed testosterone. Individuals with XXY karyotype generally have normal to low-normal intelligence, but many display subtle verbal disabilities, while their non-verbal abilities are spared (6,7,8,9,10,11). Dyslexia and attention deficit disorder are diagnosed more frequently in children with the XXY syndrome than in their XY peers (12,13). Behavioral abnormalities reported range from depression to bipolar disorder to schizophrenia, although the majority of XXY men are psychiatrically normal. KS is significantly more frequent among hospitalized patients with schizophrenia than the general population reviewed in(14). We began a series of investigations to determine whether this naturally occurring human chromosome anomaly could serve as a neurogenetic research model for determining specific sex chromosome and/or autosomal genes whose abnormal expression may put individuals at risk for developing schizophrenia or other serious psychotic disorder. We previously reported that XXY males had gray and white matter structural brain differences compared with normal XY males and that they had an excess of psychotic symptoms, as well as verbal deficits (15).

Materials and Methods

Formal cytogenetic analysis is necessary to make a definite diagnosis, and more obvious differences in physical features tend to be associated with increasing numbers of sex chromosomes.

The cytogenetic findings from clinical diagnosis of Klinefelter syndrome 552 cases obtained between 1998 and 2010 were reviewed. The samples with clinical diagnosis of Klinefelter syndrome referred to the Medical Biology and Genetic Department Laboratory Dicle University Hospital in the city of Diyarbakir, Southeast Turkey. All samples were analyzed in the Medical Biology and Genetic Department Laboratory at Dicle University For routine cytogenetic analysis, 0.3- mL peripheral blood samples were collected from the patients into heparinized test tubes, and

then was incubated in complete lymphocyte culture medium in incubator at 37°C for 72 h. Metaphases are harvested by adding colcemid for 60 min followed by hypotonic KCl treatment for 5 min and fixation using standard 3:1 methanol-acetic fixative (all reagents were from Gibco Life Technologies Ltd., Paisley, UK).

The karyotype of each patient was determined by G-banding using trypsin and Giemsa (GTG) and C-banding using barium and Giemsa (CBG) when necessary. At least 30 cells were routinely analyzed; in cases of mosaicism, this number was increased to approximately 100 metaphases. The best metaphases were photographed to determine the karyotypes. If the case was carrier of a translocation or an inversion or unusual karyotypes, their parents or other family members were also tested. Translocations not detected by conventional light microscopy were submitted to the fluorescence *in situ* hybridization (FISH) method using whole chromosome painting (WCP) libraries (cytocell for WCP) and α-satellite DNA probes , and a minimum of 100 metaphases for each patient were examined. The karyotypic descriptions were reported according to the International System for Human Cytogenetic Nomenclature recommendations (ISCN, 1995).

Those patients who were identified as having chromosomal abnormalities received post-cytogenetic genetic counseling in our Department. The mean age was 30.51 and cases were between 18 and 47 years old.

In this study, patients were referred with the diagnosis of klienfelter evaluate the results of karyotype and in region with low levels of socio-cultural approach to the event.

Table 1.. Distribution of chromosomal abnormalities in 552 cases

Karyotypic finding	**Number of cases**
47,XXY	106
47,XXY,inv 9(p13q13)	12
47,XXY,48,XXXY (mos)	2
46,XY	392
46,XY ,9qh+	20
46,XY ,14ps+	2
46,XY ,inv 9(p13q13)	6
46,XY,1qh+	4
46,XY, 9qh+,14ps+	4
46,XY,del (13p)	1
46,XY(add Y)t(Y;16)	1
46,XY,del (Y)	2
Toplam	552

Results

A total of 552 cases with diagnosis of Klinefelter syndrome were evaluated retrospectively. One hundred twenty out of 552 (21.74%) cases showed of (47,XXY 47,XXY,inv 9(p13q13) 47,XXY,48,XXXY (mos) Klinefelter syndrome. Six cases (1.08%) 46,XY,inv(9) (p13q13) , twenty cases 46,XY ,9qh+ (3.6%) showed which is accepted to be a variant in the population. Two (0.36%) were 46,XY ,14ps+; four (0.72%)46,XY,1qh+; four (0.72%) 46,XY, 9qh+,14ps+; one (0.18%)46,XY,del (13p); one (0.18%) 46,XY(add Y)t(Y;16); two (0.36%) 46,XY,del (Y); three hundred ninetytwo (71.01%) 46,XY (Table 1)

Azospermia group involved 200 cases and oligozoospermia group involved 80 cases. The sperm counts of other cases were unavailable because of the retrospective nature of the study.

Discussion

The prevalence of chromosome abnormalities is higher in infertile men and it is well-known that the sperm count is inversely related to the existence of chromosomal anomaly.
Chromosomal abnormalities are more frequently observed in the population of azoo-and/or oligozoospermic males than in the general population (16). Lissitsina et al. reported that the incidence of sex chromosome abnormalities in azoospermia group was higher than that in the oligozoospermia group (17)

The incidence of karyotype abnormalities among infertile men has been reported to range between 2.2% and 19.6% (18,19,20) The incidence of KS was 21.74% in our study which is similar to the literature.

The most common type of karyotype abnormality in infertile cases is represented by KS, and Y chromosome long arm micro deletions represent the most frequent chromosomal structural abnormalities (21). The incidence of KS was 7.26% KS is the most common abnormality of sexual differentiation, and occurs in approximately 1 in 500 live births. KS is a form of primary testicular failure with testicular hypotrophy and elevated gonadotropin plasma levels, and it represents the most common form of male hypogonadism (22)Ferlin et al. reported that the prevalence of KS among infertile men is very high, up to 5% in severe oligozoospermia and 10% in azoospermia (23). It has been always assumed that more than 90% of nonmosaic 47,XXY males are azoospermic (23). The incidence of azoospermia was 87% in our study which is similar to the literature.

In our study we detected that 106 cases had nonmosaic 47,XXY karyotype. Pericentric inversion is one type of chromosomal rearrangement, which has been categorized as a minor chromosomal rearrangement not expected to correlate with abnormal phenotype. The inv (9) may

often cause clinical problems in offspring of the carrier and infertility with unknown mechanisms related to sex (24). We detected 12 cases that have47,XXY,inv 9(p13q13) and 6 cases (1.08 %)46,XY ,inv 9(p13q13) karyotype.

Most men with Klinefelter's Syndrome are infertile. Infertility counselling is available for men coming to terms with childlessness and its effect on them and their partner.

In our country, especially in rural areas, marriages are at an early age individuals with low levels of socio-cultural societies, male infertility unacceptable level. The reason to do not have children, especially in rural areas has been suggested that maternal origin for women born child, if ever woman accused of infertility

In this study we evaluate 120 patients with Klinefelter syndrome, 65 of them were married . 22 of the them re-married a few times due to infertility. Suggested that the cause of the desire to have children due to their wife. They receive results from us and did not want to share with their partners. Only 2 patients wanted to consult result with their partners.

12 cases were preparing to get marriage but 8 of them give up their decision after genetic counseling were given . 4 patients planned to get married with not sharing the genetics results with their partners. Genetic counseling was given after cytogenetic analysis by genetic counselors in our department.

In some cases, sperm can be found in the ejaculate of men with Klinefelter's Syndrome or may be found in the testes by biopsy. In these cases, assisted reproductive technologies such as Intracytoplasmic Sperm Injection (ICSI) can be accessed to achieve pregnancy. ICSI involves injecting a single sperm into the egg by piercing the outer covering of the egg. At this time it is still unclear in what percentage of Klinefelter's men sperm can be found. Two of patient to be having a child with a method s ISCI that has been referred to the centers.

In conclusion the results of this study and the review of the literature showed that infertile men had a higher prevalence of chromosomal alterations, even though they did not show a phenotypical feature of a particular genetic disease.

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