PHENOTYPE MANIFESTATIONS OF POLYSOMY X AT MALES

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Abstract

Klinefelter Syndrome is the most frequent form of male hypogonadism. It is an endocrine disorder based on sex chromosome aneuploidy. Infertility and gynaecomastia are the two most common symptoms that lead to diagnosis. Diagnosis of Klinefelter syndrome is made by karyotyping. Over 20 years period (1985-2004) 124 patients have been sent to "Center for Human Genetics" of Faculty of Medicine in Sarajevo from different medical centres within Federation of Bosnia and Herzegovina with diagnosis suspecta Klinefelter syndrome, azoospermia, sterilitas primaria and hypogonadism for cytogenetic evaluation. Normal karyotype was found in 99 (79,8%) subjects, and karyotype was changed in 25 (20,2%) subjects. Polysomy X was found in 14 (11,3%) examinees. Polysomy X was expressed at the age of sexual maturity in the majority of the cases. Our results suggest that indication for chromosomal evaluation needs to be established at a very young age.

KEY WORDS: polysomy X, hypogonadism, infertility

Introduction

Structural changes in gonosomes (X and Y) cause different distribution of genes, which may be exhibited in various phenotypes. Numerical aberrations of gonosomes have specific pattern of phenotype characteristics, which can be classified as clinical syndrome. Incidence of gonosome aberrations in males is 1/400 male newborn (1).

Klinefelter syndrome is the most common chromosomal disorder associated with male hypogonadism. According to different authors incidence is 1/1000 male newborns (1), 1/800-1000 (2), and even 1/600 (3). Very high incidence indicates that the zygotes with Klinefelter syndrome are more vital than those with other chromosomal aberrations.

In 1942, Klinefelter et al. published a report on 9 men with enlarged breasts, sparse facial and body hair, small testes, and inability to produce sperm. In 1959 (Jacobs & Strong), these men with Klinefelter syndrome were discovered to have an extra sex chromosome (genotype XXY) instead of the usual male sex complement (genotype XY) (4,5). Klinefelter syndrome is caused by the presence of an additional X chromosome in a male. The most common karyotype is 47,XXY, which accounts for 80-90% of all cases. Mosaicism (46,XY/47,XXY; 46,XY/48,XXXY and 47,XXY/48,XXXY) is observed in about 10% of cases. Other variants of karyotype, such as 48,XXYY, 48,XXXY, 49,XXXYY and 49,XXXXY are rare. About 1% of cases are due to structurally abnormal X in addition to a normal X and Y, such as 47,X,i(Xq) Y and 47,X,del(X)Y (5). Somatic and cognitive development is more likely to be affected in Klinefelter variants with higher-grade chromosome aneuplodies. Infertility and gynaecomastia are the two most common symptoms that lead to Klinefelter syndrome diagnosis (5). Degeneration of seminiferous tubules in 47,XXY males is a well-described phenomenon. It begins in foetus, progresses through infancy and accelerates dramatically at the time of puberty with complete hyalinization of the seminiferous tubules, although a few tubules with spermatogenesis may be present in adult life. Leydig cell secretion of testosterone is impaired early in infancy and major histological changes in testes coincided with the pubertal activation of the pituitary–gonadal axis. Low testosterone causes an increase in two other hormones, follicle stimulating hormone (FSH) and luteinizing hormone (LH). The increased amount of FSH and LH cause hyalinization and fibrosis in the seminiferous tubules. The decreased testosterone can also lead to breast development (gynaecomastia), decreased libido, incomplete masculinization, female body hair distribution (sparse facial, armpit and pubic hair) (4,6). The basic goal of this study is to evaluate cytogenetic findings in patients who have been sent to "Centre for Human Genetics" of Faculty of Medicine in Sarajevo from different medical centres within Federation of Bosnia and Herzegovina with diagnosis suspecta Klinefelter syndrome, azoospermia, sterilitas primaria and hypogonadism.

Subjects and Methods

In 20 years period (1985-2004) 124 patients have been sent to "Centre for Human Genetics" of Faculty of Medicine in Sarajevo from different medical centers within Federation of Bosnia and Herzegovina with diagnosis suspecta Klinefelter syndrome, azoospermia, sterilitas primaria and hypogonadism for chromosomal evaluation. Karyotype analyses were performed after Giemsa staining on guanosine triphosphate-banded metaphase peripheral blood lymphocytes according to standard methods.

Results

There were 38 examinees with diagnosis suspecta Klinefelter syndrome and gynaecomastia, 59 exeminees with diagnosis suspecta hypogonadism and cryptorchidism, and 27 examinees with diagnosis suspecta azoospermia, oligozoospermia and sterilitas primaria.

Karyotype analysis was done for 124 patients. Normal karyotype was found in 99 (79,8%) patients, while changes were identified in 25 (20,2%) patients. Polysomy X was found at in 14 (11,3%) examinees. Frequency of polysomy X showed statistical significance at the level $p<0,05$. Among 14 confirmed cases of polysomy X, 8 (57,2%) were sent for chromosomal evaluation because of azoospermia et sterilitas primaria, 3 (21,4) with diagnosis suspecta Klinefelter Syndrome and gynaecomastia, and 3 (21,4%) with diagnosis hypogonadism and cryptorchidism.

CLINICAL DIAGNOSIS	CYTOGENETIC FINDINGS											
	Excluded Klinefelter syndrome				Confirmed Klinefelter syndrome						Total	
	46,XY		Other chromosomal aberrations		47,XXY		46,XY/ 47,XXY		46,XY/ 47,XXY/ 48,XXXY			
	N⁰	%	N⁰	%	N⁰	%	N⁰	%	N⁰	%	N⁰	%
Sy Klinefelter	33	86,8	2	5,3	2	5,3	1	2,6	-	-	38	100,0
Azoospermia, oligozoospermia et sterilitas prim.	13	48,2	6	22,2	6	22,2	1	3,7	1	3,7	27	100,0
Hypogonadism, cryptorchidism	53	89,8	3	5,1	2	3,4	1	1,7	-	-	59	100,0
Sum	99	79,8	11	8,9	10	8,1	3	2,4	1	0,8	124	100,0

TABLE 1. Cytogenetic findings in patients with diagnosis suspecta Klinefelter syndrome, gynaecomastia, azoospermia, sterilitas primaria, hypoganadismus i cryptorchidism

Age groups	Confirmed Klinefelter syndrome	
	N0	%
0-4	0	-
5-9	1	7,1
10-14	-	-
15-19	1	7,1
20-24	2	14,3
25-29	2	14,3
30-34	2	14,3
35-39	5	35,8
40-44	1	7,1
45 and more	-	-
All	14	100

TABLE 2. Age structure of patients with confirmed Klinefelter syndrome (1985-2004)

Among 14 confirmed cases of polysomy X, 10 (71,4%) of them were in non-mosaic form - 47,XXY, 3 (21,4%) in mosaic form with two cell lines (46,XY/47,XXY), and one confirmed case (7,2%) was mosaic form with higher level of polysomy X (46,XY/47,XXY/48,XXXY). Age structure of examinees with Klinefelter syndrome confirmed with cytogenetic analysis is shown in Table 1. It is evident that the majority of cases of polysomy X were exhibited at the age of sex maturity. Thus, therapy of every individual case is complicated. Distribution of results of age structure is at level $p<0,05$.

Discussion

Klinefelter syndrome is the most frequent form of male hypogonadism. It is an endocrine disorder based on sex chromosome aneuploidy (7). The genetic cause of Klinefelter syndrome is nondisjunction of chromosomes during cell cycle. Paternal meiosis I errors account for 50% of the cases; the rest derive from maternal meiosis I and II failure as well as postzygotic errors. Although a relation of paternal age to the origin of 47,XXY is probably nonexistent, maternal age has been associated with meiosis I errors. Because maternal meiosis II errors account for about 15% of all Klinefelter patients, the higher number of homozygous men than women is explained by cloning of one maternal X-chromosome. The mosaic forms of Klinefelter syndrome are due to mitotic nondisjunction after formation of the zygote. These forms can arise from a 46,XY zygote or a 47,XXY zygote (5,7). Klinefelter syndrome has a prevalence of 0,1–0,2% within the male population. Although Klinefelter syndrome is not rare, many patients escape diagnosis. About two thirds to three quarters of all men with X-chromosome aneuploidies fail to be identified (3,8). A variety of subtle clinical signs are age-related. In infancy, males with 47,XXY may have chromosomal evaluations done for hypospadias, small phallus or cryptorchidism, developmental delay. The school-aged child may demonstrate language delay, learning disabilities, or behavioral problems. The older child or adolescent may be discovered during an endocrine evaluation for delayed or incomplete pubertal development with eunuchoid body habitus, gynaecomastia, and small testes. Adults are often evaluated for infertility or breast malignancy (9). Klinefelter syndrome is detected before or during puberty only at 10% of all cases (3). In our study two cases (14,3%) of 14 confirmed were identified in infancy and school-age. Klinefelter syndrome is the most frequent genetic cause of infertility occurring in 11% of azoospermic men (10). Klinefelter syndrome was confirmed in 7 (25,9%) of 37 examinees that had chromosomal evaluation because of azoospermia, oligozoospermia and sterilitas primaria. This value may be due to small sample size. Eighty percent of Klinefelter syndrome cases are due to 47,XXY karyotype; the others relate to higher grade aneuploidies or mosaicism (5). In our study 10 (71,4%) confirmed cases were in the form 47,XXY; 3 (21,4%) in mosaic form with two cell lines (46,XY/47,XXY); and one confirmed case (7,2%) in mosaic form with higher-grade chromosome aneuploidies (46,XY/47,XXY/48,XXXY). Despite its relatively high frequency, the syndrome frequently remains undetected. To prevent such oversights simple screening tests should be used more frequently. Barr body analysis provides a quick and reliable screening test (a specificity of 95% and a sensitivity of 85%) for the diagnosis of Klinefelter syndrome, which still must be confirmed by karyotyping (11).

Variations in Klinefelter phenotypes can be explained by the roles of androgens and the X-linked androgen receptor gene. The androgen receptor (AR) gene is located Xq11.2-q12. Differences in the AR sequence are characterized mostly by a highly polymorphic trinucleotide repeat (CAGn) in exon 1, the normal length of which is 9–37. The length of this CAG repeat is inversely associated with androgen action. Individuals with short AR CAG repeats have been found to form more stable partnerships, and to achieve higher level of education compared with individuals with long CAG repeats. Conversely, long AR CAG repeat lengths are associated with increased body height and arm span, decreased bone density, decreased testicular volume, and gynaecomastia (7). The copy number of the androgen receptor gene has became base of screening method for detection of Klinefelterov syndrome and other X-chromosome aneuploidies (12,13). The effects of testosterone substitution are pharma-

cogenetically modified. The response to androgen therapy is in connection with the length of AR CAG repeats. Under testosterone substitution, men with shorter CAGn exhibit a more profound suppression of luteinizing hormone levels, augmented prostate growth, and higher hemoglobin concentrations. Concerning prostate growth during testosterone substitution therapy those patients with shorter CAGn may need closer monitoring and possibly less testosterone (7). Androgen replacement therapy should begin at puberty, around the age of 12, in increasing dosages sufficient to maintain age appropriate serum concentrations of testosterone, estradiol, follicle stimulating hormone, and luteinizing hormone (8). Testosterone therapy may help to produce more normal development including more muscle mass, hair growth and increased sex drive. Testosterone supplementation will not increase testicular size, decrease breast growth or correct infertility (6). The Klinefelter subjects are traditionally described as infertile because of complete absence of germ cells. Although semen analysis most often reveals azoospermia, some Klinefelter men may have single-residual foci with spermatogenesis. Therefore, biological paternity is possible by testicular sperm extraction (TESE) combined with intracytoplasmic sperm injection (ICSI). Because of progressive decline of spermatogenesis in man with Klinefelter syndrome, testicular sperm extraction should be done before critical age of 35 years (4,14).

Conclusion

In 20 years period (1985-2004) 124 patients were sent for cytogenetic evaluation to "Centre for Human Genetics" of Faculty of Medicine in Sarajevo from different medical centers within Federation of Bosnia and Herzegovina because of irregular sex development. There were 38 patients with diagnosis Klinefelter syndrome and gynaecomastia. Polysomy X was found in 3 (7,9%) examinees. Hypogonadism and cryptorchidism were cause for cytogenetic evaluation in 59 patients. In 3 (5,1%) of those polysomy X was found. In 27 patients cytogenetic evaluation was indicated for azoospermia, oligozoospermia and sterilitas primaria. In 8 (29,6%) of those patients polysomy X was found.

Among 14 confirmed cases of polysomy X, 10 (71,4%) were in nonmosaic form - 47,XXY, 3 (21,4%) in mosaic form with two cell lines (46,XY/47, XXY), and one confirmed case (7,2%) was in mosaic form with higher level of polysomy X (46,XY/47,XXY/48,XXXY).

In most of the cases polysomy X was detected at the age of sexual maturity. Androgen replacement therapy should begin at puberty, around the age of 12, so indication for cytogenetic evaluation should be set up at a very young age.

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