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THE PREVALENCE OF THE KLINEFELTER SYNDROME AND ITS VARIANTS IN A SPECIFIC HUNGARIAN INFERTILE MALE GROUP

Orsolya Bellovits, Péter Sótonyi and Györgyi Bujdosó

Hungarian Academy of Sciences – Semmelweis University,
Institute of Forensic Medicine, Budapest, Hungary

Abstract: *Data from the Hungarian Central Statistical Office (KSH) show that infertility affects about 150,000 couples in Hungary. The reports have shown that female and male contribution to this problem is equal. Chromosomal abnormalities are one of the major causes of male infertility. The most common abnormality is the Klinefelter syndrome. The aim of this study was to estimate the prevalence of Klinefelter syndrome in patients with azoospermia in a specific sample. Between 2003–2006 we investigated sex chromosomal abnormalities in 62 infertile men that came from urology clinics or were investigated in paternity and crime cases. Karyotyping was performed on lymphocyte preparations of men with diagnosis of infertility. The traditional cytogenetic methods (QFQ-, GTG-, CBG-band) were combined with fluorescence in situ hybridisation. Among the investigated subjects we found three 47,XXY, one 47,XXY/49,XXXXY, and two 48,XXYY syndromes. There are few reports on very low rate spermatogenesis in occasional patients with Klinefelter syndrome, but all of our patients were azoospermic.*
Keywords: *Sex chromosome abnormalities, Klinefelter syndrome, Infertility, Azoospermia.*

Introduction

Data from the Hungarian Central Statistical Office (KSH) show that infertility affects about 150,000 couples in Hungary, which means that one in seven couples have problems in conceiving. The women were thought the main cause of the childless partnerships in the past, but the recent examinations showed that in infertile couples, the female and the male factor can be identified equally (Foresta et al. 2001, Huynh et al. 2002, Zhang and Lu 2004).

Genetical abnormalities (10–15%) are one of the major causes of male infertility (Patsalis et al. 2002, Pienna Videau et al. 2001). Numerical or structural chromosomal anomalies can be found in the background in 5–10% of the cases. Approximately 80% of these cases are due to sex chromosome abnormalities, in about 2% it occurs mixed with autosomal abnormalities (Siffroi et al. 2000, Visootsak et al. 2001, Huynh et al. 2002).

Klinefelter syndrome is the most common chromosome aneuploidy. The prevalence of the classical XXY karyotype is 0.1–0.2% in the general population and 3–10% between the infertile men. Variants of this disorder with supernumerary Xs and/or Ys also exist. The incidence of 48,XXXY and 48,XXYY is 1 per 50,000, 49,XXXXY is 1 per 85,000 male births. Many patients with Klinefelter syndrome remain undiagnosed because of substantial variation in clinical presentation. Approximately 10% of expected cases are identified prenatally and 26% are diagnosed in childhood or adult life, because of hypogonadism, gynaecomastia, or infertility, leaving 64% undiagnosed.

The aim of our study was to identify chromosomal abnormalities, mainly the Klinefelter-syndrome, in infertile men prior to medicine treatment or surgery.

Subjects and Methods

Our survey included 62 men during 2003–2006. They mainly came from Urological Clinics with the diagnosis of azoospermia. Another part of the patients were sent to our Institute from Paediatrics Clinics or law courts with physiological or mental problem.

The traditional cytogenetic methods and FISH analysis were used for chromosomal analysis of an assorted male group, who were not physiological causes in the background of the infertility. Cytogenetic and FISH studies were performed on lymphocytes of peripheral blood. The initiation of mitosis of the lymphocytes was performed in vitro with bacto phytohemagglutinin-P and M. After 72-hour growth chromosomes were stopped in mitotic metaphase by colchicine.

The used chromosomal staining methods were the followings: GTG, QFQ, CBG banding techniques and fluorescence in situ hybridization (FISH) analysis with Y painting probes and X painting probe labelling.

Results

Klinefelter syndrome and its variants were found in 6 patients (9.7%). P1–P4 was sent to our Institute because of azoospermia. Three patients (P1, P2, P3) had non-mosaic 47,XXY karyotype (Figure 1). In case of patient 4, the genetic study showed 47,XXY karyotype in most of the counted mitotic metaphases chromosome groups, but in some cells we found 49,XXXXY karyotype (Figure 2).

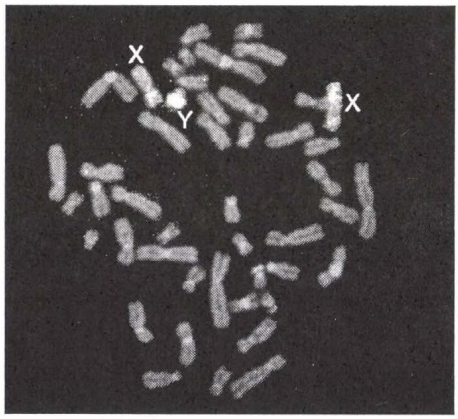

Figure 1: The karyotype of P1 patient with Klinefelter syndrome (FISH analysis).

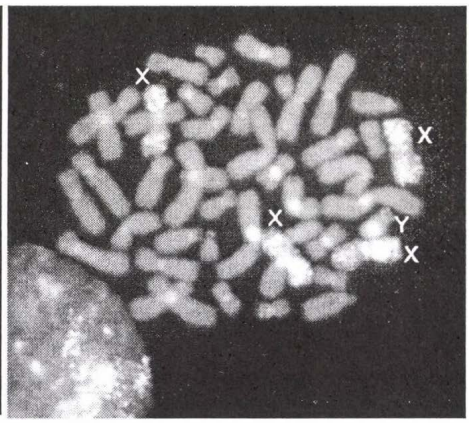

Figure 2: 49,XXXXY cell of P3 patients with FISH.

Patient 5 was examined in childhood for the asking of the Paediatrics Clinic because of epilepsy. In case of patient 6 the judge asked the chromosome examination after serial crime, because of low intelligence, too tall body-height and frequent bone-breaking. In the last two patients 48,XXYY karyotype were found (Figure 3).

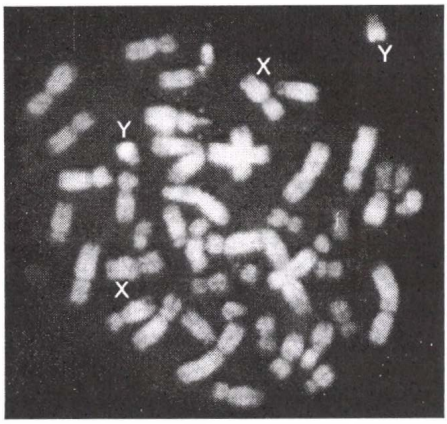

Figure 3: 48,XXYY karyotype with Q-band.

All patients were tall, and one man (P3) had gynecomastia. The testes were small and firm, and elevated FSH level was found in these men. In that patients who had andrological examination spermatozoa were not detected in the testicular biopsy specimens.

Table 1 shows the andrological, histological and cytogenetical findings of the 6 patients with Klinefelter syndrome.

Table 1. Andrological, histological and cytogenetical findings in 6 patients.

Patients	Age (yr)	Height (cm)	Weight (kg)	Testis	Ejaculate	FSH IU/l	LH IU/l	Level of testosterone	Histology of testicular biopsy	Cytogenetics
1	31	185	70	smaller and firm	0 M/ml	elevated			spermatozoa were not found	47,XXY
2	29	178	84	smaller and firm	0 M/ml	32.72	13.95	2.05 ng/ml	spermatozoa were not found	47,XXY
3	31	182	112	small	0 M/ml	25.9	13.8	12.3nmol/l	spermatozoa were not found	47,XXY
4	32	189	110	low volume and firm	0 M/ml	16.51	8.75	3.93 ng/ml	Sertoli cell only syndrome	47,XXY/ 49,XXXXY
5	10	150	36	smaller	–	–	–	–	–	48,XXYY
6	21	219	–	–	–	–	–	–	–	48,XXYY

Discussion

The XXY syndrome is the most common genetic cause of human male infertility. Approximately 80% of the cases is the classical 47,XXY, and 20% displays higher-grade chromosome aneuploidies, mosaicism or structurally abnormal X chromosomes.

In this survey, the Klinefelter syndrome was also the most frequent chromosome aberration between infertile men (9.7%) similar to literature data (3–10%). The cause of the high prevalence of this syndrome in our study could be the specific, assorted sample.

We found non-mosaic 47,XXY syndrome in three patients, 47,XXY/49,XXXXY mosaicism in one patient and 48,XXYY variants in two patients.

Patients with 47,XXY syndrome was phenotypically normal, except the smaller testis, and the gynaecomastia in one patient. The cause of their examination was the infertility.

There are few reports of very low rate spermatogenesis in occasional patients with Klinefelter syndrome, and very rare cases from paternity tests. Earlier our laboratory reported one case in a legal paternity action, but the paternity was excluded (Bujdosó et al. 1976, Bielanska et al. 2000, Pienna Videau et al. 2001, Visootsak et al. 2001, Huynh et al. 2002, Lanfranco et al. 2004). In our sample each patient was azoospermic, and in the testicular biopsy specimens spermatozoa sufficient for ICSI were not found.

In poly-X Klinefelter syndrome the phenotype progressively deviates from normal as the number of X chromosomes increases, and these patients has greater incidence of mental retardation. In our survey the two patients with higher grade chromosomal aneuploidies have more physical and mental problem, such as mental retardation, low intelligence, behavioural problem, cryptorchidism, myopia, osteoporosis. Even so much problem, the syndrome was recognised in 10 and 21 years of age.

The numerous undiagnosed patients with Klinefelter syndrome prove that similar to several other abnormalities this well-known syndrome need higher acquaintance. The first step towards this goal was taken by starting the Human Phenome Project (Freimer et al. 2003, Méhes and Kosztolányi 2006).

Conclusion

Many patients with Klinefelter syndrome remain undiagnosed because of substantial variation in clinical presentation. But the early recognition of the syndrome would be very important for these patients, because hormonal treatment can prevent serious consequences, such as hypogonadism, osteoporosis, can increase masculinity, and substantially improves quality of life, although it will not reverse infertility.

As well very important to diagnose this syndrome before fertilization treatment, because of the higher risk of fathering a child with sex chromosomal hyperploidy or autosomal aneuploidies.

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Levelezési cím: Orsolya Bellovits
Mailing address: Hungarian Academy of Sciences – Semmelweis University
Institute of Forensic Medicine
H-1091Budapest
Üllői u. 93.
Hungary
bellovor@yahoo.com