Research Article

Chromosomal Abnormalities in a Population of Infertile Males from Algeria

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ABSTRACT

Chromosomal abnormalities are one of the most frequent genetic causes associated with spermatogenic failure. In the present study, it is aimed to investigate the frequency and types of chromosomal abnormalities of infertile males with non-obstructive azoospermia and severe oligozoospermia in Algeria. A total of 80 infertile men (49 azoospermic and 31 oligo-asthenoteratozoospermic) were studied for the cytogenetic evaluation. Karyotyping was performed on peripheral blood lymphocytes according to standard methods. Of 80 cases, 70 had normal karyotype (46,XY). The total prevalence of chromosomal abnormalities was found to be 12.5% (10/80). Among them ten were numeral sex abnormalities including five patients with Klinefelter Syndrome, four patients with 47,XYY syndrome, one patient with 46,XX caryotype. All patients with Klinefelter Syndrome had azoospermia. The occurrence of chromosomal anomalies among infertile males strongly suggests the need for routine genetic testing in Algeria. Moreover, a genetic investigation could minimize the risk of transmitting genetic abnormalities to future generations.

Keywords: Male infertility, Chromosome abnormalities, Karyotype, Oligo-astheno-teratozoospermia, Azoospermia

INTRODUCTION

Subfertility is defined by the World Health Organization (WHO) as failure to conceive over 12 months of unprotected frequent intercourse and affects approximately 15% of all couples attempting pregnancy, and among these half are male-related[1].

A marked decline in male reproductive health and an increase in the population of subfertile males in both high- and low-income countries have been reported by several studies[2-4].

Many factors may have an influence on the spermatogenic process. Chromosomal aberrations are one of the most important factors of male infertility including numerical or structural abnormalities, and involve sex chromosomes or autosomes[2,4]. Some aberrations are inherited, while others arise de novo. Such disorders may arrest germ cell production and maturation or lead to the production of non functional spermatozoa.

There are many studies on the nature and frequency of chromosome anomalies associated with azoo- or oligozoospermia in infertile[5-10]. The overall incidence of chromosome abnormalities in infertile men was estimated to be around 5.8% and this frequency increases as the sperm concentration in ejaculate decreases[11-12]. This percentage increasing to 10-15 per cent in patients with azoospermia (AZ)[13]. Among the chromosomal mutations found in infertile men, sex chromosome abnormality are predominant in azoospermic men (12.6%) particularly the 47,XXY karyotype that characterizes the Klinefelter Syndrome (KS), whereas autosome anomalies (3.0%) are the most frequent in oligozoospermic men such as robertsonian translocations, balanced translocations, inversions (pericentric or paracentric) and additional marker chromosomes[14-16].

Several studies in various countries have determined the contribution of chromosomal abnormalities in patients with AZ or oligoasthenoteratospermia (OATS). No such studies have been undertaken in Algeria. We aimed to evaluate the contribution of chromosomal aberrations in a group of Algerian infertile male using standard cytogenetic methods. Furthermore, we compared our results with reports from other regions of the world.

MATERIALS AND METHODS

Subjects

The study involved 80 infertile men whose infertility was related to testicular problems. Individuals presenting pre- or post-testicular problems were excluded from the study. The sample consisted of 49 patients (49/80 = 61.25%) with azoospermia, 31 patients (31/80 = 38.75%) with OATS. Their sperm count range is from several thousands to $20x10^6$ ml and aged from 24 to 48 years. All patients included presented one or more years of primary infertility. The participants were recruited from Ibn Roch clinic and Ibn Sina laboratory between May 2009 and May 2013. Informed written consent was obtained from all patients.

Somatic Cytogenetic Analysis

Whole blood was collected in a sodium heparinized vacutainer. Lymphocytes were cultured and prepared using routine laboratory protocol. Metaphases were stained with Giemsa and analysed by GTG or RHG technique.

A minimum of 20 metaphases were analyzed for each patient, but if mosaicism was suspected then 50 or more cell counts were undertaken. Karyotypes were described according to the International System for Human Cytogenetic Nomenclature[17].

RESULTS

Karyotyping was carried out in 80 infertile men with idiopathic AZ (n=49) or OATS (n=31). Genetic abnormalities were found in 12.5% of all infertile men studied (Table 1). As shown in Table 1, of these patients, a total of 10 patients (1 with OATS and 9 azoospermic patients) had chromosomal abnormalities, including 5 patients with KS (47,XXY), 4 patients with 47,XYY syndrome, one patient was diagnosed as a 46,XX male.

Considering only the patients with OATS, the frequency of chromosomal abnormalities was 3.22% (1/31), while in those with AZ it was 18.37% (9/49). The commonest chromosomal anomaly was 47,XXY (KS); three cases were pure types and two were mosaics. AZ was found in all these patients. The second frequent sex chromosome anomaly was 47,XYY seen in four patient (4/11). 3 of these patients have azoospermia and one with OATS (Table 2). The case of 46,XX male syndrome had an atrophic testicles.

DISCUSSION

Among the numerous etiologic factors of male infertility, chromosomal abberations play an important role. The exact mechanism by which these anomalies induce infertility is not clear. It was suggested that pairing anomalies within the sex chromosomes are implicated in the disruption of spermatogenesis with meiotic arrest, and subsequent oligozoospermia or azoospermia[18].

The frequency of chromosomal abnormalities found in the several studies varies depending on a number of factors; the most important of these is the criteria for selection of patients based on the sperm counts and ranges from 7.3[19] to 14%[20].

In the present study, the rate of chromosomal anomalies observed among infertile men (<20 million/ml) was 12.5%. The highest frequency of abnormal karyotype 11.25% (9/80) was found among patients with AZ.

This figure is comparable to that reported in some studies[5,6,21-25], but higher[26-31] or lower[9,32-36] than reported from others published data.

In the literature, the frequency of chromosomal anomalies are 14.2% in males with azoospermia and 6.5 % in men with oligozoospermia is within the range of 10-15 and 5-7 % respectively[13,37]. Our results (11.25% for azoospermia and 1.25% for OATS) were consistent with these previous reports.

Among the chromosomal abnormalities found, the most common chromosomal aberration was KS. This anomaly represents the most common genetic cause of human male infertility with a prevalence of 1 in 660[38]. In the current study, KS was present in 50% (5/11) of all chromosomal abnormalities. This is in accordance with previously published studies. For example, in Carrara report, the 47,XXY karyotype was the most frequent chromosomal alteration[27]. Also, Ferlin reported that the prevalence of KS among infertile men is very high, up to 5% in severe oligozoospermia and 10% in azoospermia[15]. Mahjoubi have also reported that the most prevalent chromosomal abnormality in the infertile men was 47,XXY, which was detected in 94 (58.38%) men[7]. In addition, in the study of Zhang the KS was the most common anomaly occurring in 82.41% of all patients[36].

The majority of KS patients have a homogeneous XXY karyotype but approximately 15–20% of them are mosaics with variable phenotypes[32,39]. In this study, a mosaic 46,XY/47,XXY karyotype was found in two azoospermic men. Ghorbel found that three of the ten patients with KS had mosaic form[9].

Some men with mosaicism have normal testicular size and spermatogenesis at puberty, but germ cells are progressively lost overtime[40,41]. As we know in general, male with KS have infertility. In a very small number of cases, males with 47,XXY have been able to produce children through assisted reproductive techniques[39].

The XYY syndrome is characterized by an extra copy of the Y chromosome, with an incidence of 1 in 1000 males[42]. Four patient with 47,XYY were found in our studied group (5%). This anomaly have been also found in many reports[5,22,34,43].

The 46,XX males represents the most common condition in which testicular development occurs in the absence of a Y chromosome. This disorder occurs at a frequency of 1/25.000 newborns[42]. In our study population, there was one patient who presented a 46,XX karyotype actually known as 46,XX testicular disorder of sex development (DSD).

Ghorbel have reported two men with 46,XX karyotype[9]. Another cytogenetic study enrolled by Akin revealed one patient with 46,XX DSD[8]. A review by Hofherr is based on larger numbers of patients. In total, data from 2,242 men have been evaluated, a frequency of 14.3% of abnormal karyotypes including 7 46,XX males[22]. Phenotypically the adults are similar to patients with KS.

Three groups have traditionally been described, based on phenotype: males with normal male phenotype, males with ambiguous genitalia, and true hermaphrodites[44-45].

Several etiologies have been proposed and subsequently observed, on the basis of a genetic heterogeneity, to explain 46,XX male: (i) translocation of the testis-determining factor (TDF), equated more recently with the sex-determining region Y gene (SRY), from the Y to the distal short arm of the X chromosome during male meiosis; (ii) mutation in an autosomal or X chromosome gene which permits testicular determination in the absence of TDF[14].

In conclusion, this work describes one of the largest studies of male infertility and includes the first results of cytogenetic analysis of 80 Algerian infertile males.

When comparing this study to prior reports, the frequencies of abnormalities are similar.

This incidence was high in our samples. We conclude that all patients with non obstructive azoospermia and OATS should be referred for cytogenetic investigation.

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Table 1: Different types of chromosomal aberrations encountered in 10 of 80 infertile men

Chromosomal aberrations	Karyotype	Number of patients	Spermparameters			Hormonal analysis		
			Sperm Count (million/ml)	Motility %	Morphology %	FSHmU/ml	LH mU/ml	TEST ng/ml
Female Karyotype	46,XX	1	0	0	0	0.9	0.38	10.6
Numerical	47,XXY							
	1	5				24.34	18.81	0.28
	2					NA	NA	NA
	3		0	0	0	27.5	16.56	1.37
	47,XXY / 46,XY							
	1.		0	0	0	NA	NA	NA
	2.		0	0	0	12.74	5.5	1.5
	47,XYY							
	1.	4	0	0	0	NA	NA	NA
	2.		3.1	4	14	8.48	5.48	1.1
	3.		0	0	0	35.1	4.01	4.34
	4.		0	0	0	NA	NA	NA

NA: not available

Table 2: Sex chromosomal abnormalities in a sample of infertile men with AZ or OATS

Chromosomal Abnormalities	Sperm Disorder		Total	% of Total
	Azoospermia	OATS		
46,XY (normal)	**40**	**30**	**70**	**87.5**
47,XXY	3	-	3	3.75
47,XXY / 46,XY	2	-	2	2.5
47,XYY	3	1	4	5
46,XX	1	-	1	1.25
Total	49	31	80	100

AZ: azoospermia; OATS: oligoasthenoteratozoospermia

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