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Pattern of Chromosome Abnormalities Related to Male Infertility in Senegal: A Prospective Study of 67 Cases

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Abstract

Introduction: Infertility may result from male or female factors or a combination of both. It is known that male factors are responsible for 50% of all infertility. Genetics is part of the management of male infertility, and karyotyping is highly recommended in men with nonobstructive azoospermia, severe oligozoospermia (sperm count <5 million/ml), or no palpable vasa. The purpose of our study was to determine the prevalence and profile of the chromosomal abnormalities of this subgroup in a cohort of patients followed for male infertility in the laboratory of cytogenetics and reproductive biology at the University Hospital Center Aristide Le Dantec in Dakar, Senegal.

Material and methods: Sixty-seven (67) patients with primary infertility were selected for our study. After semen analysis and evaluation of serum levels of FSH, a standard karyotype with R banding was performed.

Results: The global prevalence of chromosome abnormalities was 16.41% (n=11), with essentially numerical abnormalities (n=10). In terms of prevalence, Klinefleter syndrome was the most represented abnormality, with a global prevalence of 11.93% and a frequency of 2.988% in mosaic forms. Were also registered, respectively, a case of 47, XYY, and a case of XX male, 46,XX.

Conclusion: Primary infertile males with NOA and severe oligozoospermia have a non-neglectable rate of chromosomal aberrations, justifying the requirement of cytogenetic testing in order to pursue assisted reproductive treatment.

Keywords: Chromosomal abnormalities • Klinefelter syndrome • Mosaicism • Male infertility • Non-obstructive azoospermia

Introduction

Infertility is considered a global public health issue with an increasing incidence [1]. Fifteen (15%) of couples of reproductive age are affected by this condition [2], and the prevalence of infertility is estimated at approximately 50 to 80 million people worldwide [3]. Infertility may result from male or female factors or a combination of both. It is known that male factors are responsible for 50% of all infertility [4]. Even if a lot of etiologies or factors can be identified and treated (urogenital tract infection, cryptorchidism, infections, varicocele, endocrine disturbances, systemic disease, environmental factors, etc.), about 40% of the cases remain idiopathic [5]. The recent development of molecular biology and medical genetics led to new perspectives in the identification of some etiologies as responsible genes [6]. The prevalence of chromosomal abnormalities in infertile males has been estimated to fall within the range of 2.4% to 16.4%. In the case of azoospermia, the incidence of chromosomal abnormalities is particularly high, varying from 13.1% to 23.6% [7].

Currently, three genetic tests are commonly performed and recommended by major urologic associations: Karyotype Analysis (KA), Y-chromosome microdeletion testing, and CFTR mutation testing. Karyotype is indicated when a patient has findings on a history or physical exam concerning chromosomal abnormalities, azoospermia, or severe oligospermia (count <5 million/mL). This testing is justified by two important reasons: the first is to avoid the transmission of a genetic condition to offspring by the short cut of ART, and the second is to evaluate and maybe predict the outcome of the assisted reproductive techniques [6,7].

In Africa, an increased number of couples are undergoing ART procedures [8], contrasting with a lack of data concerning their genetic conditions. The purpose of our study was to report the profile of the chromosomal abnormalities identified in a cohort of patients followed up for male infertility.

Materials and Methods

A prospective study was carried out from May 2020 to May 2023 in the genetic and reproductive unit of the laboratory of cytology, cytogenetics, and reproductive biology of the University Teaching Hospital Aristide Le Dantec and the Laboratory of Histology, Embryology, and Cytogenetics of the Faculty of Medicine of Cheikh Anta Diop University in Dakar (Senegal). Sixty-seven (67) patients with primary infertility referred for couple infertility were selected.

We included patients with severe Oligozoospermia (OZS) (sperm count < 5 million/ml) and Non-Obstructive Azoospermia (NOA). Written consent was obtained, and we received the approval of the ethical committee of our university. Were excluded from the study cases with no hormonal data, more precisely with no FSH serum level.

Standard karyotype

Five (5) ml of peripheral blood samples were withdrawn from all the participants in sodium heparin sterile tubes for cytogenetic study and hormonal assay, respectively.

0.5 ml of heparinized peripheral blood samples from each patient were cultured for 72 h in RPMI-1640 medium supplemented with fetal bovine serum and phytohemagglutinin. Colchicine was added 50 min before the end of the culture, and after hypotonic treatment and fixation with Carnoy solution (3:1 acetic acid and methanol), the remaining pellet was suspended in 1 ml and harvested on superfrost slides. RHG-band chromosomal denaturation was performed. Twenty (20) metaphases were counted as well for each case, and ten (10) were analyzed by cytovision software, version 450–550 band

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resolution. ISCN 2016 was used to identify chromosomal abnormalities [9]. When mosaicism was suspected, 30 additional metaphases were analyzed in each case.

FSH serum level determination

Follicule-Stimulating Hormone (FSH) was measured by electrochemiluminescence using the Vidas® 2016 Serum Chemistry Analyzer (Biomérieux SA, Marcy L'étoile, France) immunoassay, according to the manufacturer's instructions.

Semen analysis

Sample collection was done following abstinence from ejaculation for 3 days, by masturbation in a room dedicated, in the laboratory. The semen analysis was performed in accordance with the method described in the 5th manual of WHO guideline for semen analysis, version 2010. Strict criteria of Krüger were used to evaluate morphology [10].

Statistical analysis: Data were collected and entered in Microsoft Excel software, then imported into SPSS software for analysis. Descriptive statistics were calculated and expressed as frequency and proportion.

Results

Age

A total of 67 patients met the criteria of the study. Ages ranged from 24 to 56 years, and the mean age was 36.2 ± 6.2. All were concerned by primary infertility, with a mean duration of 4 (± 2,17) years.

Semen profile of the sample of study

In our sample study, 26.86% (n=18) of patients suffered from Non-Obstructive Azoospermia (NOA), and 73.13% (n=49) were concerned by severe Oligozoospermia (OZS). The mean sperm count in that pattern was 2,15 (± 1,6) million/ml. In that case (severe OZS), the most associated abnormalities were asthenozoospermia and teratozoospermia (Figure 1).

Level of serum FSH

In NOA (n=18), the mean level of FSH was 15.58 UI/L ± 6.7 and 5,45 ± 2,1 UI/L in the case of OZS (n=49).

Chromosomal abnormality profile

The global prevalence of chromosome abnormalities in this series was 14.92% (n=10) with essentially numerical abnormalities (n=9) and a case of XX male with 46, XX karyotype. In case of NOA (n=18), we found 7 cases of chromosomal abnormalities (7/18) and 3 cases within the patients with OZS. (3/49). So the relative frequencies of chromosomal abnormalities were respectively 38,88% in NOA and 6,12% in case of OZS. The numerical abnormalities were represented by 6 cases of Klinefelter 47, XXY (Figures 2 and 3), and 2 cases of mosaic Klinefelter, with respectively a case of mos 46, XXY/46, XX and a case of mos 46, XXY/46, XY. One case of double Y chromosome was identified (47, XYY). Klinefelter syndrome was the most prevalent syndrome with a proportion of 11.93% (Table 1).

The patients with chromosomal abnormalities were mainly concerned by azoospermia (7/10). Otherwise, the results of the semen analysis identified two main profiles in the semen that were oligoasthenoteratonecrozoospermia (n=2) and oligoasthenoteratozoospermia (n=1) (Figure 4).

Discussion

Prevalence of chromosomal abnormalities

Globally, the prevalence of chromosomal abnormalities among infertile patients may vary between 2% and 18.9% [1,8,11] in the different studies according to the investigated populations. In some regions, this prevalence can be very high, like in North India, Kashmir, with a prevalence of 60% [12].

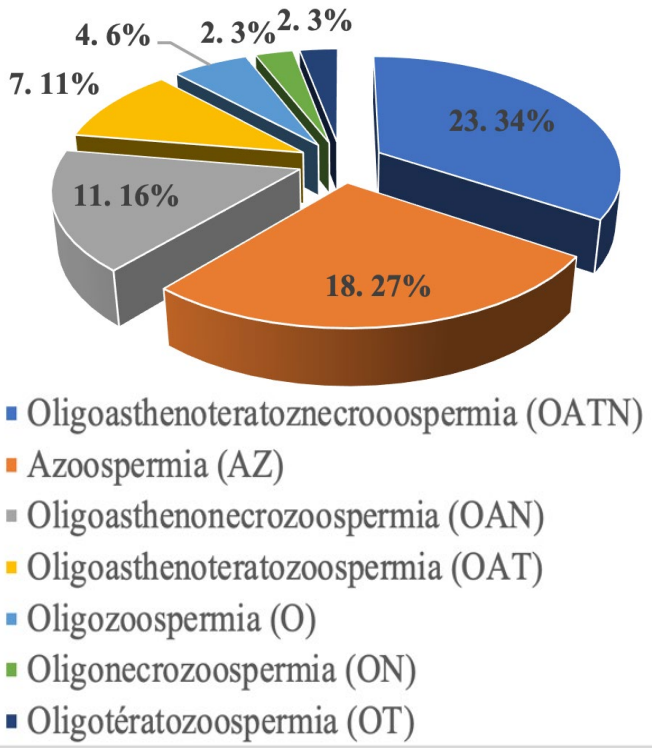

Figure 1. Profile and repartition of the semen abnormalities of selected cases (N=67 cases).

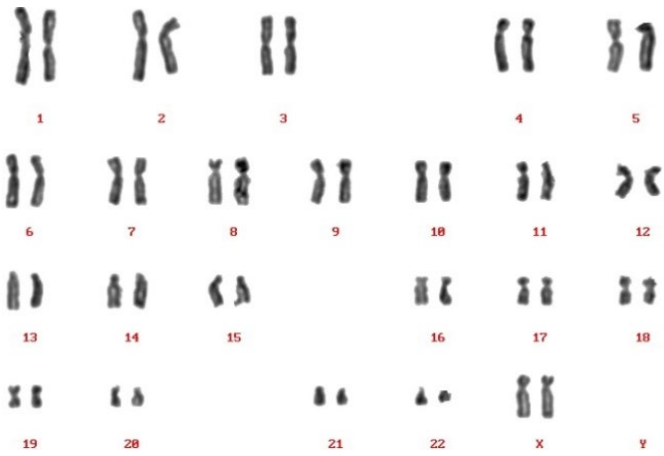

Figure 2. Male XX with 46, XX.

In our study, the prevalence of chromosomal abnormalities in infertile men was 14.92%.

This prevalence was close to some results reported in some regions of India [13], with 16% of the prevalence, or from some parts of eastern Europe, like Bulgaria [2], with a frequency of 16.16%. In Rwanda, this prevalence was higher (20,58%) in comparison with our study [14,15]. Lower frequencies were reported in Egypt (13,5%), [15] and in Europe, with 13.1% in Croatia and 13.4% in Estonia [16,17].

Azoospermia and oligozoospermia

The large scale of variation in frequencies of chromosomal abnormalities among infertile patients all around the world may change according to numerous factors like geographical region, ethnicity, consanguinity, size of the samples, et cetera. Nevertheless, in the literature, there is a high prevalence of chromosomal abnormalities among patients with azoospermia and oligozoospermia, and this prevalence is reported to be much higher in the case of non-obstructive azoospermia. In our study, the relative proportion of chromosomal abnormalities among the patients with NOA was 38.88%. (7/18).

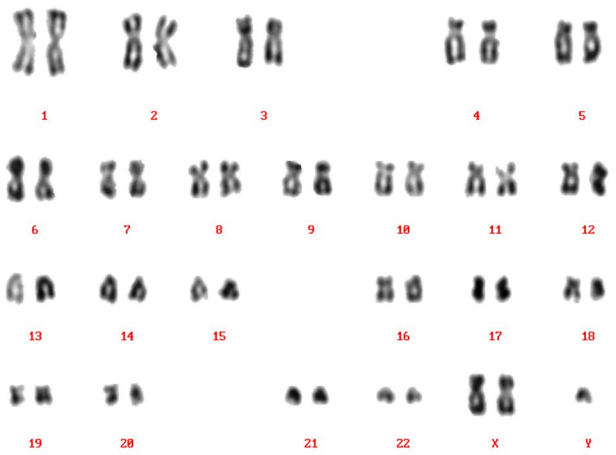

Figure 3. Klinefelter syndrome, 47, XXY.

Table 1. Repartition of chromosomal abnormalities in case of NOA and severe OZS.

Results of Karyotype	NOA n=18	Severe OZS n=49	Total n=67	Global Frequency
Normal 46, XY	11	45	56	83.58%
Klinefelter syndrome 47,XYY	4	2	6	8.95%
Mosaic Klinefelter 47,XXY [27]/46, XX [3]	1	0	1	1.49%
Mosaic Klinefelter 47,XXY [24]/ 46, XY[6]	1	0	1	1.49%
Double Y 47,XYY	0	1	1	1.49%
XX male 46, XX	1	0	1	1.49 %

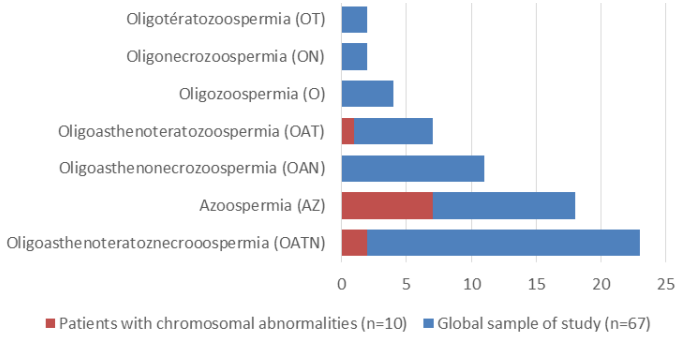

Figure 4. Semen profile in the global sample and within patients with chromosomal abnormalities.

We noticed the same tendency in a study from Taiwan [18]. In that case, 25.53% of patients with nonobstructive azoospermia and 8.88% of patients with oligozoospermia had abnormal findings. Chromosomal abnormalities concerned 32.81% of patients with NOA in Azimi South [19] and 30% in southern China [20].

These observations are confirmed by recent reviews on the subject, considering a large number of studies [21,22]. This high proportion of aneuploidy in severe OZS and NOA justifies the recommendations by scientific societies [23,24], and committee practice [25] to perform karyotyping for those patients.

Profile of chromosomal abnormalities

The Klinefelter syndrome was the most representative case in our study, with a prevalence of 11,94% (8/67). In the Ceylan C and Ceylan GG review [26], Klinefelter Syndrome (KS) is considered the most prevalent chromosomal abnormality in cases of male infertility and was found to be prevalent in 5% of men with severe oligozoospermia and 10% in cases of azoospermia. KS has mainly two types (1): non mosaic, 47, XXY; and mosaic, 47, XXY/46, XY [27]. The mosaic form 47, XXY/46, XX is very rare, and only a few cases have been reported in the literature [28]. In the Curado study [4], all cases of KS concerned patients with azoospermia. We found in our sample some cases of KS, both in patients with azoospermia and with severe oligozoospermia.

Karyotyping testing and recommendations

According to Hassold T, et al. [29], it is estimated that up to 60% of conceptions that are aneuploid are spontaneously aborted, and more than half of the Products Of Conceptions (POCs), i.e., 50.4%, are found to be karyotypically abnormal [30]. There is an increased number of patients undergoing assisted reproductive techniques, and their procedures require genetic testing to avoid the transmission of a genetic condition to offspring and to also be able to request a preimplantation genetic diagnosis for aneuploidy. According to the majority of expert committees, it is wise to perform routine karyotyping prior to IVF/ICSI in infertile men with unexplained spermatogenic failure and a reduced sperm count (less than 10 million sperm per ml) and Y chromosomal microdeletion analysis in men with severe oligozoospermia (less than 5 million) [24].

This high impact of pregnancy loss in aneuploidy could explain why PGT-A was introduced to overcome this obstacle and improve success rates in IVF [31]. Nervetheless, the impact of A-PGT is still a subject of controversies, and according to some authors, PGT-A may not be a universal test to improve the reproductive potential in IVF, based on their population, skills, and limitations [32]. This is a preliminary study, and according to our first data, the rate of chromosomal abnormalities among infertile men in our population is not neglectable at all. In the case of NOA, it concerned more than a third of the patients, for we highly recommend karyotyping in that pattern, especially for patients undergoing ART procedures.

Conclusion

A non-negligible rate of chromosomal abnormalities was identified after karyotyping with our patients with NOA and severe OZS. Patients with non-obstructive azoospermia had a high frequency of chromosomal aberrations (38.88%). Our findings justify strong recommendations for cytogenetic testing, particularly if an ART procedure is scheduled.

Perspectives

This is a preliminary study that we would like to extend to be able to propose, according to the results, an adapted algorithm of prescription considering accessibility to karyotyping and ART procedures.

Limitations of the Study

Being a single-center study, our series comprised a small number of patients that might be insufficient to represent the entire population of infertile males from different ethnicities.

Ethical Considerations

Data security, privacy, and confidentiality were considered based on recommendations from the Research Ethical Committee of the Faculty of Medicine at our university.

Funding

None.

Conflicts of Interest

We declare none.

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