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Investigation of Cytogenetic Abnormalities in Infertile Men with Idiopathic Spermatogenesis Disorder

Mahboubeh Mirzaei[1], Mohammadali Bagherinasabsarab[1,2*], Ali Asghar Ketabchi[1], Reza Mohammadi[1], Fatemeh Yazdanpanah[3]

[1]Department of Urology, Kerman University of Medical Sciences, Kerman, Iran
[2]Department of Urology, Tehran University of Medical Sciences, Tehran, Iran
[3]Department of Dermatology, Kerman University of Medical Sciences, Kerman, Iran

***Corresponding Author:** Mohammadali Bagherinasabsarab, Email: m.bagherinasab@kmu.ac.ir

Abstract

Background: Infertility is one of the most common sexual health problems in the world affecting around 15% of couples. Males are responsible for the main cause of infertility in 50% of infertile couples, and the results of sperm analysis are abnormal in 25% of infertile men without any known etiology (i.e., idiopathic male infertility), where clinical history, physical examination, and hormonal analyses usually render normal results. Advances in various biomedical fields have allowed researchers to determine the role of interactions between genetic and environmental factors in the pathogenesis of infertility. Therefore, this study aimed to investigate cytogenetic abnormalities in men with idiopathic infertility.

Methods: This cross-sectional descriptive-analytical study was conducted on 135 infertile men (aged between 18 and 45 years) whose spouses seemed healthy in terms of fertility and were aged < 35 years old. The patients initially underwent clinical examinations and paraclinical tests (hormonal tests, including FSH, LH, and testosterone). Spermogram was performed twice with an interval of 2 weeks following the standard criteria published by the World Health Organization (WHO), according to which men with known causes of infertility and obstructive azoospermia were excluded. Finally, only patients with idiopathic spermatogenesis disorder (normal clinical history, physical examination, and hormonal tests) were included in the study. All patients were subjected to cytogenetic analysis (karyotype). The data were analyzed using descriptive statistics and the independent t-test and chi-square test by SPSS version 20 software.

Results: The results showed that out of 135 patients studied, 73 patients (54%) had cytogenetic abnormalities, while no abnormalities were found in 62 (46%) patients. The comparison of men with cytogenetic abnormalities with those without abnormalities showed statistically significant differences in terms of age, duration of infertility, and spouse's age ($P=0.001$). In patients carrying cytogenetic abnormalities, 33 (45%) patients had sex chromosome problems (the most common defect was 46, XY, del (Y) (q11.2-qter)) while 40 (55%) patients revealed abnormalities in autosomal chromosomes (the most common autosomal chromosomal defect was 46, XY, inv (1) (p22q24)). Oligoasthenoteratozoospermia (OAT) was the most common spermatogenesis disorder in patients carrying cytogenetic abnormalities (n = 15, 20%), followed by non-obstructive azoospermia (NOA) (n = 12, 16%). Overall, deletions constituted the most frequent cytogenetic defects observed in those carrying abnormal karyotypes (n = 30, 41%).

Conclusion: Considering the high incidence of chromosomal abnormalities in infertile men with OAT and NOA, it is strongly suggested to conduct cytogenetic analysis in these patients to detect microdeletions in chromosome Y before administering assisted-reproductive technology techniques.

Keywords: Cytogenetic abnormalities, Male infertility, Disorders of spermatogenesis

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Introduction

According to the World Health Organization (WHO), infertility is defined as the inability of a couple to conceive after one year of unprotected intercourse. Infertility is one of the most common sexual health problems in the globe, which affects around 15% of couples. Male infertility is responsible for 50% of infertility causes among couples (1,2). In around 70% of male infertility cases, etiology is known, while the other 30% of cases remain idiopathic, most of which are recognized with a cytogenetic abnormality (3,4).

The most important causes of male infertility include sperm count, morphology, and structural problems, as well as hormonal disturbances and genetic factors (5,6). So far, genetic factors identified to be involved in male infertility include chromosomal problems, single-gene or single-chromosome diseases, disparities during meiosis, and endocrine problems (7).

Nevertheless, around 25% of infertile men with abnormal sperm analysis results reveal no clear etiology, which is known as idiopathic male infertility (8). These individuals generally present with unremarkable clinical history, physical examination, and hormonal tests; however, a slight increase in FSH hormone is occasionally observed, which cannot justify the spermatogenesis problem. Idiopathic male infertility is frequently associated with sperm nucleus problems and DNA structural defects (9-11). Also, infertile men show a relatively higher prevalence of chromosomal abnormalities, which has been reported in up to 5% of these individuals according to the latest literature (1).

Aneuploidy is the most common chromosomal abnormality in infertile men (7). Particularly, males with non-obstructive azoospermia (NOA) show a high incidence of aneuploidy (8), especially in sex chromosomes (12,13). Klinefelter syndrome comprises the most common sex chromosome aneuploidy in men. This syndrome, which is highly prevalent in infertile males, is the most common cause of hypogonadism in men (9). Aneuploidy can also result from chromosomal translocations. Autosomal translocations occur at about 4-10 times higher rate in infertile men than in their fertile peers (14-16). Robertsonian translocation, which occurs between acrocentric chromosomes, is the most common chromosomal structural abnormality in humans (1,17).

Chromosome Y abnormalities, such as microdeletion, are key contributors to azoospermia and severe oligozoospermia (< 20 million sperms per mL of semen) (3,5). Microdeletions most commonly occur in the long arm of chromosome Y (i.e., Yq), which frequently leads to spermatogenesis abnormalities (18-20). This region encompasses a segment called the azoospermia factor region (AZF), which harbors several genes indispensable for the growth and development of sperms. This region is subdivided into three subregions known as AZFa, AZFb, and AZFc (21,22), and most often, the genes located at AZFb and AZFc are deleted, leading to a variety of infertility phenotypes (7). Microdeletions in the AZF region are also found in azoospermic and oligospermic men who have normal karyotypes (21). Besides, a variety of autosomal genes can play a role in male infertility (23-26). Many genes located on the X chromosome are expressed in the testes and are involved in gametogenesis (27,28). The gene encoding androgen receptor (AR) is located on the long arm of X chromosome and is involved in meiosis and the differentiation of spermatocytes to spermatids during spermatogenesis (29).

In parallel with continuous progress in various biological disciplines, researchers have begun to understand the link between infertility and genetic and environmental factors. Nevertheless, acquiring a complete understanding of the exact genetic signature of infertility demands tremendous efforts in the future so that better therapeutic decisions can be taken using assisted reproductive technology techniques. Moreover, the identification of infertility-associated genetic abnormalities sheds light on the inheritance of these genetic defects from parents to offspring. In addition, the resultant acquired deletions may lead to sexual ambiguity in the offspring of affected people. Therefore, genetic analyses can inform the affected person about the prognosis and possible outcomes of complementary fertility treatments. According to the aforementioned, we here aimed to investigate cytogenetic abnormalities in infertile men.

Methods

This cross-sectional descriptive-analytical study was conducted on infertile men with idiopathic spermatogenesis disorder and NOA referred to the infertility clinic of the Afzalipur Hospital of Kerman city in 2022. A total of 153 patients entered the research, 135 of whom completed the study. Eighteen patients did not complete their follow-up. All patients signed an informed consent form before participation in the study (Ethical code: IR.KMU.REC.1399.577). Following the instructions of the WHO, all patients initially underwent clinical examinations and paraclinical testing (serum levels of FSH, LH, and testosterone), as well as spermogram analysis (on two occasions with a 2-week interval). Some patients also underwent ultrasounds as needed.

Inclusion criteria included the diagnosis of idiopathic spermatogenesis disorder or NOA, age of 18-45 years, the absence of any known infertility problems, and having healthy spouses younger than 35 years old. Exclusion criteria included age above 45 years or below 18 years old and the diagnosis of a known infertility problem or obstructive azoospermia. All eligible patients underwent cytogenetic analysis (karyotype). For this purpose, 5 mL of venous blood was collected into tubes containing 500 µL of EDTA. The samples were stored at -20°C until karyotype analysis for finding chromosomal abnormalities. Chromosome Y, sperm DNA, and genomic DNA from peripheral blood lymphocytes were extracted using specialized extraction kits (Stemmera™ Cell Karyotyping Analysis Kit, YchromStrip kit, SpermFunc® DNAf kit) (30). Finally, the extracted DNAs were scrutinized for possible karyotype abnormalities. The data collected were recorded into a checklist and analyzed by SPSS version 20 software.

Results

In this cross-sectional descriptive-analytical study, out of 153 infertile men diagnosed with idiopathic spermatogenesis disorder and NOA initially entering the study, 135 remained in the study until the end. These patients underwent cytogenetic (karyotype) testing, revealing that 73 (54%) of the patients carried cytogenetic abnormalities, and 62 (46%) patients showed normal karyotypes. The two groups (i.e., those with cytogenetic

defects and those with normal karyotypes) had statistically significant differences in terms of age, duration of infertility, and age of spouse ($P=0.001$); however, the two groups were comparable regarding hormonal tests (LH, FSH, and testosterone) and testicle size ($P>0.05$, Table 1).

Oligoasthenoteratozoospermia (OAT) was the most common type of spermatogenesis disorder among the patients regardless of cytogenetic status (n=35, 25%). There was no significant difference between patients with or without cytogenetic abnormalities regarding the type of spermatogenesis disorder ($P>0.05$, Table 2).

Also, OAT constituted the most common spermatogenesis disorder among infertile males with cytogenetic abnormalities (n=15, 20%), followed by NOA as the second most common spermatogenesis disorder (n=12, 16%), and the least common spermatogenesis disorder in this group was cryptozoospermia (n=5, 6%, Table 2).

Among the cytogenetic abnormalities detected, deletions constituted the most common among infertile men (n=30, 41%), and the least cytogenetic abnormalities were chromosomal translocations (n=9, 12%, Table 3).

Table 1. Demographic features of infertile men with or without cytogenetic abnormalities

Variables	With cytogenetic abnormalities		Without cytogenetic abnormalities		*P* value
	Mean	SD	Mean	SD	
Age (y)	35.6	3.8	25.2	2.6	0.001
Duration of infertility (y)	9.8	5.2	4.6	3.1	0.001
LH (mIU/mL)	9.6	1.2	5.2	1.01	0.334
FSH (mIU/mL)	15.2	3.3	7.4	2.12	0.158
Testosterone (ng/ mL)	11.4	8.21	14.5	9.09	0.43
Right testis volume (mL)	3.2	1.01	14.5	9.09	0.43
Left testis volume (mL)	3.8	1.91	5.1	2.23	0.71
Spouse's age	28.3	2.6	21.6	1.6	0.001

Note: data showed statistically significant differences in terms of age, duration of infertility, and spouse's age ($P=0.001$).

Table 2. The frequency of cytogenetic abnormalities in males with spermatogenesis disorders (no statistically significant differences)

Spermatogenesis disorders	With cytogenetic abnormalities		Without cytogenetic abnormalities		*P* value
	No.	%	Frequency	%	
Oligozoospermia	8	10.95	5	8.06	0.87
Asthenozoospermia	7	9.58	6	9.97	0.98
Oligoasthenozoospermia	7	9.58	5	8.06	0.98
Oligoteratozoospermia	8	10.95	10	16.12	0.75
Asthenoteratozoospermia	11	15.06	8	12.90	0.89
Oligoasthenoteratozoospermia	15	20.54	20	32.25	0.44
Cryptozoospermia	5	6.84	4	6.45	0.98
Azoospermia	12	16.43	4	6.45	0.62
Total	73		62		

Table 3. The frequency distribution of chromosomal abnormalities in infertile men

Spermatogenesis disorders	Chromosomal abnormalities				Total
	Deletion	Inversion	Insertion	Translocation	
Oligozoospermia	4 (50)	2 (25)	1 (12.5)	1 (12.5)	8
Asthenozoospermia	3 (42.58)	1 (14.28)	2 (28.58)	1 (14.28)	7
Oligoasthenozoospermia	4 (57.14)	0 (0)	1 (14.28)	2 (28.58)	7
Oligoteratozoospermia	2 (25)	2 (25)	1 (12.5)	3 (37.5)	8
Asthenoteratozoospermia	5 (45.45)	2 (18.18)	0 (0)	4 (36.36)	11
Oligoasthenoteratozoospermia	7 (46.66)	1 (6.66)	1 (6.66)	6 (40)	15
Cryptozoospermia	2 (40)	1 (20)	1 (20)	1 (20)	5
Azoospermia	3 (25)	2 (16.66)	2 (16.66)	5 (41.66)	12
Total	30 (41.09)	11 (15.06)	9 (12.3)	23 (31.5)	73

Note: Data are expressed as No. (%).

Overall, sex and autosomal chromosome abnormalities were found in 33 (45%) and 40 (55%) patients, respectively. Among those with sex chromosome defects, the most common abnormality was 46, XY, del(Y) (q11.2-qter), which was detected in 12 (36%) men, and the least common abnormalities constituted 45, X (azoospermia) and 46, XY (Yp-), each of which was observed in only one patient (3%) (Table 4).

The most frequent autosomal chromosome abnormality was 46, XY, inv (1) (p22q24), which was seen in 7 (17%) participants, and the least common defect was 46, XY, t (5;14) (q10; q10), which was detected in one patient (2.5%) (Table 5).

Discussion

This study aimed to investigate cytogenetic abnormalities in infertile men. Out of 135 men diagnosed with infertility, cytogenetic abnormalities were found in 73 (54.07%). The most frequent spermatogenesis disorder associated with cytogenetic defects among our OAT patients (15 out of 135, 20.54%). Deletions were the most frequent genetic abnormalities found in 30 patients (41.09%). Overall, a considerable ratio of our participants revealed chromosomal abnormalities, including defects in sex chromosomes, which were observed in 33 infertile men (constituting 45% of all patients with cytogenetic abnormalities and 24% of all patients).

In a study by Mierla et al, the incidence of sex chromosome abnormalities was evaluated in infertile men, and it was reported that patients with azoospermia had a significantly higher rate of chromosomal abnormalities compared to counterparts with other male infertility etiologies (31). In our study, however, OAT patients revealed the highest incidence of chromosomal abnormalities, followed by NOA as the second most common spermatogenesis disorder associated with cytogenetic defects. Likewise, several other studies have reported the highest frequency of chromosomal abnormalities among patients with azoospermia (32,33), which opposes our finding in this study.

In the study by Rabbani et al, out of 842 infertile men examined, 172 (20.4%) were diagnosed with azoospermia, including 28 (16.3%) with obstructive azoospermia and 144 (83.7%) with NOA, constituting 17% of all patients. Most cases with NOA were detected with no clear causes (i.e., idiopathic) (34). In this study, we did not include patients with obstructive azoospermia, and among 135 infertile men enrolled, 16 patients (11.8%) were found to have NOA, most of whom (n = 12, 75%) presented with chromosomal abnormalities as the causative factor. Also, 35 (25%) patients were diagnosed with OAT, 15 of whom (42%) carried chromosomal defects.

In a study by Kalantari et al, chromosomal abnormalities were detected in 8 (11%) infertile men studied, of whom 31.4% had azoospermia while 68.6% had oligospermia. In the recent study, the duration of infertility was at least 2 years among the studied population, and the most frequent 47-chromosome aneuploidy included XXY (i.e., Klinefelter syndrome), which was observed in 85.7% of the participants (35). Likewise, Zhang et al reported a prevalence of 10.5% for chromosomal abnormalities among infertile men, and the most common chromosomal abnormality was Klinefelter syndrome (30). In our study, chromosomal abnormalities were found in 73 (54%) of the participants, indicating a higher incidence compared to the two above studies. The most common spermatogenesis disorders in our study were OAT (n = 15, 20.54%), followed by azoospermia (n = 12, 16.4%) and oligozoospermia (n = 8, 10.9%). Moreover, the average duration of infertility among our participants was 9.8 years, and 46, XY, del(Y) (q11.2-qter) comprised the most prevalent sex chromosome abnormality (n = 12, 36.36%). On the other hand, the most common autosomal chromosome abnormality was 46, XY, inv (1) (p22q24), which was observed in 7 (17%) individuals. Overall, three patients (9%) were detected with the XXY genetic signature (i.e., Klinefelter syndrome), showing a considerably lower rate compared to the above-mentioned studies.

In a study by Fu et al on 1333 infertile males, chromosomal

Table 4. The frequency distribution of sex chromosome abnormalities in infertile men

Sex chromosome abnormalities	Frequency	%
46, XY, del(Y) (q11.2–qter(	12	36.36
46, XY, del(Y)(q11.2–qter) (90%)/47, XXY (10%)	2	6.06
46, XY, del (Y) (q11.2–qter)/47, XXY (9.09%)	3	9.09
46, XY(Yp-)	1	3.03
45, X (Azoospermia)	1	3.03
46, XY (65%)/45, X (35%)	2	6.06
46, XY, inv(Y) (p11.3–11.22)	6	18.18
46, XY, dup(Yq)	3	9.09
47, XXY (Azoospermia)	3	9.09

Table 5. The frequency distribution of the abnormalities of autosomal chromosomes in infertile men

Autosomal chromosome abnormalities		Frequency	%
Inversions	46,XY,inv(9)(p13q34)	5	12.5
	46,XY,inv(1)(p22q24)	7	17.5
Reciprocal translocations	46,XY,t(15;22)(q23;q13)	4	10
	46,XY,t(1,14)(p22;q22)	3	7.5
	46,XY,t(7,14)(q11;q22)	5	12.5
	46, XY,t(8,14)(p21;q13)	2	5
	46,XY,t(5;14)(q10;q10)	1	2.5
	46,XY,t(8:10)(q22;q11.1)	4	10
	46,XY,t(10;13)(q26;q14)	2	5
Robertsonian translocations	45,XY,der(13;14)(q10;q10)	4	10
	45,XY,der(14;21)(q10;q10	3	7.5

abnormalities were detected in 154 (11.55%). Out of 945 patients, 139 (14.71%) were diagnosed with azoospermia, and 15 out of 388 (3.87%) patients suffered from severe oligozoospermia. In comparison, we identified chromosomal abnormalities in 73 (54%) of our patients, and OAT was the most prevalent spermatogenesis disorder (n = 15, 20.54%), followed by azoospermia (n = 12, 16.4%) and oligozoospermia (n = 8, 10.9%) (36).

Pylyp et al identified chromosomal abnormalities in 17% of patients with spermatogenesis disorders, 35% with azoospermia, and 12.7% in patients with oligozoospermia (37). In our study, chromosomal disorders were found in 73 (54%) of the patients, and OAT, azoospermia, and oligozoospermia comprised 15, (20.54%), 12 (16.4%), and 8 (10.9%) of the patients, respectively.

In the study of Arafa et al, the prevalence of chromosomal abnormalities was 9.59%, and azoospermia was identified in 63.6% of the participants, of whom 10.8% carried chromosomal abnormalities. Oligozoospermia was detected in 36.4% of the patients, 7.5% of whom presented with chromosomal defects (38). In our study, chromosomal abnormalities were seen in 73 (54%) patients. Moreover, out of 11.8% of patients with azoospermia, chromosomal problems were found in 75% compared to 61% of those diagnosed with oligozoospermia (9.6% of total patients). Overall, OAT was found in 25% of the patients, of whom 42% had chromosomal abnormalities. In general, the prevalence of chromosomal abnormalities was higher in our study.

In our study, autosomal chromosomal abnormalities constituted 58% (n = 40) of all abnormalities observed, showing an overall prevalence of 32% among all infertile patients. Mierla et al reported the prevalence of autosomal abnormalities as 1.43%, 1.33%, and 1% in individuals with OAT, oligozoospermia, and teratozoospermia, respectively (31), reflecting a considerably higher rate of autosomal chromosomal abnormalities in our study.

In the present study, deletions comprised the most common types of cytogenetic defects among infertile men (n = 30, 41.09%). In another study, patients with a clinical diagnosis of azoospermia were most frequently identified with chromosome 9 inversions (39). Moreover, the commonest sex chromosomal abnormality in this study was 46, XY, del(Y) (q11.2-qter), which was detected in 12 (36.36%) individuals while 46, XY, inv (1) (p22q24) was the most common autosomal abnormality, which was detected in 7 (17%) patients. In comparison, Mierla et al found inv (9) (p11q12)/inv (9) (p11q13) as the most common chromosomal abnormality (31).

The exact mechanisms underlying the link between chromosomal abnormalities and infertility are still not fully understood. Some researchers propose that abnormal chromatin structures during meiosis can disrupt the spermatogenesis process (40). The genetic abnormalities interfering with spermatogenesis can lead to developmental problems in fetuses, thereby resulting in recurrent abortions (41,42). Infertile men who show normal karyotypes are generally evaluated for microdeletions on the long arm of Y chromosome at three susceptible loci in the AZF region (Yq11). Azoospermia, severe oligozoospermia, and oligozoospermia are characterized by the complete absence of sperm in semen and sperm counts of $< 5 \times 10^6$/mL and $5\text{-}20 \times 10^6$/mL of semen, respectively. Microdeletions in the long arm of Y chromosome at the three loci of the AZF region (Yq11) severely damage testicular development, leading to infertility in 2% of carriers (43-45). The prevalence of chromosome Yq microdeletion reaches 15%-20% among infertile men with severe oligozoospermia or NOA (46-49). Infertile men are also more susceptible to major chromosomal rearrangements, which can underlie male infertility (50). Understanding the genetic signature of infertility helps make more informed decisions on the use of assisted-reproductive technology tools. Also, the identification of genetic causes of infertility not only clarifies their inheritance pattern but also, according to more extended secondary deletions, explains possible sexual ambiguities in the offspring of affected individuals. Therefore, genetic studies, cytogenetic analyses, and detecting microdeletions on chromosome Y can offer prognostic values in predicting the potential applicability of complementary fertility techniques.

Conclusion

Our findings showed that infertile men with OAT and NOA carried higher rates of chromosomal abnormalities compared to other groups of patients. Chromosomal deletions comprised the most common types of genetic abnormalities. Considering the high incidence of chromosomal abnormalities in infertile men with OAT and NOA, it is highly advisable to evaluate these patients by performing cytogenetic analyses and molecular assays to detect karyotype defects and chromosome Y microdeletions before using assisted reproductive techniques.

Authors' Contribution

Conceptualization: Mahboubeh Mirzaei, Ali Asghar Ketabchi, Mohammadali Bagherinasabsarab.

Data curation: Mohammadali Bagherinasabsarab, Mahboubeh Mirzaei.

Formal analysis: Mohammadali Bagherinasabsarab, Reza Mohammadi.

Investigation: Reza Mohammadi.

Methodology: Reza Mohammadi, Mahboubeh Mirzaei.

Project administration: Mahboubeh Mirzaei, Reza Mohammadi, Mohammadali Bagherinasabsarab.

Resources: Mohammadali Bagherinasabsarab.

Software: Fatemeh Yazdanpanah.

Supervision: Mahboubeh Mirzaei, Ali Asghar Ketabchi.

Validation: Mohammadali Bagherinasabsarab.

Visualization: Mohammadali Bagherinasabsarab, Mahboubeh Mirzaei.

Writing–original draft: Fatemeh Yazdanpanah, Mohammadali

Bagherinasabsarab.

Competing Interests
The authors declare that they do not have any conflict of interest.

Ethical Approval
This study was approved by the ethics committee of Kerman University of Medical Sciences (Ethics No. IR.KMU.REC.1399.577).

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