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Frequency of Chromosome Disorders In Patients with Sperm Number Anomaly

Sperm Sayısı Anomalisi Olan Hastalarda Kromozom Bozukluklarının Sıklığı

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ABSTRACT

Objective: Chromosome abnormalities play an important role in male infertility. The rate of chromosome disorders in infertile men is higher as 5.8% when compared to the normal population (0.5%).

Methods: This study aimed to determine the frequency of cytogenetic abnormalities in infertile men with abnormal sperm counts and to show that rare chromosomal rearrangements can be detected by karyotyping.

Results: In our clinical practice, we detected nearly all chromosome numerical and structural anomalies involved in infertility. It includes inversions, translocations, deletions, insertions, complex rearrangements, isochromosomes, Klinefelter syndrome, mosaicism, and 47, XYY.

Conclusion: Our results emphasize the importance of conventional cytogenetic analysis for infertile males. The detection of rare or known chromosome abnormalities will prevent unnecessary investigations and enable us the application of precision in medicine.

Keywords: Abnormal sperm counts, chromosome abnormalities, genetic counselling

ÖZ

Amaç: Kromozom anormallikleri erkek infertilitesinde önemli bir rol oynamaktadır. İnfertil erkeklerde kromozom bozuklukları oranı normal popülasyona (%0,5) göre %5,8 kadar yüksektir.

Yöntemler: Çalışmamızda sperm sayısı anormal olan infertil erkeklerde sitogenetik anormallik sıklığının belirlenmesi ve nadir görülen kromozomal yeniden düzenlemelerin karyotipleme ile tespit edilebileceğinin gösterilmesi amaçlanmıştır.

Bulgular: Klinik pratiğimizde infertiliteye yol açan kromozomların sayısal ve yapısal anomalilerinin neredeyse tüm spektrumunu tespit etmekteyiz. Bu, İnversiyonları, translokasyonları, delesyonları, insersiyonları, karmaşık yeniden düzenlemeleri, izokromozomları, Klinefelter sendromunu, mozaikliği ve 47, XYY'yi içermektedir.

Sonuç: Sonuçlarımız infertil erkeklerde geleneksel sitogenetik analizin önemini vurgulamaktadır. Nadir veya bilinen kromozom anormalliklerinin tespiti, gereksiz araştırmaları önleyecek ve kişiye özel tedavilerin uygulanmasına olanak sağlayacaktır.

Anahtar Sözcükler: Anormal sperm sayısı, kromozom anomalileri, genetik danışma

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INTRODUCTION

Infertility is increasing in various global communities and is defined as the inability to achieve pregnancy after continuous, unprotected sexual intercourse for at least a year or more. Around 15% of couples are affected by this condition. 40-50% due to male factors (1,2). Mechanical issues, unexplained cases, and identifiable genetic defects are the predominant factors contributing to male infertility. Genetic defects include four groups: (1) Y chromosome deletions, (2) single gene disorders, (3) multifactorial causes, and (4) structural and numerical chromosome abnormalities (3). Male infertility generally lies in abnormal semen analysis. Abnormal semen analysis does not always indicate infertility; it only lowers the probability of pregnancy. Patients with nonobstructive abnormal sperm counts have an increased risk of chromosomal abnormalities. Infertile men exhibit a higher chromosome anomaly rate (5.8%) in contrast to the lower rate observed in the general population (0.5%) (4). This means a fold increase. Chromosomal anomalies are documented at rates of 10.00-23.62% in cases of nonobstructive azoospermia and 1.10-13.33% in cases of severe oligozoospermia (5). Complex chromosomal rearrangements (CCR) refer to structural abnormalities that entail a minimum of three chromosomes, each with three or more breakpoints (6). CCRs are rare occurrences and can manifest as balanced, unbalanced, familial, or spontaneous occurrence. The majority of individuals carrying CCR are female, with a minority being male (7). The identification of most male carriers with CCRs has been through infertility assessment, whereas a minority has been identified through abnormalities in children or recurrent abortions (8,9,10). The risk of conceiving offspring with diverse anomalies and experiencing reproductive failure is heightened among CCR carriers because of segregation of the derivative chromosome or meiotic failure (11,12,13). Female CCR carriers are typically identified following the occurrence of babies with congenital abnormalities or experiencing recurrent abortions. Nevertheless, male CCR carriers do not always exhibit infertility or subfertility; in several cases, infertility issues arise as a result of hypospermatogenesis or spermatogenic failure. Several documented cases highlight the occurrence of CCRs in males diagnosed with oligozoospermia or azoospermia (14). In this study, we aimed to determine the types and frequency of chromosome abnormalities in patients with abnormal sperm counts.

MATERIALS AND METHODS

Karyotype results of patients with abnormal sperm counts who applied to the cytogenetic laboratory of Başkent University Genetic Diseases Diagnosis Center between January 2007 and December 2019 were retrospectively evaluated. Numerical and structural chromosomal anomaly distribution was determined according to sperm counts. 968 males were divided according to the sperm count of semen analysis into azoospermia (group 1), oligozoospermia (group 2), and oligoastenozoospermia (group 3). This study was approved by Başkent University Institutional Review Board (approval number: KA 24/108, date: 06.03.2024) and supported by Başkent University Research Fund.

Statistical Analysis

Standard cytogenetic investigations were conducted using established methods for phytohemagglutinin-stimulated cultures of peripheral blood lymphocytes. Chromosome spreads underwent processing for the analysis of GTG bands. Chromosomes were subjected to GTG banding following the standard karyotyping protocol, with an examination of 30 metaphases and interpretation carried out at resolution levels of 450 and 650 bands. Fluorescence in situ hybridization (FISH) was conducted on metaphases from transformed lymphoblast cell lines using human probes, following standard protocols and manufacturer's manuals (15).

RESULTS

All detected anomalies in our cases fall into the first group. The number of patients with sex chromosome abnormalities was higher than that of patients with autosomal chromosome anomalies (17.56 and 0.72 %, respectively (Table 1). Although the numerical anomaly rate was 15.9%, the structural anomaly rate was lower (2.37%) (Table 2). A total of 154 numerical anomalies were detected. Klinefelter syndrome (KS) was the most common finding 15.56% (151 patients), from which mosaic karyotypes were identified as 47, XXY/ 46, XY in 12 patients. There is also another mosaic patient with 47, XXY/ 48, XXXY karyotype. 47, XYY karyotype was detected in one patient. A total of 21 structural anomalies were detected. We had 9 patients with 46, XX karyotype in whom was detected translocation between chromosome X p arm with chromosome Y p arm. The SRY gene is shown on the derivative X-chromosome's p arm by FISH. In total, 16 reciprocal translocations were performed. Deletions were detected in 2 patients. The other structural abnormalities included one complex abnormality, one insertion, and one isochromosome.

Complex Chromosomal Rearrangement

The proband (Figure 1, III-4) is a 38-year-old man with primer infertility. He has been married for 2 years and has no consanguinity with his wife. They have not tried assisted reproductive treatment (ART). He had a normal phenotype and hormone profile, azoospermia, and no sperm in TESE. He has no Y-chromosome microdeletion. Karyotype analysis (Figure 2a) is 46,XY,t(2;12) (p24:q21), ins(4;2) (q21;p13p24) and the result is confirmed by metephase FISH (Figure 2b). Proband has 2 brothers and 1 sister, all of whom have normal offspring. A

Table 1. Identified chromosomal anomaly frequencies in study groups.

Patients	Sperm anomaly	Autosomal abnormality n (%)	Sex chromosome abnormality n (%)	Total n (%)
Group 1	Azoospermia (n=920)	7 (0.72)	170 (17.56)	177 (18.28)
Group 2	Oligozoospermia (n=1)	-	-	0 (0)
Group 3	Oligoasthenospermia (n=37)	-	-	0 (0)
Total	(n=968)	7 (0.72)	170 (17.56)	177 (18.28)

family study for segregation analysis was offered, but it could not be done because the couple did not accept.

DISCUSSION

We retrospectively evaluated the karyotype results of 968 patients with abnormal sperm counts and detected chromosomal disorders only in patients with azoospermia. In our cohort of patients with azoospermia, the rate of chromosomal abnormalities was 18.28 %, which was close to that reported by Pylyp et al. (1) in Ukrainian patients (17%), Kleiman et al. (12) in Israel (16.6 %), and higher than previously reported by Kumtepe et al. (16) in Türkiye (12 %), Wang et al. (17) in China (8.5 %), Lakshmi Rao et al. (18) in India (7.9 %), and Gekas et al. (19) in France (6.9 %) (1,12,16,17,18,19). Being the most prevalent X-chromosome abnormality, KS is the most prevalent X-chromosome abnormality and is the most frequent genetic factor contributing to male infertility. Individuals diagnosed with pure KS (47, XXY), mosaic, or variant KS often experience significant impairment in spermatogenesis, resulting in severe oligozoospermia or azoospermia. Among infertile men, the prevalence of KS is notably higher, escalating from approximately 3% in unselected cases to approximately 13% in patients diagnosed with azoospermia. Hence, KS is the most common genetic cause of azoospermia (20,21). Males with KS commonly display phenotypic traits associated with hypergonadotropic hypogonadism and testosterone deficiency, only a subset (approximately 25% to 40%) of cases receive an accurate diagnosis (22,23). Lakshmi Rao et al. (18) and Kleiman et al. (12) reported the rates of KS in their cohort as (4.41%) and (5.5%) respectively (12,17). We identified 139 (14.36 %) pure KSs and 12 (1.2 %) mosaic types. This was not close to the rate reported by Pylyp et al. (1) among Ukrainian patients (64%) and (18%) respectively. Although oligozoospermia and normozoospermia patients were evaluated in the study mentioned above, all of our patients had only azoospermia. This may explain why the detected patient rates were different from ours. In the majority of cases, men with the 47, XYY karyotype are fertile, but they are observed more frequently within infertile populations, accounting for nearly 0.1%. In our study, we have one 47, XYY infertile man, which means 0.1%. Rearrangements among acrocentric chromosomes, including chromosomes 13, 14, 15, 21, and 22, result in Robertsonian translocations. This results in the loss of genetic material, resulting in a chromosomal complement of 45 chromosomes. This condition is observed in approximately 0.9% of men diagnosed with severe male factor infertility (24). Although it affects sperm production, we did not detect this in our patient group. The reciprocal translocation mechanism involves the exchange of genetic material between two or more chromosomes.

Table 2. Chromosomal disorders detected in patients

Chromosomal anomalies	Anomaly type	Karyotype	n (%)	Total number of participants (%)
Structural chromosomal anomalies	Inversions	46,XY,inv(10) (p13q22)	1 (0.1)	2 (0.2)
		47,XXY,inv(12)(p11.1q13.2)	1 (0.1)	
	Deletions	46,X,del(Y)(q11)	2 (0.2)	2 (0.2)
	Translocations	46,XY,t(5;8)(q12;p12)	1 (0.1)	16 (1.65)
		46,XY,t(Y;12)(q11.2;p13)	1 (0.1)	
		46,X,t(X;Y)(p22;p11)	9 (0.9)	
		46,XY,t(1;21)(q11;p12)	1 (0.1)	
		46,Y,t(X;3)(q26;q23)	1 (0.1)	
		46,XY,t(5;8)(q13;p13)	1 (0.1)	
		46,Y,t(X;11)(p22.1;q13)	1 (0.1)	
		46,XY,t(2;11)(q13;p15)	1 (0.1)	
	Insertions	46,XY,ins(2;5)(q13;q13.1q32)	1 (0.1)	1 (0.1)
	Complex reerangement	46,XY,t(2;12)(q24;21),ins(4;2)(q21;p13p24)	1 (0.1)	1 (0.1)
	Isochromosome	46,X,i(Yp)	1 (0.1)	1 (0.1)
Numerical chromosomal anomalies	Klinefelter syndrome	47,XXY	139 (14.36)	139 (14.36)
	Mosaicism	47,XY,i(X)(q10)/47,XXY	2 (0.2)	14 (1.4)
		47,XXY/46,XY	8 (0.8)	
		47,XXY/48,XXXY	1 (0.1)	
		45,X/46,XY	2 (0.2)	
		47,XXY/46,XX/46,XY	1 (0.1)	
	47,XYY	47,XYY	1 (0.1)	1 (0.1)

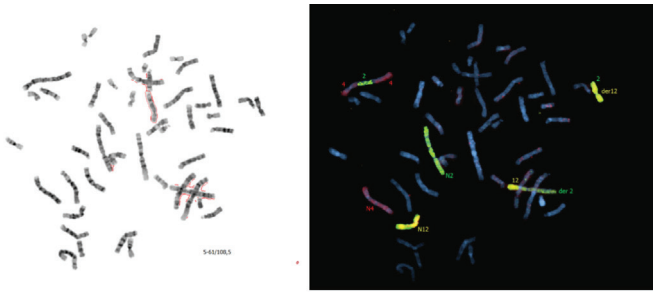

Figure 2. (a) Karyotype of the patient with complex chromosomal anomaly (left), partial karyotype of the chromosomes participating in the anomaly (right) (b), G-banded metaphase (left), and FISH imaging (right) on the metaphase by Whole chromosome probes for chromosome 2 (red), chromosome 4 (green), and chromosome 12 (yellow).

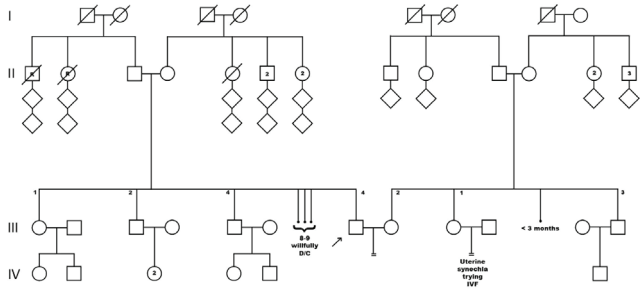

Figure 1. Pedigree of the CCR patient.

CCR: Complex chromosomal rearrangements

The prevalence of balanced chromosomal translocations is tenfold higher in infertile men, constituting a notable factor in male infertility (25). In this study, we have 16 reciprocal translocations in total. The most common (9 cases) was 46, X, t(X; Y), (p22;q11). 46 XX DSD (differences in sex development) were observed in phenotypically normal males. Various etiological theories have been proposed. SRY-positive individuals are expected to undergo crossover events between the pseudoautosomal regions of sex chromosomes during paternal meiosis (26). The existence of the SRY gene was demonstrated using FISH in all patients who were identified as XX males. Our findings support this theory. The isochromosome of Yp, i(Yp), is the least frequently observed structural rearrangement involving the Y chromosome (27). Individuals exhibiting delayed puberty, along with symptoms like gynecomastia, reduced growth rate, and infertility, and requiring testosterone treatment to induce the development of secondary sex characteristics may present with the potential effects associated with 45,X/46,X,i(Yp). We have one isochromosome 46,X,i(Yp) from 968 infertile males (0.1%). Complex chromosomal abnormalities (CCRs) are rare occurrences in the population, with approximately 255 documented cases to date (6). CCRs typically arise from either two concurrent classical translocations or jumping translocations, where a donor chromosomal segment is translocated to multiple recipient chromosome sites (28,29,30). In general, males with CCR exhibit issues related to infertility stemming from either hypospermatogenesis or spermatogenic failure (31). In this cohort, type 2 CCR was detected, and the rate of complex anomaly was 0.1%. In phenotypically normal individuals, a balanced CCR is typically observed. Such cases often have a familial component, which is primarily transmitted through female carriers. These cases are often referred for advanced maternal age, recurrent spontaneous abortion, or the birth of a malformed child (32-36). Transmission through males is a rare event (37, 38). A significant portion of CCR, approximately 70-75%, arises as de novo chromosomal rearrangements, predominantly of paternal origin (32). These are equally distributed among individuals with a normal phenotype (49%), and those displaying phenotypic abnormalities (51%). This distribution can be attributed to submicroscopic imbalances or other genetic defects (39-41). De novo balanced CCRs are often identified due to issues related to infertility, although a limited number of cases involving fertile carriers have also been documented (24,42-45). Using multicolor FISH technologies of sperm sorting studies, accurate procedures for on-site analysis of CCRs have been established to facilitate the offer of preimplantation genetic diagnosis (PGD) to couples easily. There are six cases of PGD in CCR carriers in whom spontaneous abortion did not occur (46,47). The detection of chromosomal disorders is important for predicting and preventing the risk of new pregnancies because they lead to unbalanced gametes. With karyotyping, in men with sperm number and structure anomalies, in addition to explaining the cause of their condition, future infertility treatment and options for having a healthy baby can also be determined. If any chromosomal abnormality is detected, PGD ought to be proposed to the patients as a solution to prevent such genotypic defects, which are the cause of different phenotypic abnormalities with undesired effects on health and the quality of life afterward in offspring (48). Pregnancy rates after transfer of an euploid/balanced embryo are 60%-70%, which is equivalent to the rate for euploid embryos in normal patients (49,50).

CONCLUSION

In conclusion, by chromosomal aberrations infertility in men can be caused (32). Each detected chromosomal disorder has its own hereditary and phenotypic risks. Therefore, determining the chromosomal aberration and explaining the risks specific to the detected condition to the family through genetic counseling are important for them to decide on pregnancy options and inform other family members at risk. For example, in patients with Yq del, the risk of transmission to male children and the resulting infertility should be explained. The family should decide on ART treatments after knowing these risks. Thus, the cause of men's infertility requires detailed comprehensive genetic counseling, especially to prevent recurrence in off spring. While PGD offers promise, it comes with challenges and ethical considerations. The accuracy of diagnosis, potential mosaicism, and the emotional impact on parents are critical aspects to navigate. Striking a balance between the benefits and ethical concerns is imperative to ensure the responsible and equitable application of PGD in the context of chromosomal rearrangements. Our results emphasize the importance of conventional cytogenetic analysis in infertile males. The detection of rare or known chromosome abnormalities will prevent unnecessary investigations and enable us the application of precision in medicine.

Ethics

Ethics Committee Approval: This study was approved by Başkent University Institutional Review Board (approval number: KA 24/108, date: 06.03.2024).

Informed Consent: Retrospective study

Footnotes

Authorship Contributions

Concept: M.N., E.A., Z.Y.Ç., Design: Z.Y.Ç., Supervision: Z.Y.Ç., Resources: M.N., E.A., Z.Y.Ç., Material: M.N., E.A., Data Collection or Processing: M.N., E.A., Z.Y.Ç., Analysis or Interpretation: M.N., E.A., Z.Y.Ç., Literature Search: M.N., E.A., Z.Y.Ç., Writing: M.N., E.A., Z.Y.Ç., Critical Review: M.N., E.A., Z.Y.Ç.

Conflict of Interest:

Financial Disclosure: This study was approved by Baskent University Institutional Review Board (project no: KA 24/108) and supported by Baskent University Research Fund.

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