



CHROMOSOME STUDY OF HUMAN MALE INFERTILITY IN JAMMU REGION OF JAMMU & KASHMIR

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ABSTRACT

Male Infertility is the inability of males to reproduce. Infertility is the inability of an individual to reproduce. It affects both males and females all over the world. The state of Jammu and Kashmir is no exception. Present study first of its kind in Jammu region of Jammu & Kashmir state, India, is an account of the chromosome study carried out in male individuals with history of Infertility i.e. male infertility. A total of Thirty one male individuals from six districts of Jammu region viz. Jammu, Udhampur, Kathua, Doda, Rajouri and Poonch having history of Infertility were enrolled for their chromosome study to rule out the chromosomal cause for their infertility. All the referred males were detected to be infertile initially from their semen analysis when majority of these males were found to be azoospermic and a few had oligospermia. Chromosome study was therefore carried out in every referred infertile male. Of these thirty one individuals, chromosomal abnormalities were detected in seven (22.6%) individuals and twenty four (77.4%) individuals were found normal. Of the seven individuals with chromosomal abnormalities, Mosaic Klinefelter syndrome (46, XY / 47, XXY) was found in four (57.1%) individuals and Klinefelter syndrome (47, XXY) condition was found in three (42.9%) individuals. Of the 31 individuals, Mosaic Klinefelter Syndrome (46, XY/47, XXY) was found in four (12.9%) individuals and Klinefelter syndrome with 47, XXY condition was found in three (9.7%) individuals.

KEY WORDS: Chromosomal abnormalities, Klinefelter syndrome, Mosaic Klinefelter syndrome.

INTRODUCTION

Male factor infertility is defined as the failure to father children after one year of unprotected sexual intercourse with a normal mature female. Human male infertility needs a lot of concern because it is only a normal male who alone can reproduce. Normal male requires integration of the hypothalamic-pituitary testis axis, with a functional penis, functional and descended testis and a normal 46, XY chromosome karyotype. If there is an abnormality in any of the above said factors, it always leads to the infertility among males. Male infertility is a term that refers to infertility in male humans. It is involved in a sexually paired couple's inability to conceive in a significant number of cases, with estimates ranging from 40-50% (Hirsh, 2003). In some cases, both the man and woman may be infertile or sub-fertile, and the couple's infertility arises from the combination of these conditions. In other cases, the cause is suspected to be immunological or genetic; it may be that each partner is independently fertile but the couple cannot conceive together without assistance. In about 15% of cases the infertility investigation will show no abnormalities. In these cases abnormalities are likely to be present but not detected by current methods. Possible problems could be that the egg is not released at the optimum time for fertilization that it may not enter the fallopian tube, sperm may not be able to reach the egg, fertilization may fail to occur, transport of the zygote may be disturbed, or implantation fails. It is increasingly recognized that egg quality is of critical importance and women of advanced maternal age have eggs of reduced capacity for normal and successful fertilization. Each year approximately 15% of couples

trying to conceive for the first time will be unable to do so. A sole male factor is responsible in 20% of cases, while in an additional 30% the male factor is contributory (Wong *et al.*, 200). The evaluation of the infertile male proceeds as with the evaluation of any other medical problem. A thorough history and physical examination is performed, followed by appropriate laboratory tests. Ideally, this evaluation identifies the etiology of the male's infertility and leads to appropriate and specific therapy. Unfortunately, in many cases, the etiology of the male's infertility remains unknown.

MATERIAL AND METHODS

Present study is an account of chromosomal analysis carried out in 31 males with the history of one or more causes of male infertility. These males were in different age groups, some were married and some unmarried and they were referred for their chromosome study so as to rule out the chromosomal cause for infertility. Chromosome study was carried out from the whole blood cultures and the prepared slides were G-banded following Seabright, 1971.

OBSERVATION

Present study first of its kind in Jammu region of J&K state, India, is an account of the chromosome study carried out in male individuals with history of Infertility i.e. male infertility. A total of Thirty one male individuals from six districts of Jammu region viz. Jammu, Udhampur, Kathua, Doda, Rajouri and Poonch having history of Infertility were enrolled for their chromosome study to rule out the chromosomal cause for their infertility. All the referred

males were detected to be infertile initially from their semen analysis when majority of these males were found to be azoospermic and a few had oligospermia. In all the azoospermic males, semen analysis was subjected to fructose analysis to find out whether they were fructose negative or fructose positive. All these azoospermic males who had no clinical symptoms of Klinefelter syndrome and had normal sized testis were subjected to testicular biopsies to find out the status of the spermatogonia. Majority of these males were found to have maturation arrest or that was held responsible for their infertility. These males had also been taking some medicine for the

production of sperms but none of these males responded to the medicine. These males therefore became the subject for their chromosome analysis. Chromosome study was therefore carried out in every referred infertile male. Of these thirty five individuals, chromosomal abnormalities were detected in seven (22.6%) individuals (Table-1) and twenty four (77.4%) individuals were found normal. Of the seven individuals with chromosomal abnormalities, Mosaic Klinefelter syndrome (46, XY/ 47, XXY) was found in four (57.1%) individuals and Klinefelter syndrome (47, XXY) condition was found in three (42.9%) individuals.

TABLE 1: Number and Types of Chromosomal Abnormalities detected out of 31 cases:

S. No.	Type of Chromosomal Abnormality	Number of Chromosomal abnormality	Percent of Total
A.	Total abnormalities	07	22.6
B.	Klinefelter Syndrome	07	22.6
	1. 47, XXY Condition	03	9.7
	2. Mosaic Klinefelter Syndrome	04	12.9

DISCUSSIONS

Infertility is defined as the inability to conceive after one year of unprotected intercourse. Infertility primarily refers to the biological inability of a man or a woman to contribute to conception. Infertility may also refer to the state of a woman who is unable to carry a pregnancy to full term. There are many biological causes of infertility, some which may be bypassed with medical intervention (Makar and Toth, 2002). A couple that has tried unsuccessfully to have a child for a year or more is said to be sub-fertile. The couple's fecundability rate is approximately 3-5%. Many of its causes are the same as those of infertility. Such causes could be endometriosis, or polycystic ovarian syndrome (Makar and Toth, 2002). According to the National Institutes of Health, male infertility is involved in approximately 40% of the 2.6 million infertile married couples in the United States. One-half of these men experience irreversible infertility and cannot father children, and a small number of these cases are caused by a treatable medical condition (Mark and Sigman, 2000). Around fifty percent of the problems in infertile couples are due to male factor (Wong *et al.*, 2000). In these patients, severe oligospermia or azoospermia are frequently observed and most of them undergo some kind of assisted reproductive technique (ART). Direct injection of single spermatozoa into the cytoplasm of an oocyte (ICSI) is the current standard technique. ICSI has high success rates even in cases of severely impaired spermatogenesis. Even though this method allows infertile males to have their own child without knowing the cause of their infertility, it also carries the potential risk of transmission of genetic aberrations to the descendants. The cause of alterations in sperm production is unclear, and recent work is focusing on environmental and genetic causes. Among the genetic causes of male infertility that can be passed on to the offspring are cytogenetic abnormalities, Y chromosome microdeletions and CAG repeats in the androgen receptor (AR) gene (Gottlieb *et al.*, 2005; Carrell *et al.*, 2006). The incidence of chromosomal aberrations in azoospermic males has been found to be as high as 20%, being the sex chromosomes more commonly involved (Wong *et al.*,

2000). On the contrary, aberrations have been shown to be less frequent among oligozoospermic males (0 – 8%) and when present, they are found mainly in the autosomes (Elghezal *et al.*, 2006; Levron *et al.*, 2001). Chromosomal abnormalities are common in infertile men with an incidence of 5.8% as compared to an incidence of 0.5% in the fertile population (Johnson, 1998). Chromosomal abnormalities can occur on several genetic levels: 4.2% of abnormalities occur on the sex chromosomes, whereas 1.5% occur on the autosomes. The gain or loss of an entire single chromosome results in Aneuploidy, whereas a polyploid state occurs when the entire chromosomal content is multiplied (polyploid cells are most commonly associated with malignancies). Structural abnormalities include the rearrangement or translocation of fragments of chromosomes, as in Robertsonian translocations, or deletions of single genes or portions of a chromosome. During the present work, chromosome study has been carried out in every referred infertile male. Of these thirty five referred individuals with male infertility, chromosomal abnormalities were detected in seven (22.6%) individuals (Table-1) and twenty four (77.4%) individuals were found normal. Of the seven individuals with chromosomal abnormalities, Mosaic Klinefelter syndrome (46, XY / 47, XXY) was found in four (57.1%) individuals and Klinefelter syndrome (47, XXY) condition was found in three (42.9%) individuals. During the present study, Klinefelter syndrome was found to be commonest chromosomal abnormality in the male with history of infertility. Similar finding were reported by Balwan (2008) who during his research work reported Klinefelter syndrome in four individuals out of eight male individuals with history of infertility and found Klinefelter syndrome to be commonest chromosomal abnormality among male individuals with history of infertility. Shah *et al.* (1990) in their study reported 47, XXY condition in two patients out of 144. These patients were referred as cases of Hypogonadism. These workers recorded the incidence of 47, XXY condition to be 2/144 (1.38 %) and 2/57 (3.50). Ozata *et al.* (1992) in a similar study on 29 cases of Klinefelter Syndrome reported 46, XY/47, XXY mosaic karyotypes in 24 cases. Bojesen and Gravholt (2007)

reported a frequency of 40 cases per 1,00,000 men and found that 7% of these cases had mosaic karyotype. Advanced maternal age was also found to be a significant contributing factor. Klinefelter Syndrome is usually underdiagnosed and less than 10% of cases get diagnosed before puberty. Delay in treatment may lead to decreased muscle and bone mass with subsequent risk of osteoporosis. The varied expressivities of 47, XXY in Klinefelter Syndrome results in seminiferous tubule dysgenesis, androgen deficiency, neurological and cognitive perturbations like language, behaviour problems (Simpson *et al.*, 2003). Studies on mosaic Klinefelter Syndromes reveals that the germ cells with sex chromosomal abnormalities were capable of completing meiosis (Mark *et al.*, 1999) and the individuals may reproduce with the aid of modern reproductive technology. The XXY genotype is typically associated with Klinefelter Syndrome. The Syndrome, generally not clinically recognizable before puberty, is characterized by aspermatogenesis, small testes, poorly developed secondary sexual characteristics, and eunuchoid proportions. Like the XO females, the XXY males are almost always sterile. Nielsen and Sillesen (1975) reported the incidence of Klinefelter Syndrome in their study to be 1 per 882 boys. Nielsen and Wohlert (1991) reported incidence of Klinefelter Syndrome in their study to be 1 per 576 or 1.73 per 1000 boys. All types of Klinefelter Syndrome are a form of aneuploidy where there is an extra or missing sex chromosome. The classic form of Klinefelter Syndrome is the polyploidy (extra chromosome) condition of 47, XXY which characterizes 80% of Klinefelter cases. Another 15% of the cases are mosaic types (46,XY / 47,XXY, 46,XY / 48,XXYY, 45,X / 46,XY / 47,XXY and 46,XX / 47,XXY). The other 5% are XX forms with the SRY gene (testes determining factor) translocated to an X chromosome, Poly X+Y forms, or combined mosaic and poly X+Y forms (Pinyerd and Zipf, 2003). Nuria *et al.* (2006) reported that in 53% of Klinefelter Syndrome (KS) cases studied by them the additional X chromosome was of paternal origin. The paternally transmitted Klinefelter Syndrome group of fathers showed higher frequency for XY disomy sperm as compared to those of the maternal origin group.

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