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Original research article

Male infertility in Western Region of India: a cytogenetic study of 112 patients with impaired spermatogenesis

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Abstract

Background: Male infertility due to severe oligozoospermia and azoospermia has been associated with a number of genetic factors. Chromosomal abnormalities are one of the principle genetic factors in male infertility. **Purpose:** To detect the frequency and types of chromosomal anomalies in azoospermics and severe oligozoospermics in Western region of India and to compare these with same studies of other regions of India and the world. **Method:** - To assess the chromosomal aberration, the karyotyping of 44 azoospermics and 68 severe oligozoospermics were performed on peripheral blood lymphocytes using standard G-banding technique. **Result:** Chromosomal anomalies in azoospermics 18.2% (n=8/44) and in severe oligozoospermics 7.35 % (n=5/68) with an over all 11.6% (13/112) in western parts of India were comparable with studies from Europe, Africa, Asia, South America and other regions of India. Polymorphic chromosomal variants were high 36.6% in infertile males; this incidence was similar 33.3% that found in controls. **Conclusion:** In view of the genetic risk for the next generation, the occurrence of chromosomal anomalies among infertile males strongly suggests the need for routine genetic testing and counseling prior to employment of assisted reproduction technique. It should be discussed during genetic counseling.

Key words: **Azoospermia, Severe oligozoospermia, Chromosomal alterations, Male infertility**

Introduction

Infertility is defined as the inability of a couple to conceive after 1 year of unprotected sexual intercourse. Infertility is one of the most common disorders seen in medical practice worldwide. It exhausts the couple psychologically, socially, and emotionally; furthers more it drains their financial resources. Recent studies show that the number of infertile couples in the general population is growing and about 15 to 20 % of couples of reproductive age are unable to have their own child, where the male factors are responsible for about 40 to 50% of this cases.[1]

In the country like India where the population explosion is a great problem, infertility is also a problem of immense importance due to its social, emotional and religious nature. Intrauterine Insemination (IUI) and intracytoplasmic sperm injection (ICSI) by using the donors semen has

received tremendous acceptance by the infertile couples. Also due to increased number of infertility centers, the diagnostic and therapeutic facilities are coming with in the reach of infertile couples and can be helped successfully by the use of assisted reproduction techniques. Moreover, the practice of using ICSI technique by these severely infertile men to father their own children carries the risk of passing on genetic disorders to their offspring including chromosomal anomalies.[2]

Chromosomal anomalies are considered as important causes of male infertility because there are over 4000 genes are involved in the genetic control of human spermatogenesis.[3] Major chromosomal abnormalities in infertile males have been found with the range of 2.4-16.4 % compared to the frequency in normal male population 0.3-0.4% in which azoospermia are with high frequency from 11.7%-23.6% , oligozoospermia the incidence is 2.1 -6.6 % while in severe oligozoospermia it is about 10.6%. The most frequent chromosomal abnormalities are translocations and sex chromosome abnormalities. The impact of chromosomal abnormalities on male infertility is very high and inversely related to the sperm count. [4,5,6]

Therefore, prior to the use of Assisted Reproduction Technique (ART), it is important to screen such patients for chromosomal abnormalities to prevent them being passed on to their children. This is of particular importance when abnormalities are found in the Y chromosome, as they will be passed on to any male offspring.[7]

Materials and Methods

Infertile men (n=112) from western region of India in the age group of 20 to 40 years, who sought help for infertility from our center were included in this study. Written informed consent, confirmed by the Ethics Review Committee was obtained from each participant. All men were given written as well as oral information. Each of these patients was interviewed about their medical histories, reproductive problems, and underwent a physical examination. Semen samples were obtained 7 days after period of ejaculatory abstinence and semen analysis was performed according to world Health Organization.[8] Each patient underwent semen analysis at least twice before a diagnosis of non-obstructive azoospermia or severe oligozoospermia. Blood samples were stored for cytogenetic analysis. Patient with obstructive azoospermia were excluded from this study. Severe oligozoospermia was diagnosed with a sperm count $<5\times10^6$/mL. The control group included 30 fertile men with the same age groups. Every man in the control group had fathered at least one child. All underwent the same examinations and analyses as the men in the infertile group. Chromosomal analysis was performed using G-banding technique in peripheral blood lymphocyte culture. After a 72 hr incubation period, lymphocytes were cultured in RPMI-1640, phytohaemaglutinin and fetal bovine serum, followed by treatment with colcemid. Then G-Banding of metaphase chromosome was performed. At least 20 metaphases were analyzed for each patient. Chromosomal abnormalities were described according to the International System for Human Cytogenetic nomenclature.[9]

Statistical analyses

From mean and standard deviation, the standard error of difference between two means and Z values were calculated. From the statistical table, P value was found out with reference to the calculated Z value. A probability (P) value <0.05 was considered statistically significant and all P values were two sided. In our study no major chromosomal abnormality was found in control group so the result remained statistically significant ($P<0.05$) while the incidence of polymorphic chromosomal variants in both groups were similar ($P>0.05$).

Results

Among the 112 infertile males, 44 were non-obstructive azoospermics and 68 were severe oligozoospermics. They all were examined for chromosomal alterations by GTG karyotyping method. The frequency and types of chromosomal

aberrations are summarized in table I, II& III. In the infertile group 18.2% (8/44) of azoospermics and 7.35% (5/68) of severe oligozoospermics with an over all 11.6% (13/112) had major chromosomal abnormalities. Where 7 males were found with numerical abnormalities in which 6 had Klinefelter's syndrome of classic pattern 47,XXY karyotype in azoospermic group and one case had mosaic forms of 47XXY[86]/46,XY[14] pattern in oligospermic group. However, six males were found to have structural abnormalities, in which 4 were with autosomal translocations including 3 non-reciprocal translocations in oligozoospermia and one Robertsonian translocation in azoospermia, while one case of inversion found in azoospermia and one supernumerary marker chromosome (sSMC) found in oligozoospermia (Fig 1). No major chromosomal abnormality was found in control group (P<0.05).

Polymorphic chromosomal variants were found in 41 infertile males (36.6%), this incidence was similar to that in 10 fertile men (33.3%) from the control group (P>0.05). Autosomal chromosomal variants were observed more frequently than sex chromosomal variants. Aberrations in the heterochromatin region of the chromosome 9 were the most frequently identified polymorphism in 16 (14.9%) infertile males. Among 5 (11.3%) men in azoospermics and 7 (10.3%) in severe oligozoospermics were with increased heterochromatin area (9 qh+), while 2 in each group were with smaller region (9 qh-) (Fig. 2b). One case of inversion 9 found in azoospermia is polymorphism but included in Table 1 for the sake of completeness (Fig. 1d). Polymorphic variants were also found in chromosome 1 (n=10), chromosome 16 (n=5), Y chromosome (n= 7) and in chromosome 14, 21 and 22 called satellites (Fig. 2).

Table I. Frequency and types of chromosomal anomalies in azoospermic and oligozoospermic men.

Karyotypes	Total infertile men n=112 (%)	Azoospermics n=44 (%)	Severe Oligozoospermics n=68 (%)
46, XY (normal)	99 (88.4)	36 (81.9)	63 (92.6)
Numerical aberrations	7 (8.9)	6 (13.6)	1 (1.5)
47, XXY	7 (6.2)	6 (13.6)	1 (1.5)
Structural aberration	6 (5.3)	2 (4.5)	4 (5.9)
Translocations	4 (3.6)	1 (2.3)	3 (4.4)
Inversion	1 (0.9)	1 (2.3)	_
Marker chromosome	1(0.9)	_	1(1.5)
Total aberrations	**13 (11.6)**	**8 (18.2)**	**5 (7.3)**

Table.2: The type of some structural aberrations in infertile males.

Translocations	
45,XY,rob t(15;21)(p11;q11)	Azoospermia
46,XY,t(5;3)(q32;q29)	Severe Oligozoospermia
46,XY,t(14;12)(q32;q24)	Severe Oligozoospermia
46,XY,t(15;17)(p13;q26.2)	Severe Oligozoospermia
Inversion	
46,XY,inv(9)(p21;q22)	Azoospermia
Marker Chromosome	
mos47,XY, +mar[22]/46,XY[78]	Severe Oligozoospermia

Table III. Incidence of polymorphic variants in infertile males with azoo- and oligo- zoospermia and in control group

Polymorphic Variants	Azoospermic	Oligospermic n=44(%)	Total infertile n=68(%)	Control Men n=112(%)
Total variants of Chromosome 1	5(11.3)	7(10.3)	12(10.7)	
1 qh+	4(9)	5(7.3)	9(8)	2(6.7)
Inv (1)	0(0)	1(1.5)	1(0.9)	1(3.3)
1qh-	1(2.3)	2(2.3)	3(2.6)	0(0)
Total variants of Chromosome 9	7(15.9)	9(13.2)	16(14.9)	5(16.6)
9qh+	5(11.3)	7(10.3)	12(10.7)	4(13.3)
9qh-	2(4.5)	2(2.9)	4(3.6)	1(3.3)
Total variants of Chromosome 16	2(4.5)	4(5.9)	6(4.9)	2(6.7)
16qh+	1(2.3)	3(4.4)	4(3.6)	1(3.3)
16qh-	1(2.3)	1(1.4)	2(1.8)	1(3.3)
Total variants of Chromosome Y	4(9)	3(4.4)	7(6.2)	2(6.6)
Y qh+	3(6.8)	2(2.9)	5(4.5)	1(3.3)
Yqh-	1(2.3)	1(1.4)	2(1.8)	1(3.3)
Satellites	3(6.8)	2(2.9)	5(4.5)	1(3.3)
Total variants n (%)	19(43.2)	22(32.3)	41(36.6)	10(33.3)

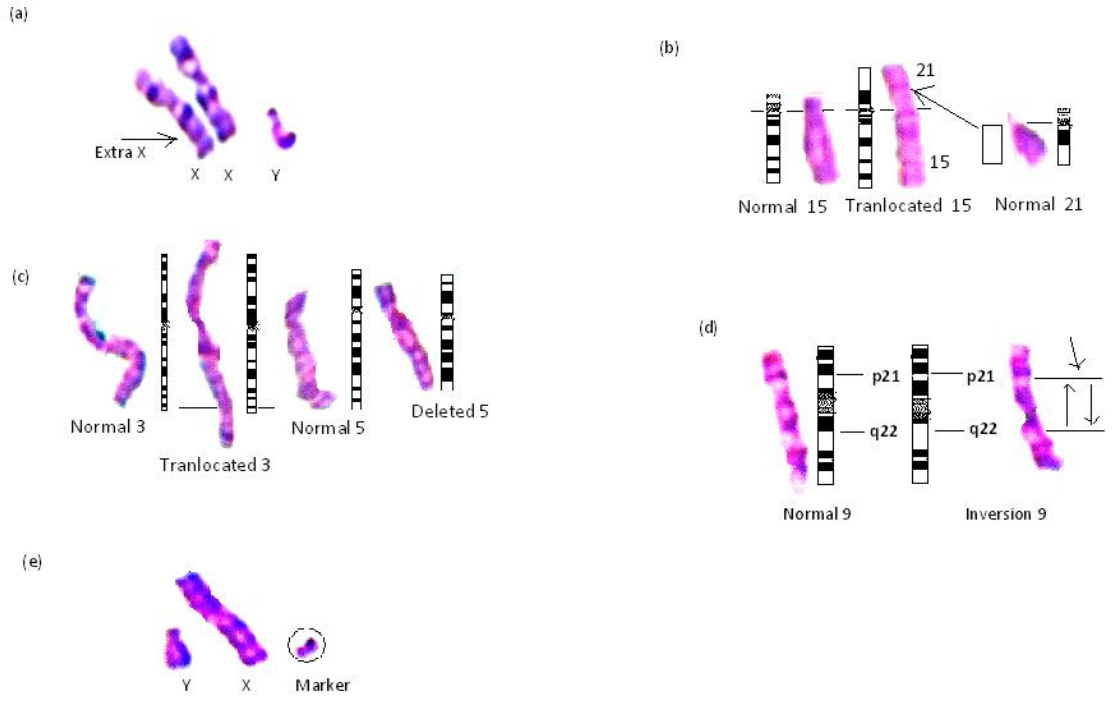

Fig.1: Major chromosomal abnormalities

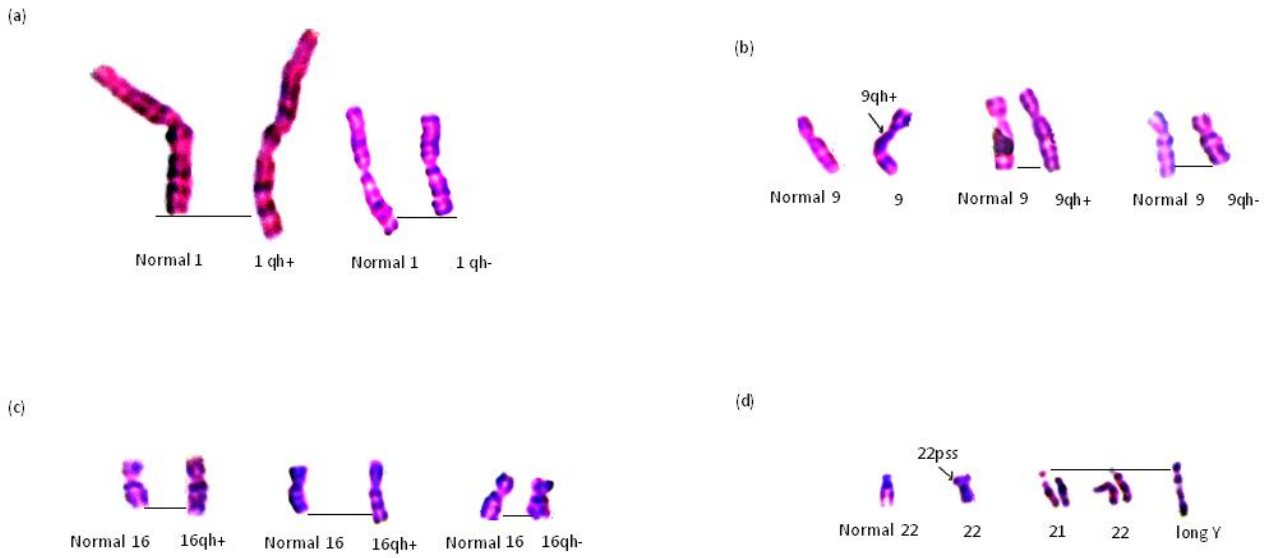

Fig.2: Heterochromatin polymorphic chromosomal variants

Discussion

Research over the past few years has clearly demonstrated that infertile men have an increased frequency of chromosomal abnormalities. These findings are further co-related by increased frequency of chromosomal abnormalities found in newborns and fetuses born from the pregnancies conceived by ICSI. As reported in literature, in half of the couples with unsuccessful pregnancy the cause of infertility is male related, and of them in about 30% genetic factors with abnormal semen parameters should be considered. The exact mechanism by which chromosomal anomalies induce the infertility is not clear. Gianotten et al. (2004) noted that there are over 4000 genes involved in the genetic control of human spermatogenesis. Both structural and numerical chromosomal abnormalities and mutations of related genes can result in the disruption of spermatogenesis. [3,4,10]

In this study, 112 infertile males with 44 non-obstructive azoospermics, 68 severe oligozoospermics and 30 control fertile males have been analysed in relation to chromosomal anomalies. The proportion of chromosomal anomalies in azoospermic males (18.2%) was higher than in severe oligozoospermic males (7.35%) with an over all occurrences of 11.6 per cent. While no major abnormalities were found in fertile control males. However, the difference between infertile males and control group was significant ($P<0.05$) only for major chromosomal abnormalities and not for chromosomal variants ($P>0.05$).

The overall occurrence of chromosomal abnormalities in infertile males depends on a number of factors; the most important of these is the selection of patients based on the sperm count. Our results demonstrated an inverse correlation between chromosomal anomalies and sperm count. The incidence of chromosomal abnormalities in azoospermic group (18.2%) and oligospermic group (7.35%) in our study was comparable to that reported in the literature for azoospermia (11.7-23.6%) and oligospermia (2.6-10.6%) by other authors.(Table IV.)

Sex chromosomal abnormalities (13.6%) was predominant in azoospermia over autosomal abnormalities (4.5%), while autosomal abnormalities (5.9%) was predominant in oligospermia over sex chromosomal anomalies (1.5%) (Table I). It was similar to literature data.

Table IV. Comparison of major chromosomal anomalies in azoospermic and severe oligozoospermic group of current study with the same studies in other regions of India and the world n (%)

Authors	Region	No of patients	Azoospermic	Severe Oligospermic	Total Chromosomal
			Males n (%)	Males n(%)	Aberration (%)
Bonaccorsi et al. [13]	Brazil, South America	89	4/23 (17.3)	7/66 (10.6)	11 (12.3)
Elghezal H. et al. [13]	Tunisia, Africa	840	81/343(23.6)	44/497(8.8)	125(14.8)
Vicdan A. et al.[11]	Turkey, Europe	208	17/119(14.3)	2/89(2.2)	19(12.5)
Mohammed F.et al. [14]	Kuwait, Asia	289	21/108(19.4)	2/181(1.1)	23(7.9)
Lissitsina J et al. [15]	Estonia		90	5/32(15.6)	7/58(12)
Vutyavanich T. et al. [16]	Thailand, Asia	104	5/50(10)	1/54(1.8)	6(4.6)
Ebru O. Etem et al. [17]	Turkey, Europe	214	19/138(13.7)	5/76(6.5)	24(11.2)
Nagvenkar P. et al. [10]	India, Asia	88	6/42(14.3)	3/46(6.6)	9(10.2)
Ng. PP et al. [21]	Hong Kong,	295	15/71(21.1)	10/224(4.4)	25(8.4)
Zhi-Bo Zhang et al. [18]	Hangchan, China ,Asia	135	14/81(17.3)	15/54(9.2)	29(14)
Akgul M. et al.[19]	Turkey, Europe	179	15/86(17.4)	5/73(6.8)	20(11.7)
Foresta C. et al.[6]	Italy, Europe	750	a		42/750(5.6)
Kleiman SE. et al.[20]	Israel, Asia	42	6/42(16.1)	a	
Current study	India, Asia	112	8/44(18.2)	5/68(7.3)	13(11.6)

All sex chromosomal abnormalities were numerical type with karyotype 47,XXY, a classical form of Klinefelter's syndrome except one, a mosaic form with 47,XXY[86]/46,XY[24] karyotype in severe oligozoospermia. This abnormality has impaired spermatogenesis associated with severe oligozoospermia or azoospermia causing infertility. This is caused by lethal dosage introduced into cell by an additional 'X' chromosome, which does not permit the development of sertoli cell and survival of germ cells in the testis, resulting in azoospermia due to advanced germ cell atresia and aplasia. Infertile men with gonosomal mosaicism have a range of spermatogonic profile ranging from severe impairment to apparent normality. Gonosomal mosaicism may be a probable cause for the failure of assisted reproduction [11,12]

The incidence of autosomal abnormalities found in 6 males (5.35%) in our study was similar with data (1.1-5.7%) given in the literature of most authors [4,6,10], but was lower than the data from some others (6.8-7.2%).[12,13,14] Of 6 infertile males, 4 had translocations, one was with inversion and one case remained with small supernumerary marker chromosome (sSMC) (Table I).

The translocation can result in a variety of sperm production phenotypes from normal spermatogenesis to an inability to produce spermatogonia. These are more common in oligozoospermic and azoospermic men.

Autosomal translocations were found to be 4-10 times more likely in infertile males in comparison with normal males.[15] The incidences of translocations in our study were significantly higher in infertile males (3.6%) than in the control group (0%) ($P<0.05$) and about two times higher than that in the literature (1.3-1.6%).[4,16] This difference may be occurring because of the differences in selection criteria of studied infertile males as all 68 oligospermics of our patients had severe oligozoospermia.

From 4 autosomal translocations, 3 were non-reciprocal [t(5;3), t(15;17) and t(14;12)] in severe oligospermia, which involved acrocentric chromosomes 14 and15 and one was Robertsonian translocations [t(15;21)] in azoospermia also involved acrocentric chromosomes 15 and 21. As the most frequent chromosomes involved in rearrangements in infertile men are reported the acrocentric chromosomes. Non-reciprocal translocations involving acrocentric chromosomes cause more severe spermatogenesis impairment because of a tendency of acrocentric chromosomes to associate with the sex body. Translocation can cause the loss of genetic material at the break points of genes, which can corrupt the genetic message and leads into the infertility. [17,18]

Reciprocal translocations form quandrivalents in meiosis, which through impairment of chromosomal segregation can lead to reduce fertility, spontaneous abortion or birth defects, depending on the chromosomes involved and the nature of the translocation.[19]

In current study, one case with sSMC had found in oligospemic group. sSMC are rare, especially in infertile males. Males carrying an sSMC are often phenotypically normal. SMC may associated with the X-Y bivalent at meiotic prophase and cause male infertility through impairment of spermatogenesis due to meiotic arrest and instability resulting in maturation arrest on spermatocyte stage.[4,15,20]

Polymorphic chromosomal variants have been well studied both in the normal population and in infertile males. The frequency of polymorphic chromosome variants in infertile men was higher in our study (36.6%), but similar to that in the control group (33.3%). It was also coincidental with the literature data in infertile males (4.9-58.7%) and in fertile males (32.6%).[10,21]

Autosomal chromosome variants were frequent than sex chromosome variants in our study: 30.8% vs. 6.2% in infertile males and 29.9% vs. 6.7% in the control group, respectively. Heterochromatic polymorphic variants are usually considered as normal variants inherited from one generation to another with low mutation rate and without any direct harmful phenotypic effect due to the scarcity of protein coding region in them. However, polymorphic variants arisen may have some clinical significance and association with clinical anomalies. The harmful effect of variants may be not direct to phenotype but indirect through the disturbing normal spermatogenesis and causing the death of germ cell and meiotic anomalies resulting in infertility or children with congenital anomalies.[21,22,23]

A large heterochromatic block in the pericentrometric region of chromosome 1 may affect the pairing of chromosomes causing meiotic arrest, death of germ cells and infertility.[13] It is suggested that 9 qh+ could be in association with repeated spontaneous miscarriages, stillbirth, multiple congenital abnormalities and chromosomal abnormalities in aborts and offspring. However, the result of our study and many other authors do not support this suggestion because of very high (13.3%) frequency of 9qh+ both in normal and infertile males (10.7%). [24,25]

We also found one case of inversion of chromosome 9 in azoospermic group. Previously, inv (9) has been reported in association with male and female infertility, recurrent miscarriages, congenital abnormalities in offspring and stillbirth. It is suggested that inv (9) may often cause infertility in men due to spermatogenic disturbance which are arisen by the loops or acentric fragments formed in meiosis. Some interchromosomal effects of inv (9) leading to a higher incidence of mitotic disturbances were also suggested.[26,27]

Y chromosome polymorphisms have been preferentially seen in azoospermic and severe oligospermic (Yqh+ and Yqh-). The variation in relative length of Y chromosome is said to be associated with male infertility. Long Y chromosome has been seen to be associated with an increased risk of fetal loss. However, another study did not show any relationship between the size of Y chromosome and the risk of abortion.[28]

Genest and Genest also reported that short Y chromosome does not see to represent an increased risk of pregnancy loss.[28] The contribution of Y chromosome variants to cause infertility is still a controversial topic and further studies are required to understand this.[29] In our study we found 'Y' chromosomal variants in 6.2% in which 7males were with increased hetrochromatin ('Y' qh+) and 5 with smaller region ('Y'qh-). Polymorphisms of acrocentric chromosomes of D and G-groups are found both in the normal population 3.3% and in infertile men 4.5%. It is reported that higher frequencies of satellite variants have been found in patients with reproductive failure and spontaneous abortions. Very large satellites of acrocentrics have been reported in infertile males, but other studies have not shown them as a risk factor of infertility.[10,21]

conclusion, the occurrence of chromosomal anomalies in infertile males (11.6%) strongly suggests genetic testing and counseling prior to the ICSI treatment. Moreover, prenatal diagnosis in the abnormalities is of utmost important. Such investigation is a prerequisite to minimize the risk of propagation of chromosomal abnormalities into the next generation. Additionally, a thorough follow-up of babies conceived through ARTs like ICSI and more advanced technique like priimplantation genetic diagnosis (PGD), in a particular the male progeny, is essential.[30]

Thus this high frequency of chromosomal abnormalities strongly suggests that chromosomal analysis should be included in routine investigations for infertile men, especially before using assisted reproduction techniques. The frequency of chromosomal anomalies in Western part India in our study was comparable with data like countries from South America, Europe, Africa, Asia and other part of India.

Consent: - Written informed consent was obtained from the patients for publication of this report.

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