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Case Report

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Four novel balanced reciprocal translocations and a novel inversion associated with recurrent spontaneous abortions

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ABSTRACT

The main objective of this study was to evaluate the cause of reproductive failures in couples by clinical and cytogenetic analysis. Couples with history of recurrent pregnancy losses (RPL) were referred to our cytogenetic laboratory for chromosomal evaluation. Chromosomal analysis from lymphocyte culture of the phenotypically normal couples was done to evaluate the role of chromosomal abnormalities in recurrent spontaneous abortion and to offer appropriate genetic counseling to them. Clinical and hormonal profile of the couples revealed normal phenotypes. Chromosomal analysis of the couples showed karyotypes such as 45,XX,der(13;14)(q10;q10), 46,XX,t(1;17)(p36.2;p13.1), 46,XX,t(9;16)(p24.2;q12.2), 46,XX,t(1;18)(q42.1;q21.2), 46,XY,inv(9)(p11.2q13.3), 46,XY,inv(Y)(p11.2q11.223), 46,XX,inv(14)(q23.2q32.1), 46,XY,(16qh+), 46,XY,t(4;18)(q13.1;q23.0), 46,XX,t(12;14)(q24.1;q32.2), and inv(11)(q23.2q24.3). Among the cases mentioned in this study four translocation cases and inversion and translocation within single individual were not previously reported in any other literatures. Novel balanced reciprocal translocations were reported as original investigation in four individuals and single case of translocation and inversion within the same individual in new break-points. The study showed chromosomal anomalies such as balanced translocation, inversion, and duplication causing RPLs from different unrelated families, and there was no history of consanguineous marriage in any of them.

KEY WORDS: Balanced translocation, chromosomal anomaly, cytogenetic evaluation, recurrent pregnancy loss, recurrent spontaneous abortion

INTRODUCTION

Pregnancy loss is a frustrating and challenging problem for couples desiring a baby as well as for the clinicians. Miscarriage is one of the most common complications of pregnancy. It also causes emotional distress significantly to the couple desiring children. This is particularly true when the patient presents with subsequent pregnancy with bad obstetric history (BOH) such as recurrent pregnancy losses (RPL) in association with primary or secondary infertility, irregular menses, absent or irregular ovulation, a known history of uterine fibroids, a family history of miscarriage, advancing age, medical history or a prior history of pregnancy complications. The cause being multifactorial and is mostly associated with the advanced maternal and paternal age, endocrine dysfunction, autoimmunity, infectious diseases, epigenetic factors such as teratogens, congenital anatomical uterine anomalies and genetic factor like chromosomal rearrangements, etc. [1].

Normally 1-5% of conceptions can show three or more consecutive spontaneous miscarriages in the first trimester of gestation [2]. During evaluating couples for RPL, an underlying contributing factor is often identified in 40-50% cases while after treatment, the prognosis for successful pregnancy outcome may reach up to 80%. The chances for a successful pregnancy remain 50-70% range in couples with no major detectable underlying problem and for a couple having last history of normal pregnancy and delivery, the prognosis also tends to be better [3].

Chromosomal abnormality, which leads to abnormal fetal growth and development during pregnancy, causes first trimester pregnancy loss in approximately 50-60% cases [3]. Fetal aneuploidy is the reason for the majority of miscarriages before 10th week of gestation. In some instances, either the maternal or paternal chromosomal makeup can predispose couples to chromosomally abnormal pregnancies. Studies showed that population frequency rates are between 1/673 and 1/1000 [4].

In this study, we dealt 10 cases where parental abnormal chromosomal makeup, balanced translocations or inversions are responsible for recurrent spontaneous abortion (RSA). The present survey thus provides additional information to the growing literature of parental balanced chromosomal abnormality in BOH cases.

CASE REPORT

In this case study, 10 cases with BOH were observed. All the observed cases experienced RPL or missed abortion in their 5-12 years of conjugal life. The incidence of IUFD (intra uterine fetal death) occurred 3-6 in numbers. As the upper age limit of the female partners was not over 38 years, advanced maternal age was not an influencing factor in these cases. Other aspects such as hormonal profile, immunological profile of both partner and ultrasonography of whole abdomen of the female individuals does not reflect any sign of abnormality. The sperm count of all male individuals was screened where in only a single case we observed severe oligospermia.

Methods

Cytogenetic analysis was performed for both the partners based on a phytohaemagglutinin-stimulated peripheral blood lymphocyte cultures. Lymphocyte culturing and GTG-banding were performed following standard protocols as described by the AGT Cytogenetic Laboratory Manual [5,6]. 20 metaphases were analyzed in all the patients, but in cases of abnormalities, the study was extended up to 50 metaphases. Karyotypes were described according to the International System for Cytogenetic Nomenclature (2013). Written informed consent was taken and kept it for future official document or necessary situation, and the complete work was approved by the Institutional Ethical Committee. The study was conducted in between April 2013 and March 2014 at Kolkata and adjoining areas.

RESULTS

Chromosome analysis of 10 clinically diagnosed infertile couples showing RSA revealed variant karyotypes such as 45,XX,der(13;14)(q10;q10), 46,XX,t(1;17)(p36.2;p13.1), 46,XX,t(9;16)(p24.2;q12.2), 46,XX,t(1;18)(q42.1;q21.2), 46,XY,inv(9)(p11.2q13.3), 46,XY,inv(Y)(p11.2q11.223), 46,XX,inv(14)(q23.2q32.1), 46,XY,(16qh+), 46,XY,t(4;18)(q13.1;q23.0), 46,XX,t(12;14)(q24.1;q32.2), and inv(11)(q23.2q24.3). The results show structural chromosomal abnormalities in 6 females and 4 males among 10 couples with RPL. The majority of the results showed the presence of balanced translocation (6 cases) along with inversions (4 cases) and duplication (single case) [Figure 1]. Only in a single case, we observed both balanced translocation and inversion present in the same individual [Figure 2]. The analysis also showed 6 normal males and 4 normal females with 46, XY and 46, XX karyotypes, respectively. Karyotype and other related data in observed RSA cases are summarized in Table 1.

DISCUSSION

Overall, incidence of BOH in literature is variable with large etiological heterogeneity. Genetic, anatomical, hormonal, immunological, and infectious factors are the main aspects for evaluating the patients with BOH, but the cause and exact percentage of influence is still often unclear. During evaluation of such cases, the chromosomal constituents of the abortus

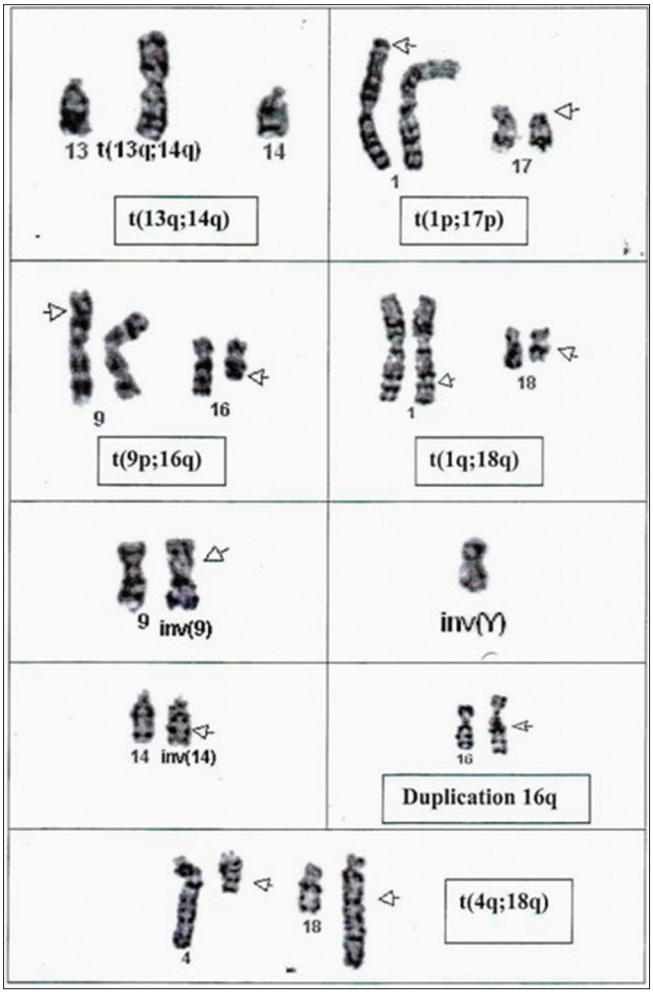

Figure 1: Chromosomal abnormalities observed in bad obstetric history cases

remain the primary interest of the clinician especially when nongenetic factors and the chromosomal constituents of the couples show normal parameters [7]. According to literature, approximately 2-4% of RSA is associated with a parental balanced structural chromosome rearrangement, dominantly balanced reciprocal or Robertsonian translocations [8]. Around 15-20% of all pregnancies in humans end in spontaneous abortions. It has been reported that the most common cause of spontaneous abortion in the first trimester (approximately 50%) chromosomal abnormalities. Cytogenetic evaluation of abortus indicates that the majority of chromosomal anomalies are numerical (95%); trisomies (60%), X monosomies (20%), and the remainder are polyploidy especially triploidy (15%) [7,9]. On the other hand, the risk of having children with a chromosomal abnormality is higher because half of the structural abnormalities may be inherited from the parent, carrying a balanced chromosomal translocation [10].

Chromosomal abnormalities in the embryo or fetus are the main cause of spontaneous recurrent abortion [11]. A spontaneous miscarriage includes an unbalanced chromosomal rearrangement which may be the result of one parent being carrier for balanced reciprocal translocation (BRT) [12]. In

Figure 2: Translocation and inversion observed within the same individual

Table 1: Karyotype and related data in observed RSA cases

No of cases	Sex	Indication	Age	Karyotype	Remark
1	Female	P (0+3)	29	45, XX, der (13;14)(q10;q10)	Reported
2	Female	P (0+3)	31	46, XX, t (1;17)(p36.2;p13.1)	New mutation
3	Female	P (0+4)	30	46, XX, t (9;16)(p24.2;q12.2)	New mutation
4	Female	P (0+3)	28	46, XX, t (1;18)(q42.1;q21.2)	Reported
5	Male	P (0+3)	36	46, XY, inv (9)(p11.2q13.3)	Reported
6	Male	P (0+4) and Severe oligospermia	35	46, XY, inv (Y)(p11.2q11.223)	Reported
7	Female	P (0+4)	38	46, XX, inv (14)(q23.2q32.1)	Reported
8	Male	P (0+3)	34	46, XY,(16qh+)	Reported
9	Male	P (0+6)	39	46, XY, t (4;18)(q13.1;q23.0)	New mutation
10	Female	P (0+3)	29	46, XX, t (12;14)(q24.1;q32.2), inv (11)(q23.2q24.3)	New mutation

RSA: Recurrent spontaneous abortion

4-8% of couples with RSA at least one of the partners probably has balanced chromosomal abnormalities [13]. Usually, one in 500 people carries a BRT and the risk of miscarriage in future pregnancy is approximately doubled if either one of the couples carries BRT [14]. Literature study also shows that in 68% of phenotypically normal couples with reproductive problems, and BRT remains a major cause [15].

There have been reports of reciprocal translocation carriers with varying combination of the involved chromosomes, resulting in RSA, and reproductive failure [16]. The size of the chromosomal segment involving their positions and the frequency of the breakpoints has a key role in reproduction. In couples with BOH, chromosomal rearrangements are non-random during the process of translocation [17]. The frequently involved chromosomes in the translocations in this study were 1, 4, 9, 11, 13, 14, 16, 17, 18, and Y. As per our knowledge, the four novel translocation cases mentioned in this study was not reported earlier involving those breakpoint regions. These novel new balanced translocations reported in this study are 46,XX,t(1;17)(p36.2;p13.1), 46,XX,t(9;16)(p24.2;q12.2), 46,XY,t(4;18)(q13.1;q23.0), and 46,XX,t(12;14)(q24.1;q32.2). In a single case, balanced translocation with inversion in new breakpoint region was observed within a single individual. Introduction of such molecular characterizations to clinical practice often helps in identifying the precise breakpoint regions which could be helpful in assisted reproduction where the zygote could be checked or sperm chromosomal constituents could be considered for further evaluation.

Along the above-mentioned novel balanced translocation, other reported translocation, inversion, and duplication were also observed during this study. It is reported that robertsonian translocation between chromosome no 13 and 14 causes mild to severe oligospermia in male and recurrent miscarriage in female individuals and children with the same translocation have endocrine disorder like hypogonadotrophic hypogonadism [18]. Balanced translocation between chromosomes number 1 and 18 in male cause's first and second trimester spontaneous abortion [19]. The presence of paracentric inversion in chromosome like 14 in both male and female, pericentric inversion in chromosome 9 in male and heterochromatic polymorphism in chromosome 16 in male also causes repeated miscarriage [20,21]. As the spermatogenesis controlling gene which is known as azoospermia factor genes (AZF) located in Yq11.3 region [22], inversion in the long arm of chromosome Y may affect the AZF gene, and this may produce single observable severe oligospermic male as reported in this study. This observation in this study thus agrees with the previous literature.

The patients carrying BRT have two very important and specific characteristics. The first one is the absence of phenotypic expression, and the second is the high risk to give birth to children with unbalanced chromosomal rearrangements. Hence, the cytogenetic evaluations of patients with BOH become very essential for further management. Detection of chromosomal abnormalities in either of the parents is essential to evaluate the prognosis of future pregnancies because the risk of miscarriages in couples with BRT is approximately 25-50%, and with robertsonian translocation, it is approximately 25% [23]. All the couples with BRT, therefore, should be strongly advised to monitor their future pregnancies by prenatal diagnosis for the presence of unbalanced chromosomal constituents in zygote. Thus, the genetic information detected by chromosomal analysis acts as a good genetic tool for further counseling and management.

CONCLUSION

This study thus reported several chromosomal abnormalities involving four novel BRTs and a single case where translocation and inversion occurs simultaneously which could result in generation of unbalanced gametes due to meiotic errors associated with RPL. Chromosomal analysis, therefore, should be an absolute need for all the couples with RSA and abnormal reproductive outcome. The carriers of such abnormalities should be also informed about the risk of birth defects in their offspring due to *de novo* submicroscopic rearrangements. It can be concluded that genetic counseling strategies should be offered which could allow the affected couples to make an informed decision regarding subsequent pregnancies.

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