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RECIPROCAL CHROMOSOME TRANSLOCATIONS IN 437 COUPLES WITH REPRODUCTIVE DISORDERS

ABSTRACT: Chromosomal abnormalities are the major contributors to genetic causes of reproductive disorders. The aim of this study was to determine the occurrence of reciprocal chromosome translocations in couples with reproductive disorder from the Prešov region (Slovakia) in 1998–2010. We analyzed the karyotypes of 437 couples with clinical diagnosis of reproductive disorder including infertility, recurrent fetal loss, congenital anomalies in the offsprings and sterility. The karyotypes were determined using cytogenetic banding techniques (GTG-banded metaphases). Routine cytogenetic analyses involved a total of 48 aberrant karyotypes corresponding to an abnormality frequency of 5.5%. Reciprocal chromosome translocations were found in six couples (1.4%), four female (0.9%) and two male (0.5%) partners. The identification of chromosomal abnormalities as the etiology facilitated the counseling and appropriate management.

KEY WORDS: Chromosome aberrations – Reciprocal translocations – Reproductive disorders

INTRODUCTION

Chromosomal translocations involve the transfer of genetic material from one chromosome to another, and can be reciprocal, involving the breakage of two non-homologous chromosomes with an exchange of segments, or Robertsonian, involving breakpoints close to the centromere of two acrocentric chromosomes. The importance of translocations relates to the pattern of segregation during meiosis. The patterns of inheritance are complex and depend on the particular chromosomes involved and the size of the rearrangements (Stern *et al.* 1999).

Reciprocal translocations are one of the most frequently observed structural chromosome abnormalities. They are defined by a segment exchange between two non-homologous chromosomes. A great number of different translocations exist since any chromosome can be involved in the translocation and the position of the breakpoint can

vary. Reciprocal chromosome translocations are the risk factor for the occurrence of reproduction disturbances, such as infertility, spontaneous abortion and congenital anomalies in the offspring. The degree of risk depends to a large extent on which chromosome segments are in the state of imbalance in the offspring, due to various mechanisms of abnormal meiotic segregation (Midro 1992). The uniqueness of chromosome translocations with respect to the type of chromosomes involved in translocations, and the location of breaking sites is the reason for the necessity of construing large pedigrees for the evaluation of the degree of risk.

MATERIAL AND METHODS

The aim of this study was to determine the occurrence of autosomal balanced translocations in the couples with

reproductive disorders. Chromosome analyses were performed over a period of 13 years (1998–2010). The study objects were 437 couples from the Prešov region (Eastern Slovakia) with reproductive disorders including infertility; recurrent fetal loss; congenital anomalies in the offsprings and sterility. Couples with infertility were counseled by gynecologists regarding the techniques. Male partners of infertile couples underwent an andrological examination according the World Health Organization standards (WHO 1999). Cytogenetic preparations were obtained from phytohaemagglutinin (PHA) stimulated peripheral blood lymphocytes. For cytogenetic analysis, peripheral blood samples were prepared according to the standard laboratory protocol (Rooney, Czepulkowski 1992). The cultures were incubated for 72 hours at 37 °C in RPMI-1640 medium. The cell divisions were arrested in the metaphases by adding colchicine 4×10^{-5} M for 30–40 minutes before harvesting the cultures. The cultures were treated with 0.4% potassium chloride hypotonic solution and fixed in 3:1 methanol-acetic acid mixtures. The banded slides were microscopically analyzed using G-banding methods according to ISCN nomenclature (Mitelman 1995). Chromosome analyses were carried out on G-banded metaphases with a minimum of 30 cells routinely examined. An additional 20–40 cells were examined if chromosomal mosaicism was suspected.

RESULTS

Routine cytogenetic analyses of 437 couples with reproductive disorder in the Prešov region (1998–2010) revealed a total of 48 aberrant karyotypes corresponding to an abnormality frequency of 5.5%. Numerical chromosome aberrations were detected in 2.1% of cases, structural chromosome aberrations in 3.4% of individuals. Reciprocal chromosome translocations were found in 1.4% of couples (6/437) with reproductive disorder, four findings were in female (0.9%) and two findings in male (0.5%) partners. In one case of infertile female, reciprocal chromosome translocation in mosaic form was detected. Description of reciprocal chromosome translocations identified in couples with reproductive disorders is presented in *Table 1*.

Translocations of Robertsonian type in 2% of cases were detected.

DISCUSSION

Chromosomal abnormalities are major contributors to genetic causes of reproductive disorders. Chromosomal abnormalities, particularly translocations, are known to be implicated in various forms of reproductive failure, ranging from defective gametogenesis (Crosignani, Rubin 1982) to recurrent spontaneous miscarriage (Campana *et al.* 1986). Autosomal balanced translocations have also been implicated in patients with infertility, particularly male infertility. In the literature, many studies of male infertility due to balanced translocation are reported (Aydos, Tukur 2006, Šeliga *et al.* 2008a, 2008b). There is an increased risk for males with autosomal abnormalities to have oligospermia, and chromosome studies on spermatozoa show an unbalanced karyotype in variable proportions, e.g. 54% for reciprocal translocations and 13.7% for Robertsonian translocations (Martin *et al.* 1993). There is only limited information available about the effects of structural aberrations on oogenesis. It is not clear why reciprocal translocations cause male factor infertility. According to one hypothesis, translocated chromosomes and their homologues align themselves in a quadrivalent form to pair during meiosis (Matsuda *et al.* 1986). The quadrivalent can segregate during anaphase I in different ways during meiosis. The frequency of contacts has been seen to be inversely correlated with sperm count. Conversely, oogenesis is relatively preserved in presence of such chromosomal aberrations as seen in the number of families with balanced chromosomal structural rearrangements associated with female fertility. But the ova may be chromosomally unbalanced, resulting in abortion of the unbalanced conceptus (Paolini-Giacobino *et al.* 2000). According Goel and Phadke (2010) non-Robertsonian balanced translocations are associated with a normal phenotype but may have a strong impact on the spermatogenesis process and thus lead to azoospermia. Oogenesis is relatively preserved in balanced translocation in females, but unbalanced translocation in fetus may result in recurrent spontaneous abortions.

TABLE 1. Reciprocal chromosome translocations in the couples with reproductive disorder in the Prešov region (Slovakia).

| <i>Cytogenetic findings</i> | Men (n = 437) | Women (n = 437) |
|----------------------------------|-------------------------|------------------------------|
| Normal chromosomes | n=407 (93.1%) | n=419 (95.9%) |
| Chromosomal aberrations | n=30 (6.9%) | n=18 (4.1%) |
| Reciprocal translocations | n=2 (0.5%) | n=4 (0.9%) |
| | | 46,XX,t(17;19)(q12;p13) |
| | 46,XY,t(15;16)(p15;q13) | 46,XX,t(1;15)(p34;q15) |
| | 46,XY,t(6;15)(q16;q12) | 46,XX,t(4;5)(q25;q32) |
| Mosaicism | | 46,XX/46,XX,t(7;14)(q22;q21) |

The frequency of translocations in couples with recurrent spontaneous abortions is 20-fold higher than that of the general population. In couples with recurrent spontaneous abortion, a balanced translocation has been found in one partner in about 5–7% of cases, depending on the number of previous miscarriages (Campana *et al.* 1986). Balanced parental translocations may be implicated in the pathogenesis of IVF-implantation failure (Stern *et al.* 1999).

The inheritance pattern of translocations is relatively unpredictable, and is determined by various modes of segregation at meiosis I. The pattern of segregation and the implications for progeny gametes depend on the particular chromosomes involved and the size of the rearrangement. While some authors have attempted to correlate quantitative chromatin imbalance with the risk of miscarriage or having a live born affected child (Cohen *et al.* 1994), the risks of pre- and peri- implantation loss associated with balanced parental translocations are largely unknown. This makes counseling for couples with infertility and reproductive failure extremely difficult.

CONCLUSION

This study has shown that couples with otherwise unexplained reproductive disorder have a greater than expected chance of carrying a balanced chromosomal translocation. Cytogenetic findings of reciprocal chromosome translocations strongly support the recommendation of genetic screening of couples with reproductive disorder. The identification of chromosomal abnormalities as the etiology facilitated counseling and appropriate management. Chromosomal examination should be considered as part of the investigation of the couples with reproductive disorder, and genetic counseling and consideration of pre-implantation diagnosis should be an integral part of planning of further treatment strategies.

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