Case Report

Genetic counseling in carriers of reciprocal translocations involving two autosomes

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One of the main genetic causes involve in the pathogenesis of recurrent abortion is parental chromosomal abnormalities. The central concept in genetic counseling with such families is to estimate the probability of recurrence of unfavorable pregnancy outcomes. The main questions that consultants usually ask are: Why did this happen? What is the risk to be done again?

Our cases were two families with repeated miscarriage. The pedigrees were drawn, the chromosomes of couples were studied, and estimation for recurrent risk was done. We tried to answer those two main questions and clear the results for them.

Parental chromosome abnormalities were founded after karyotyping with GTG technique at 450 band resolution, revealing 46 chromosomes with balanced translocation of autosomes in one of the partner in both families. Recurrent risk was estimated as "high" for their future pregnancies in each family.

Couples in which one partner is the carrier of such balanced translocation have increased risks of infertility, recurrent abortion, and delivery of chromosomally abnormal offspring. Genetic counseling of such couples, therefore, presents a unique challenge and should be considered in dealing with such families.

Key words: Abortion, family planning, genetic counseling, reciprocal translocation, repeated miscarriages

Introduction

The presence of chromosome abnormalities in couples with repeated spontaneous abortion is known even if the phenomenon is far from a complete assessment.[1] Patients carrying balanced reciprocal translocation are subject to meiosis nondisjunction risk. Indeed, the mispairing of translocated chromosomes during the first meiotic division can give rise to different forms of segregation, which can result in aneuploidy of the translocated chromosomes.[2] A compilation of the cytogenetic results taken from 79 published surveys of couples with two or more pregnancy losses (comprising 8208 women and 7834 men) showed an overall prevalence of major chromosome abnormalities of 2.9%. This is five to six times higher than that of the general adult population.[3] Results of different studies have shown that chromosomal reciprocal translocations in one of the partners will cause majorities of unfavorable pregnancy outcomes.[4-7]

The main question that usually genetic counselors should answer to their consultants is to estimate the probability of recurrence of unfavorable pregnancy outcomes (abortion, stillbirth, and birth of malformed child) among their future pregnancies. In case of chromosomal translocations, estimates are made on basis of segregation analyses in actual pedigree. If we have a few of pedigree members,then risk estimate should be performed on basis of our combined data and empiric data from literature.[8] Families with balanced chromosomal changes ascertained by unbalanced progeny, miscarriages, or by chance are interested in their probability for unbalanced offspring and other unfavorable pregnancy outcomes. This is usually done based on the original data published by Stengel-Rutkowski *et al.*(1988), several decades ago.[9]

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Different risks are estimated for unbalanced offspring at birth or at second trimester prenatal diagnosis for abortions or stillbirths/early deaths. These risk estimates varied considerably from translocation to translocation. Here, we present two different family in which one of the partners were carriers of balanced translocation.

Case Report

Our cases were two families living in Hamadan as described below. They were referred to our clinic because of their repeated spontaneous abortion:

a. Family number I: Female partner was 26 and male partner was 32 years old. They had consanguineous marriage (first cousin). Their medical history has showed four miscarriages during the first trimester of pregnancies. Figure 1 shows their pedigree chart. As it can be seen, the male partner had two siblings who died at the first month after birth. His karyotype with GTG banding technique showed that he was a balanced carrier of reciprocal translocation between two autosomes, numbers 2 and 12 [Figure 2]. The results of his karyotype was 46, XY, t(2;12)(p21;q22). The karyotyping of his wife showed that she was 45, XX (normal female karyotype). Figure 2 shows the photographs of normal and translocated chromosomes numbers 2 and 12, displaying also schematic representation of the breakpoint positions.
b. Family number II: Female partner was 38 and male partner was 50 years old at the time of our study. They had a non-consanguineous marriage. Their medical history has showed two miscarriages during the first trimester of pregnancies. Figure 3 shows their pedigree chart. As it can be seen, the female partner had mother with three abortions in her medical history. His karyotype with GTG banding technique showed that he was a balanced carrier of reciprocal translocation between two autosomes, numbers 1 and 12 [Figure 3]. The results of her karyotype was 46, XX, t(1;12)(p31;q13). The karyotyping of her husband showed that he was 45, XY (normal male karyotype). Figure 4 shows the normal and translocated chromosomes numbers 1 and 12, and also it representsschematic diagrams of the breakpoint positions.

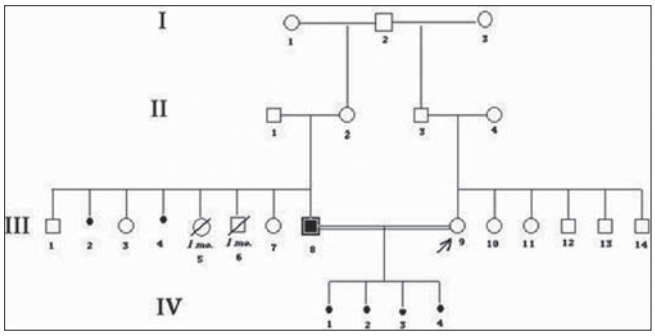


Figure 1: Pedigree chart of Family number I, see text for details

Discussion

The estimation of the occurrence probability for individual carriers of two different autosome-autosome translocations with breakpoints at different positions is usually done based on the original data published by Stengel-Rutkowski *et al*.(1988) several decades ago. That data set has never been updated.[9]

For example, probability rates of unbalanced progeny at birth and at second trimester of prenatal diagnosis as well as of unkaryotyped miscarriages and stillbirth/early death of newborn for RCT carriers related to the total number of pregnancies after ascertainment correction are calculated according to the method of Stengel-Rutkowski *et al*.[10] The ascertainment correction according to Stene and Stengel-Rutkowski[11] is performed by elimination of probands (or index sibships) and carriers with the proband in direct line of descent. The probability rate

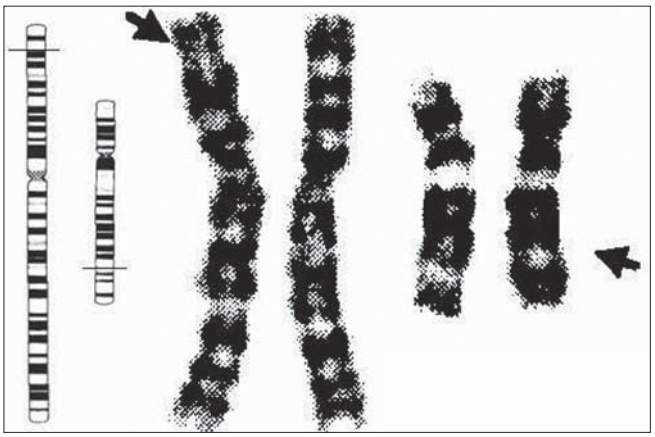


Figure 2: Photographs of normal and translocated chromosomes numbers 2 and 12, displaying also schematic representation of the breakpoint positions

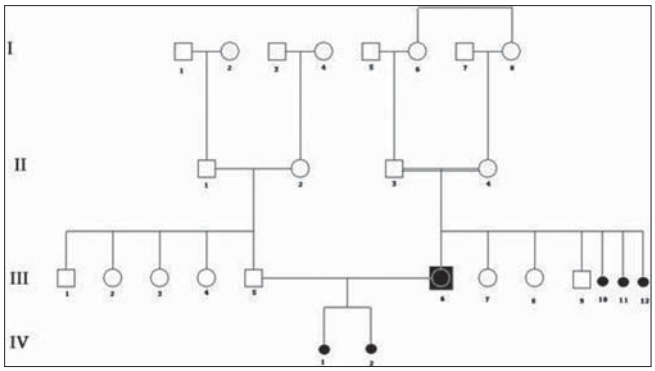


Figure 3: Pedigree chart of Family number II, see text for details

estimates for unfavorable pregnancies are presented as:

$$p = \frac{a}{n} S = \sqrt{\frac{a(n-a)}{n^3}} \quad (1)$$

p, risk value; *a*, number of unfavorable pregnancies after ascertainment correction; *n*, number of all pregnancies after ascertainment correction; and *S*, standard deviation.

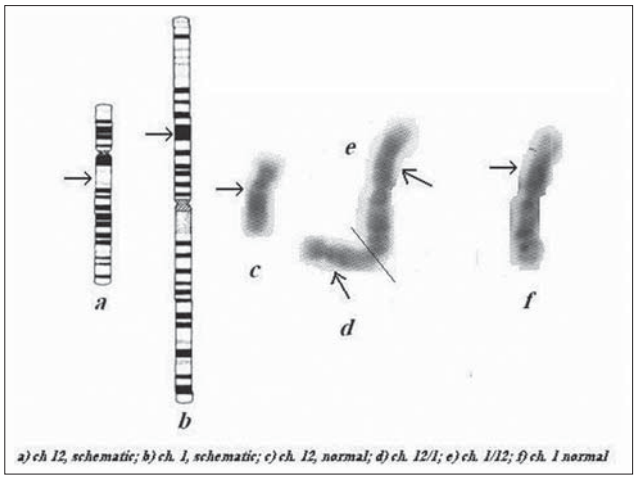
If the number of abnormal pregnancies after ascertainment correction be 0, the maximal risk estimate *m*, corresponding to the upper limit of the risk interval, is calculated using the formula:

$$m = 1 - e^{-\frac{1}{2n}} \quad (2)$$

m, maximal risk where e=2.71828 is the base number for natural logarithms.

It is clear that the larger pedigrees result in accurate estimations. Also, using such formula in clinics takes a lot of time and usually the patients feel that the counselors are doing a lot for noting!

The families usually do not care about such estimations; they want know why those miscarriages, stillbirths/early deaths happened; are they in a high risk for those bad experiences or not? And finally, if the answer is "yes," they are eager to know the genetic counselor's views about those complex estimations. In another word, they want to hear if there is a high, moderate, or low risk for unfavorable pregnancy outcome in a RCT carrier. So, perhaps if the genetic counselors try to adopt their estimations to the roles of segregation during miosis and gametogenesis in carriers of balanced reciprocal translocations,[12] the patients will get a better idea to reach to a final decision. Based on the segregation role,



a) ch 12, schematic; b) ch. 1, schematic; c) ch. 12, normal; d) ch. 12/1; e) ch. 1/12; f) ch. 1 normal

Figure 4: Photographs of normal and translocated chromosomes numbers 1 and 12, displaying also schematic representation of the breakpoint positions

the risk of unfavorable outcomes, in such situations, as we saw in our cases, are high (about one-sixth) and we advised for PGD or prenatal diagnosis.

In addition of those two questions that are the cores of genetic counseling from the patients' side and so genetic counselors might answer and explain them in an comprehensible way, there are two more points that although are in a limited probability, geneticists should bring them to light and pay enough attention. Firstly, the people that are balanced carrier of, at least, some kinds of reciprocal translocation are at a higher risk for malignancy.[13-16] Therefore, carriers of such translocations should be noticed to have routine check-up for early detection of malignancies. Secondarily, sometimes RCTs lead to abnormalities in other chromosomes, phenomenon called inter-chromosomal effect (ICE);[17,18] so the risk of unfavorable outcomes in future pregnancies of such individuals may be more than primary estimations. Because matters such as what we mentioned recently are studies called the sensitive studies,[19-21] talking about them must be with special attention.

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