Familial Translocation (2;18) Ascertained Through Recurrent Spontaneous Abortions

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We report a young woman who presented with a reproductive history of two recurrent spontaneous abortions. Genetic etiology of recurrent fetal loss is determined by the demonstration of parents' chromosomal constitution. Analysis of the family members from 2 generations revealed 3 phenotypically normal individuals carying the same reciprocal translocation. The great majority of apparently balanced translocations are associated with multiple miscarriages and normal phenotype. The proband's karyotype was identified as 46, XX, t (2;18) (p15; p11.2) by giemsa banding techniques. The karyotypes of the proband's father and brother are 46, XY, t (2;18) (p15;p11.2). Her sister had two spontaneus abortions, her chromosomal analysis could not be determined because she was living in another city. Cytogenetic studies of unbalanced miscarriages are difficult due to the growth failure of early loss and usually macerated abortions. Reciprocal translocations are of great clinical importance. The carriers of balanced reciprocal translocations have increased risk of creating gametes with unbalanced chromosome translocations leading to miscarriages or children with abnormalities. Genetic counseling and genetic testing is often offered o families carrying a translacation.

Key Words: Recurrent spontaneous abortions, Familial translocations, Chromosomal abnormalities

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Introduction

Of all recognized pregnancies, about 10-15% ends in a miscarriage or spontaneous abortion. The majority of spontaneous abortions occur during the first trimester, and over 50% of these early miscarriages are chromosomally abnormal.[1,2]

Carriers of balanced chromosome rearrangements can present with a history of infertility, spontaneous abortion, stillbirth or the birth of a child with multiple congenital abnormalities and/or mental retardation.[3,4] Chromosomal abnormalities, mainly balanced rearrangements, are common in couples with reproductive disorders including recurrent abortions.[5,12]

A translocation refers to the transfer of genetic material from one chromosome to another. The overall incidence of reciprocal translocations in the general population is approximately 1 in 500 and about 1 in 600 newborns.

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We report a phenotypically normal woman with an apparently balanced reciprocal translocation between chromosomes 2 and 18 [46, XX, t (2;18) (p15; p11.2)].

Case Report

The couples were non-consanguineous and married for 6 years. The woman was 32 years old and man was 31 years old. Spouses referred to our cytogenetic laboratory, because of three spontaneous abortions at 9 weeks of gestational age.

Cytogenetic Studies

Standard GTG banding (550-600 bands level), were performed on metaphases obtained from peripheral blood PHA-stimulated lymphocytes from spouses' and wife's parents' blood samples according to standard procedures.

The proband's karyotype has been identified as 46, XX, t (2;18) (p15;p11.2) (V-4 in the pedigree), while her spouse's karyotype has normal by giemsa banding techniques. GTG-banded chromosomes, obtained from peripheral blood lymphocytes of all members of families showed normal karyotype in all 20 analyzed metaphases.

The karyotype of the proband's father (IV-3) and two brothers are 46, XY, t (2;18) (p15; p11.2) (V-7 and 9). Her sister has two spontaneous abortions, her chromosomal analysis could not be determined, because she lived in another city. Cytogenetic studies of the embryonic tissue derived from any of her spontaneous abortions were not studied. Cytogenetic

studies of unbalanced miscarriages are difficult due to the growth failure of early loss and usually macerated abortions. The pedigree and karyotypes of our family are shown in Figure 1, 2, 3.

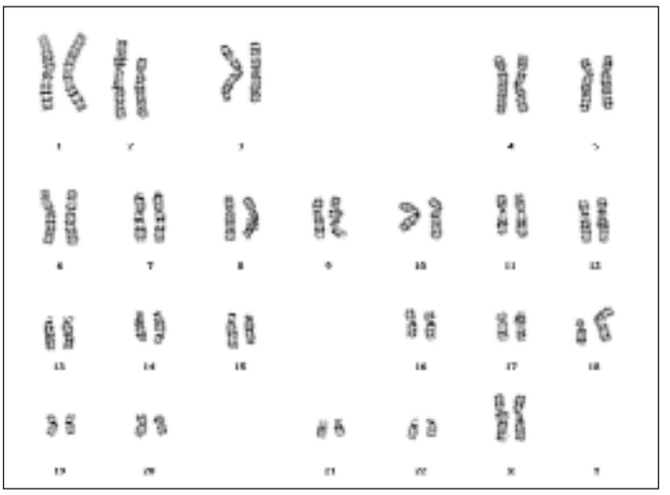

Figure 1: Karyotype of the proband

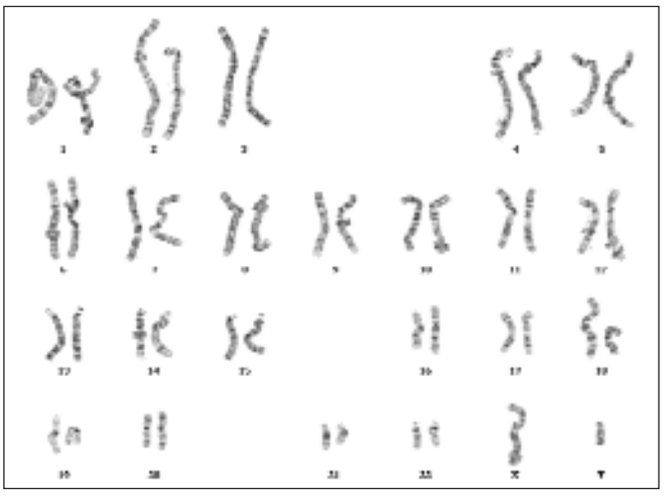

Figure 2: Sample karyotype of the fathers and two brothers of the proband

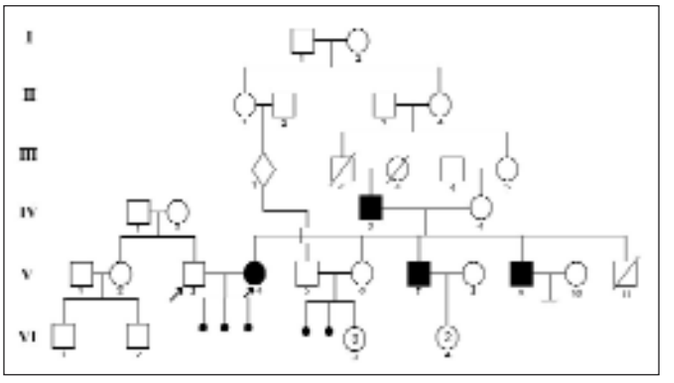

Figure 3: Pedigree of our family

Discussion

Recurrent miscarriage continues to be a challenging reproductive problem for the patient and clinician. Identifying a cytogenetic cause for a miscarriage can be psychologically important to overcome grief and loss, as well as deciding on whether to try again. Cytogenetic analyses of previous miscarriages are an important component in the assessment of couples with a history of recurrent miscarriage.

Chromosome abnormalities are identified in approximately 50% of all spontaneous abortions. Many spontaneous abortions occur very early in the pregnancy, and may occur prior to the recognition of the pregnancy; therefore, the miscarriage may be unrecognized.

Balanced chromosome rearrangements are found in 5% of couples experiencing recurrent spontaneous abortions.[3,4] Because chromosome ends may have a similar banding pattern or because reciprocal translocations may be too subtle to be cytogenetically identifiable, it is possible that some of these couples are carriers of cryptic subtelomeric rearrangements. Several recent studies have addressed the question of presence of cryptic terminal chromosomal rearrangements in couples experiencing recurrent pregnancy loss.

Balanced chromosome translocations, in which sections of chromosomes change their geographical position on the chromosomal map without any loss or gain of important genetic material, are an important cause of recurrent miscarriages because they are common; one in 500 people carries a balanced translocation. When one member of a couple carries a balanced chromosome translocation, the risk of having a miscarriage is approximately doubled. In 3-5% of couples with recurrent miscarriage, one partner has a balanced translocation. Peripheral blood karyotyping of both partners is considered a mandatory investigation of couples with recurrent miscarriage but, Franssen et al raise the question of whether other factors, such as family history of miscarriages, should be taken into consideration when deciding who should be karyotyped. When a balanced translocation is identified, it is useful to karyotype miscarriage products to see if they are the result of unbalanced translocations.[13,14]

Reciprocal translocations are of great clinical importance. The carriers of balanced reciprocal translocations have increased risks of creating gametes with unbalanced chromosome translocations leading to miscarriages or children with abnormalities. Genetic counseling and genetic testing is often offered to families that may carry a translocation. When counselling a carrier of a balanced translocation it is necessary to consider the particular rearrangements to determine whether it could result in the birth of an abnormal baby. This risk will usually lie somewhere between 1% and 10%.

This study illustrates the importance of cytogenetic analyses of miscarriages in couples with a history of recurrent miscarriage.

Partial monosomy of the short arm of the chromosome 18 is the most common cytogenetic abnormality. The phenotype of 18p deletion syndrome is well characterized and varies from severely affected to near normal physical development, and from severe to mild intellectual development,[15] whereas, partial duplication of the long arm of chromosome 18 is a rarer syndrome.[16,17] Miscarriages of our cases may be due to partial trisomy of chromosome 18 which occurs as a result of imbalanced meiotic segregation. This duplication is mainly characterized by an Edwards's syndrome phenotype with, microcephaly, upturned nose, micrognathia and short neck. Wilson et al.,[18] based on review of duplication of different 18q regions, suggest that no one region is sufficient to produce the phenotype of trisomy 18. Turleau et al.,[19] suggest that the trisomy 18 phenotype results from interaction of several chromosome 18 regions, which may produce a quite different phenotype when duplicated in isolation.[20]

Further studies of sperm chromosomes in reciprocal translocation carriers are required, because very few researches have been reported. Information from these studies will provide estimates of the frequency of chromosomally unbalanced gametes. This study will also help us to elucidate some of the factors that influence the production of recombinant chromosomes at meiosis.

As for genetic counselling in such families it is important to discover all carriers in order to advise a prenatal diagnosis in all pregnancies and explain the option of Preimplantation Genetic Diagnosis (PGD).

Tekrarlayan Spontan Abortus Sayesinde Tespit Edilen Ailesel Translokasyon (2;18)

Rapor ettiğimiz olgunun reprodüktif öyküsünde tekrarlayan 2 spontan abortusu vardı. Tekrarlayan gebelik kaybının genetik etyolojisi ebeveynlerin kromozom analizleriyle ortaya kondu. Analiz edilen 2 jenerasyona ait 3 bireyde fenotipik olarak normal aynı resiprokal translokasyon tespit edildi. Dengeli olarak gözüken translokasyonların büyük çoğunluğu tekrarlayan düşükler ve normal fenotiple ilişkiliydi. Giemsa bantlamasıyla probandın karyotipi 46, XX, t (2;18) (p15; p11.2) şeklindeydi. Probandın babası ve erkek kardeşinin karyotipleri de 46,XY, t (2;18) (p15;p11.2) olarak bulundu. Kız kardeşi başka şehirde yaşadığından ve 2 spontan abortusun kayotiplerine ulaşılamadı. dengesiz düşüklerin sitogenetik analizleri, büyüme geriliğine, erken kayıplara ve masere düşüklere sebep olduğundan zordur. Resiprokal translokasyonların klinik önemi büyüktür. Dengeli resiprokal translokasyon taşıyıcılarının düşüklere veya anomalili çocuk sahibi olmaya sebep olan dengesiz translokasyonlu gamet oluşturma riskleri artmıştır. Translokasyon taşıyıcısı ailelere genetik danışma ve genetik testler önerilir.

Anahtar Kelimeler: Tekrarlayan gebelik kaybı, Ailesel translokasyon, Kromozom anomalisi

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