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CLINICAL ARTICLE

Complex chromosomal rearrangements in couples affected by recurrent spontaneous abortion

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ABSTRACT

Objective: To determine the proportion of couples affected by recurrent spontaneous abortion in which one partner carries balanced translocations among three chromosomes. *Methods:* In a retrospective study, G-banded chromosome complements were analyzed for couples affected by recurrent spontaneous abortion who were referred to Niigata University Hospital, Japan, between January 1, 1990, and December 31, 2011. The frequency of couples in whom one of the partners carried balanced translocations among three chromosomes was determined, and the clinical outcomes for affected couples who subsequently achieved term pregnancies were reviewed. *Results:* Of 1415 couples with recurrent spontaneous abortion during the study period, there were two (0.1%) in which one of the partners (the woman in both cases) carried balanced translocations among three chromosomes. Both couples achieved a subsequent pregnancy that continued successfully and resulted in a phenotypically normal neonate. *Conclusion:* The frequency of balanced translocations among three chromosomes was estimated to be approximately 0.1% in a population affected by recurrent spontaneous abortion. With appropriate treatment based on careful examinations, affected couples can go on to achieve a successful pregnancy outcome.

1. Introduction

The frequency of balanced reciprocal translocation between two chromosomes in the general population is estimated from prenatal and newborn studies to be approximately 1 in 625 [1]. Couples in which one partner is the carrier of a balanced translocation have increased risks of infertility and recurrent spontaneous abortion, and are more likely to have children with chromosomal abnormalities. Balanced translocations between two chromosomes are present in approximately 5% of couples affected by recurrent spontaneous abortion [2–4]. Although the proportion of couples in which one individual is affected by reciprocal exchanges between three or more chromosomes—complex chromosomal rearrangements (CCRs) [5]—does not seem to have been reported, it is thought to be very low. Genetic consultation for affected couples is considered to be very difficult. Some case reports [6–8] have described CCRs in patients with reproductive failure.

The aim of the present study was to determine the proportion of couples affected by recurrent spontaneous abortion in which one partner carries balanced translocations among three chromosomes. A secondary aim was to report the clinical course of patients in whom a subsequent pregnancy continued successfully.

2. Materials and methods

In the present retrospective study, the frequency of balanced translocations among three chromosomes was determined in couples affected by recurrent spontaneous abortion (two or more consecutive spontaneous abortions) who were referred to Niigata University Hospital (Niigata, Japan) between January 1, 1990, and December 31, 2011. The study protocol was approved by the Institutional Medical Ethical Review Committee of Niigata University School of Medicine and management of the participants conformed to the provisions of the Declaration of Helsinki. Written informed consent was obtained from the patients and their partners for publication of the clinical features of their cases. Data anonymity was maintained and patient identity was protected.

During the study period, chromosome analysis was performed for all affected couples as one of the routine examinations for recurrent

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spontaneous abortion. Chromosome preparations were obtained from peripheral blood lymphocyte cultures, and karyotyped by Giemsa staining (G-banding) as previously described [9].

For the present study, the number of couples in whom one of the partners carried balanced translocations among three chromosomes was determined. In addition, the clinical course and outcomes were reviewed for the couples who were subsequently able to achieve a term pregnancy. Regarding data analysis, frequency was reported as simple descriptive statistics.

3. Results

During the study period, 1415 couples with recurrent spontaneous abortion underwent chromosome analysis. Of those, there were two in which one of the partners (the woman in both cases) carried balanced translocations among three chromosomes. Thus, the frequency of couples with recurrent spontaneous abortion in which one partner was the carrier of a balanced translocation among three chromosomes was 0.1%.

In the first case, chromosome examination showed that the male partner had a normal karyotype (46, XY). The woman (a housewife aged 25 years, gravida 2, para 0) had the karyotype: 46, XX, t (4;12;8) (q33; q22; q21.2) or 46, XX, t (4;12;8) (4pter → 4q33::8q21.2 → 8qter;12pter → 12q22::4q33 → 4qter;8pter → 8q21.2::12q22 → 12qter) (Fig. 1).

The couple had been referred to Niigata University Hospital because the woman had had two spontaneous abortions. During both pregnancies, the fetus had developed but a fetal heart beat was not detected. There was no information available regarding the karyotypes of the fetuses. Routine examinations indicated that the woman had no müllerian anomalies, hormone deficiencies, infectious diseases, or metabolic disorders. Autoimmune examinations demonstrated positive findings for antiphospholipid antibodies (the anti-cardiolipin IgG level was 72 units/mL [MESACup cardiolipin test; Medical and Biological Laboratories, Nagoya, Japan; cutoff value 10 units/mL]), and negative findings for anti-cardiolipin β2-glycoprotein I antibodies and lupus anticoagulant.

During the genetic consultation, the possibility of the successful continuation of a new pregnancy was estimated to be 25% or less according to the possible karyotypes of oocytes (Fig. 2). To treat the positive antiphospholipid antibodies, the Japanese traditional herbal medicine Sairei-to (Tsumura, Tokyo, Japan; 9 g/day), which might have a pharmacological effect similar to corticosteroid hormone, and low doses of aspirin (Bufferin; Eisai, Tokyo, Japan; 81 mg/day) were administered in accordance with a previously reported protocol [10,11]. The titer of anti-cardiolipin antibodies normalized after the administration of Sairei-to. The woman became pregnant for the third time, and the pregnancy continued beyond her critical period of 10 weeks. She delivered a female neonate weighing 2890 g with an Apgar score of 9. The neonate demonstrated a normal appearance and her neonatal course was uneventful. Karyotype analysis was not performed in accordance with the parents' decision.

In the second case, chromosome examination showed that the male partner had a normal karyotype (46, XY). The woman (a housewife aged 32 years, gravida 3, para 0) had the karyotype: 46, XX, t (4;8;16) (q27; q11.2; q22) or 46, XX, t (4;8;16) (4pter → 4q27::16q22 → 16qter;8pter → 8q11.2::4q27 → 4qter;16pter → 16q22::8q11.2 → 8qter) (Fig. 3).

The couple had been referred to Niigata University Hospital because the woman had had three spontaneous abortions. In the first and second pregnancies, only the gestational sac had appeared. In the third, a fetal heart beat was detected, although it later disappeared at an early stage of pregnancy. There was no information available regarding the karyotypes of the fetuses. Routine examinations indicated that the woman had no müllerian anomalies, hormone deficiencies, infectious diseases, metabolic disorders, or autoimmune abnormalities.

A genetic consultation was offered, and the couple was encouraged to try to conceive again. The woman subsequently became pregnant for the fourth time, and the pregnancy continued beyond her critical period of 10 weeks. She delivered a male neonate weighing 3128 g with an Apgar score of 9. The neonate was phenotypically normal and

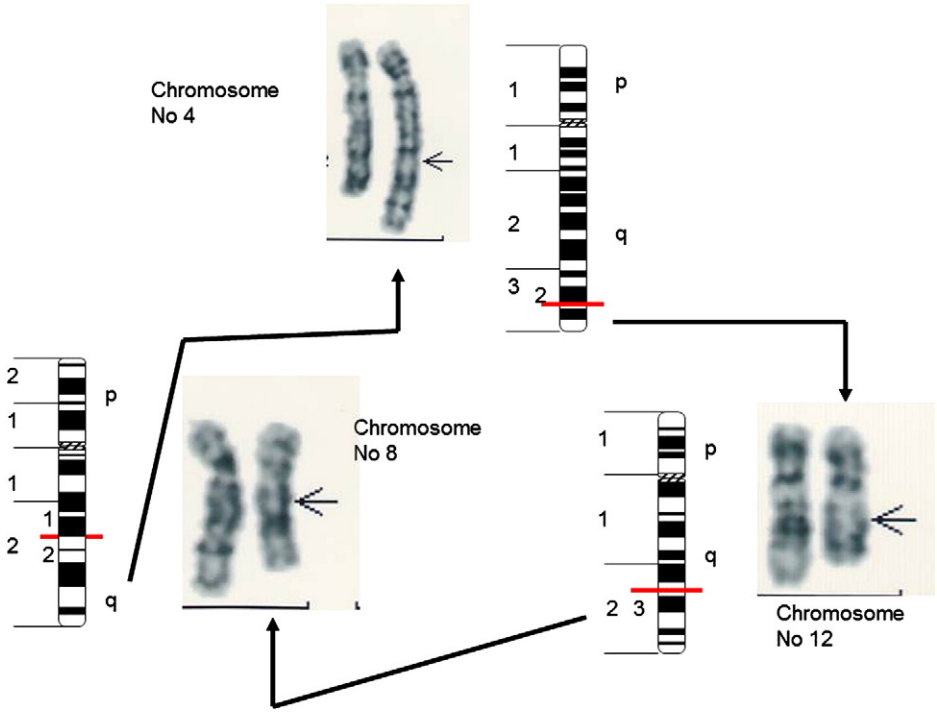

Fig. 1. The reciprocal translocations among three chromosomes in the woman in the first case: 46, XX, t (4;12;8) (q33; q22; q21.2) or 46, XX, t (4;12;8) (4pter → 4q33::8q21.2 → 8qter;12pter → 12q22::4q33 → 4qter;8pter → 8q21.2::12q22 → 12qter).