PRENATAL DIAGNOSIS OF TRANSLOCATION 13;13 PATAU SYNDROME: CLINICAL FEATURES OF TWO CASES

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ABSTRACT

Patau syndrome is associated with extra chromosome 13 material, either free as in the 47,+13 or in a Robertsonian translocation or another rearrangement. We report on two fetuses with trisomy 13 who were diagnosed prenatally via cord blood and amniocentesis, respectively. They showed *de novo* Robertsonian translocation between chromosome 13 and 13, and had normal parents. One was detected cytogenetically at 24 weeks of gestation with a karyotype of 46,XX, rob(13;13) and lived only 1 month after birth. Holoprosencephaly, proboscis, microphthalmia and heart septal defects were present. The other fetus was examined at 14 weeks gestation because of cystic hygroma, hydrothorax and hyperechogenic kidneys and had the karyotype 46,XY, rob(13;13). After abortion the fetus was found to have a cleft lip and palate, postaxial polydactyly of the feet, micrognathia, omphalocele, low-set ears with abnormal helix and to be small for the gestational age. Due to the difference in chromosomal makeup seen in non disjunction, there may be differences in expression of several of the features often seen with trisomy 13, either classical type (as in the 47,+13) or *de novo* Robertsonian translocation type (as in the 46).

Key words: Trisomy 13, Patau syndrome; Robertsonian translocation; Dysmorphic features

INTRODUCTION

Changes in number or structure of chromosomes are a major cause of congenital anomalies and intellectual impairment. Trisomy 18 is the second and Trisomy 13 the third most common autosomal trisomy at birth [1,2]. Non disjunction is the failure of one or more pairs of homologous chromosomes to separate following the first or second meiotic division. Trisomy 13 usually involves a maternal meiotic error but paternal errors also occur [3]. When reduction (separation pairs of homologous chromosomes) does not occur, non disjunction occurs and is responsible for autosomal trisomies. Studies suggest a common mechanism for occurrence with all trisomies [2,4]: maternal first meiotic division (40% of cases); maternal second meiotic division (40% of cases); paternal first meiotic division (20% of cases)

About 80% of trisomy 13 cases result from fresh mutations, and the remainder occur as a result of chromosomal translocation. During translocation, chromosomes misalign and join at their centromeric region with subsequent loss of part of a chromosome. This is called a Robertsonian translocation. During Robertsonian translocation, the long arms of two acrocentric chromosomes fuse at the centromere and the two short arms are lost. Common Robertsonian translocations are confined to acrocentric chromo-

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somes 13, 14, 15, 21, and 22, as the short arms do not contain essential genetic material. Chromosome 13:14 Robertsonian translocations account for up to 33% of all Robertsonian translocations. Parents may have children with a normal number of chromosomes, a trisomy, a monosomy, or a balanced translocation [1]. Robertsonian translocations are the most common human structural chromosomal abnormalities with an incidence of 1.23/ 1000 live births [5,6]. They are mainly observed in group D chromosomes (*i.e.*, 13, 14, 15) and group G (*i.e.*, 21 and 22). The D/D translocation is the most frequent type, with a high predominance of 13;14 translocations [6,7]. In Robertsonian translocations, the pericentric regions of two acrocentric chromosomes fuse to form a single or two centromeres. The resulting balanced karyotype has only 45 chromosomes including the translocated one, which is a result of a fusion of the long arms of two chromosomes. Malsegregation (unbalanced segregation) of Robertsonian translocation, results in trisomy or monosomy of complete chromosomes [8].

Patau syndrome is associated with extra chromosome 13 material, either free as in the 47,+13 genotype or in a Robertsonian translocation or another rearrangement. This genotype occurs in: 1) about 0.8-1.0% of spontaneous abortuses; 2) about 0.4% of early neonatal deaths; and 3) amniocentesis, higher than in live births, at least for mothers 40 years and over [9]. Trisomy 13 occurs in about 1 out of 10,000 live and still births. However, the actual prevalence of trisomy 13 is difficult to estimate because many pregnancies involving a prenatal diagnosis of trisomy 13 are terminated shortly after the diagnosis has been made [10]. The frequencies of 47,+13 was 0.162% and the frequencies of D/13 translocations was 0.04% according to our laboratory results of 4,300 prenatal diagnoses with amniocentesis (unpublished data). The results of Hook *et al.* [9] in a total of 113,045 studied live births and our laboratory are shown at Table 1. In this study we report the clinical features, genetic (cytogenetic screening for all chromosomal disabilities) and autopsy findings of two trisomy 13 cases.

MATERIALS AND METHODS

The two cases described here were diagnosed with abnormal USG (ultra sonography) findings at the Department of Gynecology and Obstetrics, Faculty of Medicine, Çukurova University, Adana, Turkey. Chromosomal analyses of cord blood, peripheral blood lymphocytes and of amniotic fluid cells were performed according to standard cytogenetic methods using a G-banding technique. Lymphocytes were cultured in RPMI 1640 (Sigma-Aldrich Inc., Munich, Germany). Chromosome slides were made according to routine procedures [11]. Twenty metaphases of each individual were examined for chromosomal aberrations after solid Giemsa staining and were recorded according to the International System for Human Cytogenetic Nomenclature [12]. Chromosomes were photographed, destained, and subsequently GTG-banded (G bands by trypsin using Giemsa) for evaluation. Histopathologically examined features were described for the two fetuses.

RESULTS

We checked the features of our two cases against the common features of trisomy 13 reported by Rios *et al.* [2] as shown in Table 2.

Case 1 was a pregnant woman, 27 years of age, who was referred to our laboratory because of a history of malformations detected by USG. The karyotype was 46,XX, rob t(13;13) and the baby girl lived for only 1 month after birth. The parent's karyotypes were normal.

Autopsy Findings. The female fetus at 24 weeks of gestation weighted 300 g and measured 32 cm crown-heel, 23 cm head circumference. The most striking anomaly was a single eye in the mid-forehead (cyclopia), in the face, there was no nasal aperture. Holoprosencephaly, proboscis, microphthalmia and heart septal defects were present in the newborn.

Table 1. The frequencies in amniocentesis and in live births

The Frequencies of (%):	Reference	47,+13	D/13 Translocations
Live births	[9]	8.84	3.53
Amniocentesis	Our laboratory results	0.162	0.04

Table 2. Common Features of Trisomy 13

General (in previous series)	Incidence (%)	Our Laboratory Results	
Clinical Features	Reference [2]	Case 1	Case 2
Antenatal Findings:			
• Polyhydramnios	15.0	–	–
• Oligohydramnios	10.0	–	–
• Growth restriction (mid-trimester)	–	–	–
Central Nervous System:			
• Holoprosencephaly	40.0-70.0	[+]	–
• Meningomyelocele	–	–	–
• Agenesis of the corpus collosum	19.9	–	–
• Enlarged cisterna magna	15.0	–	–
• Microcephaly (10th percentile)	58.7	–	–
• Sloping forehead	–	–	–
• Wide sagittal sutures and fontanelles	–	–	–
• Scalp defects in occipital area	–	–	–
Eyes:			
• Hypotelism: close-set eyes	–	–	–
• Hypertelism: wide-spaced eyes	–	–	[+]
• Microphthalmia: small globes	–	[+]	–
• Monophthalmia: single eye	–	–	–
• Synophthalmia: fused midline orbit	–	–	–
• Cyclops: refers to either monophthalmia or synophthalmia	–	–	–
• Anophthalmia: complete absence of ocular structures	–	–	–
• Coloboma of iris	35.5	–	[+]
• Retinal dysplasia	–	–	–
Nose:			
• Depressed and broad nasal formation	–	–	[+]
• Ceboccephaly: single, flat nostril	–	–	–
• Proboscis: absent or rudimentary nasal structures positioned above the orbit	–	[+]	–
• Arrhinencephaly: nasal malformations	–	–	–
Mouth:			
• Micrognathia	–	–	[+]
• Cleft lip and palate	45.0-68.0	–	[+]
Ears:			
• Low-set ears with abnormal helix	80.0	–	[+]
Extremities:			
• Polydactyly	50.0	–	[+] (feet)
• Rocker-bottom feet	–	–	–
• Overlapping fingers	44.4	–	–
• Extremities flexion	–	–	–
• Hyperconvex narrow fingernails	–	–	–
Associated Defects:			
• Congenital heart defects: ventral septal defect; hypoplastic left heart; double-outlet	10.0-20.0	[+]	–
• Right ventricle; endocardial cushion defects or dextrocardia	–	–	–
• Omphalocele	–	–	–
• Cystic hygroma	–	–	[+]
• Renal abnormalities: hydronephrosis; polycystic kidneys;	–	–	–
• hydrourter	–	–	–

The following conditions were not found in either study: skin (capillary hemangioma); tone (hypotonia/hypertonia); genitalia abnormalities (male: cryptorchidism, hypospadias, anomalous scrotum); (female: bicornuate uterus, duplicating system).

Figure 1. (a) Karyotype of the second case; (b) ideogram and G-banded images showing normal chromosome and translocation in chromosomes 13;13.

Case 2 was a pregnant women, 28 years of age, who was referred to our laboratory for prenatal diagnosis at 14 weeks gestational age due to the history of malformations detected by USG. Prenatal ultrasound scanning revealed cystic hygroma, hydrothorax and hyperechogenic kidneys. The karyotype was 46,XY, rob(13;13) (Figure 1a and 1b). The mother was induced to give birth after karyotype analyses were completed. The parent's karyotypes were normal. The aborted fetus was the first pregnancy of this mother and was examined histopathologically.

Autopsy Findings. The male fetus weighed 35.1 g and measured 13 cm crown-heel, 9 cm crown-rump, 8 cm head circumference and 1.1 cm foot length. There were cleft lip and cleft palate, and micrognathia of the face. There was postaxial polydactyly of the feet. There was also omphalocele. Histopathologically, the internal organs of the fetus were unremarkable.

DISCUSSION

Genetically unbalanced embryos usually miscarry. Most of the miscarriages occur in the first trimester as is true for all miscarriages, regardless of the cause [1]. The incidence of having a baby with this syndrome is in the range of 0.04-0.162% (unpublished data, our labo-

ratory results). Although our two cases had rob(13;13) in their karyotypes, the expression of several of the features often seen with trisomy 13 were different in these two cases. Due to the difference in chromosomal makeup seen in non disjunction vs. translocation, there may be differences in expression of several of the features often seen with trisomy 13 [2].

Bugge *et al.* [13] used 20 polymerase chain reaction (PCR)-based DNA polymorphisms to determine whether trisomy 13 due to *de novo* rea(13q;13q) in six cases is caused by translocation (13q;13q) or isochromosome (13q;13q), and to determine the parental origin of the rearrangements and the mechanisms of formation. They found that the six probands were three live born children with clinical features characteristic of Patau's syndrome and three fetuses diagnosed prenatally by amniocentesis for chorionic villus sampling (CVS). Five cases were isochromosomes with two identical q arms, one of maternal and four of paternal origin. Only one case was a Robertsonian translocation of maternal origin. On the cytogenetic level, it was not possible to distinguish an isochromosome i(13q) from a Robertsonian translocation of two homologous chromosomes 13. DNA studies of trisomy 21 due to *de novo* rea(21q;21q) have concluded that the majority is due to isochromosomes i(21q) and not translocations between two chromosomes 21 [14-17]. Similar

studies of trisomy 13 with *de novo* *rea*(13q;13q) have shown similar results, but the number of cases studied has been very limited [18-21]. Our cases of trisomy 13 due to *de novo* *rob*(13q;13q) were translocations on the cytogenetic level. We could not determine the parental origin and mechanisms of formation, and compare these findings with previously published cases.

Trisomy 13 remains a lethal disorder. The geneticist and/or genetic counselor can provide specifics on inheritance, recurrence risk, and the implications for further genetic testing of family members.

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