

CLINICAL CASE

Down's syndrome associated with a balanced Robertsonian translocation 13;14 maternally transmitted in the product of a twin diamniotic pregnancy

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ABSTRACT

Background. Robertsonian translocations involve the long arm of acrocentric chromosomes with chromosomes 13q;4q being predominantly involved. This defect can be transmitted along several generations, giving rise to chromosomally abnormal products with complete aneuploidy. It is unusual to observe this type of mutation associated with another chromosomal anomaly involving chromosome 21. The objective of this study was to describe the case of a newborn with Down's syndrome (regular trisomy 21) associated with a 13q;14q Robertsonian translocation.

Case report. We report the case of a newborn male who was the product of a twin pregnancy. At birth, the newborn demonstrated the following: absent Moro's reflex, brachicephaly, slanting ocular fissures, depressed nasal bridge, low-set ears, short neck, transverse palmar crease, clinodactyly of the fifth finger, undescended right testicle, and a heart murmur. Chromosomal study revealed 46,XY, t(13;14)(q10;q10), +21. Cytogenetic analysis of the family revealed in the mother (II-1) 45,XX, t(13;14)(q10;q10), the father (II-2) 46,XY; mother's uncle (II-3) 46,XY; the newborn's older sister (III-1) 46,XX; twin brother 45,XY, t(13;14)(q10;q10).

Conclusions. This was an unusual case of the association of Down's syndrome with a maternally transmitted balanced Robertsonian translocation of chromosome 13;14.

Key words: Down syndrome, Robertsonian translocation, chromosomal abnormalities, trisomy 21.

INTRODUCTION

Down syndrome, the most common form of mental retardation, is caused by a microscopically demonstrable chromosomal aberration and phenotypic changes and is characterized by distinctive and well-defined phenotypic changes. It is caused by the presence of an extra complete chromosome (trisomy) or of a critical portion of chromosome 21.¹

During meiosis or during postzygotic mitotic division, longitudinal division of the centromere and the separation of sister chromatids of each of the 23 pairs of chromosomes occurs, a process known as disjunction. However, there is the possibility that one or more chromosomes do not undergo the disjunction, leading to cells with extra chromosomes (trisomy) or missing chromosomes (monosomy), i.e., chromosomal aberrations in the number known as aneuploids.² Trisomy 21 is caused by the phenomenon of nondisjunction in which ~95% of patients have trisomy 21 (three copies of chromosome 21) and in 5% a copy of chromosome 21 is translocated to another acrocentric chromosome of group D (13-15) or G (21-22), i.e., an extra chromosome 21 is attached to any of the chromosomes of groups D and G. This phenomenon is known as Robertsonian translocation. The most common are those that occur on chromosome 14 (14,21) or chromosome 21 (21,21). From 2 to 4% of cases with trisomy 21 are due to mosaicism (the presence of more than one cell line) to cells with three copies of chromosome 21 or normal cells with two copies of chromosome 21.³⁻⁶ It is known that a third of these translocations are inherited. This has been

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proven in epidemiological studies performed between 1989 and 1993 in Great Britain.⁷

The majority of the balanced Robertsonian translocations involve the long arm of two acrocentric chromosomes. The most common is 13q,14q, which is transmitted over several generations and leads to chromosomal abnormalities with complete aneuploidy.⁷ The meiotic error involved in trisomy 21 occurs two times more frequently in females than in males.⁸

Studies such as the present one acquire importance due to the lack of information that exists regarding this genetic abnormality, both nationally and throughout Latin America. This study aims to report the case of a child with Down syndrome with regular trisomy 21 in which there coexists a balanced Robertsonian translocation 13q,14q.

Case Report

We present the case of a 5-day-old male (propositus III-2) (Figure 1) from the municipality of Centro, Tabasco, Mexico. The newborn was a twin product of the second gestation of nonconsanguineous parents. The mother was aged 37 years and the father was 46 years of age. There was no history of similar illness in other family members. Pregnancy duration was 35 weeks culminating in a cesarean section. There was no evidence of neonatal hypoxia. At birth, the parents were informed of the presence of dysmorphic data consistent with Down syndrome. On physical examination, weight of the newborn was 3050 g coinciding with percentile (P) 3. Length of the newborn was 51 cm (between P 10 and 25). Head circumference was 35 cm (between P 25 and 50). The following characteristics were noted: skin had a marble appearance, Moro reflex was absent, skull was brachycephalic with narrow forehead, oblique palpebral fissures to the outer edge tilted upward, epicanthus, flat nasal bridge (Figure 2), high arched palate, low-set ears, hypoplasia of the helix on both ears, short neck, hypertelorism of nipples, shortened hands and fingers, transverse palmar crease, clinodactyly of fifth finger, right unilateral cryptorchidism, unusual path between the first and second toes on plantar region of both feet, and precordial auscultation with cardiac murmur. Routine studies of blood count, blood chemistry and urinalysis were normal. Thyroid profile was normal and echocardiography resulted in tetralogy of Fallot with infundibular stenosis and severe pulmonary valve defect.

The karyotype in peripheral blood was reported as 46,XY,t(13;14)(q10,q10), +21 (Figure 3).

Because of the presence of Robertsonian translocation 13,14, other family members, parents (II-1 and II-2), a brother of the mother (II-3), and siblings of the patient (III-1 and III-3) were cytogenetically investigated. (Fi-

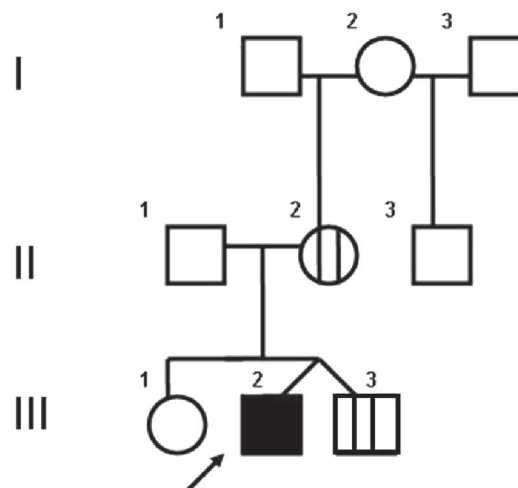


Figure 1. Family pedigree that represents the propositus (III-2), mother (II-2) and the twin counterpart of the propositus (III-3), carriers of a balanced translocation 13,14.



Figure 2. Characteristic facies, oblique palpebral fissures, epicanthus, flat nasal bridge, micrognathia.

gure 1). The results were as follows: the father showed a chromosomal complement 46,XY; the mother's brother, 46,XY; the older sister, 46,XX. The mother showed 45,XX t(13;14) (q10,q10) (Figure 4) and twin brother demonstrated 45,XY t(13;14) (q10,q10).

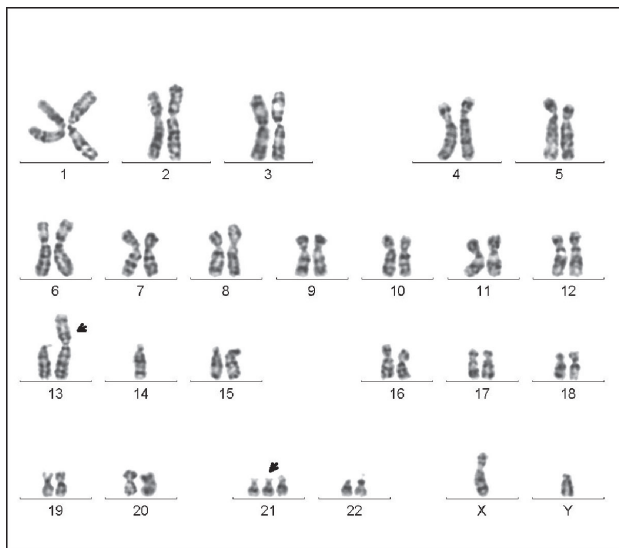


Figure 3. Metaphase and karyotype of the proband showing the chromosomal complement 46,XY, t(13-14) (q10,q10), +21.

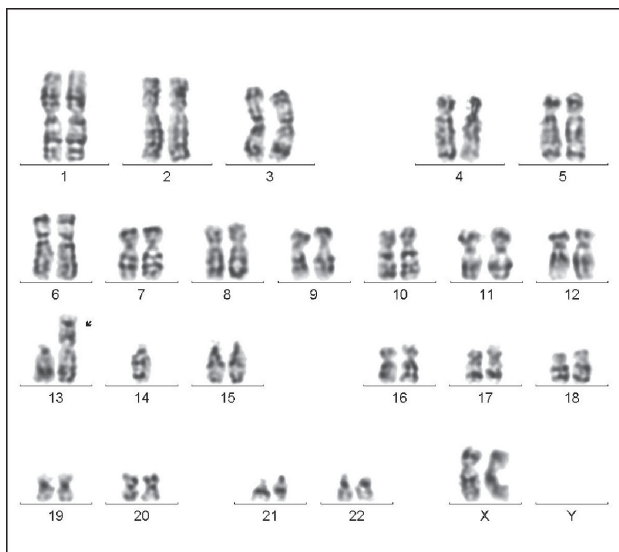


Figure 4. Metaphase and karyotype of the mother of the proband who is a carrier of a balanced Robertsonian translocation 13,14.

DISCUSSION

The basic defect in Down syndrome is related to a faulty distribution of chromosomes; therefore, all patients with this disorder have three copies of chromosome 21: regular trisomy 21, also called free or homogeneous 47,(XX or XY) +21, trisomy 21 by translocation 46,(XX or XY) der(14-21 or 21-21) or 21 by mosaic trisomy 47,XX XY +21/46,XX or XY.^{9,10} Segregation of chromosomes 14 and 21 from a carrier of balanced translocation occurs so that the translocated chromosome becomes the vector of the possibilities of separation of the genetic information of the chromosomes in the resulting gametes, thus determining different probabilities in the genotype of the descendants.^{4,5} In recent years the occurrence of cytogenetic abnormalities in different disorders, both malignant and those where mental retardation is a derived complication, has been noted. It has been able to identify 90% of chromosomal abnormalities with the improvement of cultivation techniques and methods of chromosomal banding.^{11,12}

The association between translocation 13,14 and Down syndrome is rare. Moraes et al.¹³ and Bandyopadhyay et al.¹⁴ in studies of morbidity and mortality in the first year of life in children with Down syndrome found that 93.3% of patients had regular trisomy 21 and 6.7% trisomy by 14,21 translocation. Leal et al. reported the case of a newborn girl with two distinct Robertsonian translocations: 14q;21q and 21q;21q.¹⁵ Iurov et al. described a rare case of Robertsonian translocation 13,14 of maternal origin combined with regular 21 trisomy 46,XX, der (13,14) (q10,q10) mat, +21, with Down syndrome phenotype.⁸ These same authors, from the molecular standpoint, demonstrated the extra chromosome 21 present in the patient's mother and argued that the nondisjunction of chromosome 21 occurred during the first meiotic division. Shaw et al. on studying ten patients with Robertsonian translocation found that 60% were de novo and 40% had paternal or maternal origin.¹⁶ Of de novo cases, chromosome 21 came from the mother in five cases, whereas only one was of paternal origin. The patient described in this report is the product of a twin pregnancy, which is an even rarer event.

Harris et al. studied four generations of a family affected by balanced Robertson translocation 13q,14q and found that the proband, in addition to having inherited translocation 13q,14q, also had regular trisomy

21.¹⁷ Scriven et al. in a diagnostic genetic study of preimplantation in 4/5 couples studied showed cytogenetic findings corresponding to balanced Robertsonian translocation 45,XX or XY der 13;14.¹⁸ In a review of 1223 cases with cytogenetic diagnosis of trisomy 21, Kovaleva et al. documented that 5.7% of cases with trisomy 21 corresponded to translocations between chromosomes of group D and G and that 0.5% of all patients had an association with other structural or numeric chromosomal abnormalities. In this review, these authors reported only one case with Down syndrome and Robertsonian translocation 13;14.¹⁹

In the present investigation we studied, from the cytogenetic point of view, two generations in which balanced Robertsonian translocation was found in the mother (II-2) and two of her male offspring (III-2 and III-3). The maternal grandparents of the propositus (I-1 and I-2) are alive but, due to the distance of their residence in northern Mexico, cytogenetic studies were not able to be performed (Figure 1).

For genetic counseling purposes, it should be taken into consideration that the carrier of a balanced Robertsonian translocation 13,14 is usually asymptomatic and, therefore, the offspring will have no pathological symptoms, provided that the chromosomal aberrations were inherited in a balanced manner. However, the following segregation possibilities can occur: 1) the offspring receives two normal chromosomes from each parent and is healthy; 2) the offspring of the parent carrier receives the two chromosomes involved in the translocation and from the other parent the two normal chromosomes, in which case the newborn will show the same chromosomal aberration of the balanced carrier parent; and 3) in each pregnancy there is a risk that the offspring may be born affected because the newborn may receive a normal chromosome from the affected parent and another chromosome with the translocation, whereas from the other parent the offspring receives the two normal chromosomes. Most products with these types of chromosomal abnormalities have gestational losses during the first trimester.²⁰⁻²³

We conclude that the case reported here corresponds to a child with Down syndrome who was the product of a twin pregnancy. In addition to the presence of regular trisomy 21, the newborn presented with a maternally transmitted Robertsonian translocation 13q,14q.

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