A complex three way translocation resulting in two sibs with partial trisomy 3p23→3pter

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SUMMARY A male infant with multiple congenital anomalies and psychomotor retardation was found to have a translocation resulting in partial trisomy for the distal part of chromosome 3p. An older sister with similar clinical findings had an identical karyotype. Chromosome studies in the phenotypically normal parents revealed a balanced translocation in the mother involving chromosomes 3, 11, and 18. An identical translocation was found in one of the normal children.

Partial trisomy 3p has been described in more than 20 patients.¹⁻¹⁶ The clinical findings in the various cases are quite consistent and were recently reviewed by Van Regemorter *et al*¹⁵ and Charrow *et al*.³ The most prominent clinical features common to most of the cases are microcephaly, frontal bossing, square face, hypertelorism, long philtrum, downturned corners of the mouth, micro- or retrognathia, congenital heart disease, genital abnormalities, and psychomotor retardation. The great majority of cases resulted from segregation of familial translocation mainly through the mother.

In this report we describe a brother and sister with trisomy 3p23→3pter. They inherited a derivative chromosome 11 segregating in the mother, who is a balanced carrier of a complex translocation: t(3;11;18)(p23;q25;q21·1). Four phenotypically normal sibs, five maternal aunts and uncles, and the maternal and paternal grandmothers were karyotyped. The significance of the clinical and cytogenetic findings will be discussed.

Family data

Fig 1 shows the pedigree of the family. The parents are second cousins of Arab Moslem origin. The father is 42 and the mother 34 years of age. The mother has had six pregnancies and four children are phenotypically normal and in good health. The two last pregnancies resulted in affected children who are presented in this report. The maternal grandparents were first cousins and had 11 children of whom three died as infants. There is no clinical information

concerning these infantile deaths. In addition they had three early abortions. The paternal grandparents were unrelated and had 12 children of whom 10 died as infants or young children. No detailed clinical data could be obtained concerning the dead children.

CASE 1

The proband (fig 2), an 11 month old male infant, was admitted for investigation of severe failure to thrive and recurrent respiratory infections.

The mother reported vaginal bleeding during the first trimester of pregnancy and had a normal home delivery at term, birth weight 2 kg. From the age of a few days he developed recurrent attacks of coughing, occasionally associated with cyanosis. He also required repeated admission to hospital for recurrent respiratory infections. Weight gain was extremely slow despite adequate caloric intake and there was no history of diarrhoea or vomiting. Severely delayed psychomotor development was manifested by poor head control and minimal spontaneous movement; he tried to reach out to grasp objects but did not attempt to roll over. Hearing and vision were normal and he recognised members of his family. It is worth noting that he had a very weak cry and did not bubble.

On admission he appeared small for his age: weight 6 kg (50th centile for 3·5 months); length 72 cm (50th centile for 11 months); head circumference 40·8 cm (50th centile for 4 months); anterior fontanelle 2 × 2 cm.

Special features noted were a flat occiput, frontal bossing, bilateral temporal wasting, hypertelorism square facies, epicanthus, long philtrum, large mouth with downturned corners, micrognathia, short neck

FIG 1 Pedigree of family.

FIG 2 Case 1 at 11 months of age.

with a very wide jugular notch, low set nipples with an accessory left nipple, early systolic murmur grade 2/6 at the left sternal border, liver 3 cm below the costal margin, spleen not palpable, one 2×4 cm café-au-lait spot beneath the right costal margin, micropenis, hypoplastic scrotum with small testes palpated in the inguinal canal, severe muscular hypoplasia and

FIG 3 Partial karyotypes of (a) the proband, (b) his sister (case 2), and (c) their mother.

hypotonia with brisk deep tendon reflexes, and hyperextensibility of the small joints of the hand.

Routine biochemistry and muscle enzymes (CK, LDH, aldolase) were within normal limits. Immunological screening, which included immunoglobulins and complement T and B cell number and function, was within normal limits. The bone age was compatible with 6 months of age. IVP was normal.

Cardiological investigations, including ECG, chest x-ray, echocardiography, Tc⁹⁹ angiography, and cardiac catheterisation, showed an atrial septal defect with bidirectional shunt and buckling of the innominate artery. (Detailed cardiological description will be published separately.) EEG showed bilateral frontal flattening, no asymmetry, and no paroxysmal activity. CT scan showed mild dilation of ventricles and cisterns.

Following the period of investigation the child was discharged to his home and has remained under our surveillance, his clinical condition remaining stable.

CASE 2

The sister of the proband, aged 2 years and 8 months, was born following a normal pregnancy, birth weight 3.5 kg (mother's report). Her phenotype very much resembled that of her brother. Weight gain was fair (11 kg, 50th centile for 19 months), head circumference 44.5 cm (50th centile for 10 months), length 91 cm (50th centile for 30 months). Psychomotor development was delayed; she was not yet walking unaided or speaking but she understood simple commands. On physical examination she also had one 3 × 5 cm café-au-lait spot on the buttock and hyperextensibility of the small joints of the hands.

FIG 4 Full karyotype of the mother carrying the complex translocation $t(3;11;18)$.

The main physical finding which differed from her brother was the absence of a cardiac abnormality, although right ventricular predominance and dilation were demonstrated on ECG and echocardiography.

Materials and methods

Chromosome preparations were made from conventional phytohaemagglutinin stimulated cultures of whole blood. Prometaphase chromosomes were obtained according to the methotrexate-thymidine synchronisation method.¹⁷

Skin fibroblasts were grown in F10 medium (GIBCO) supplemented with 20% fetal bovine serum (GIBCO). Chromosome preparations were made 48 hours after trypsinisation of the fibroblasts. The metaphases were G banded following a modified trypsin-Giemsa banding procedure.¹⁸

Cytogenetic findings

In the proband (case 1) and his sister (case 2) over 20 metaphases were scored in peripheral blood lymphocytes and 46 chromosomes were found in all cells. One abnormal chromosome 11q+ was observed in each cell (fig 3). The additional segment on chromosome 11 seemed to consist of the distal region of 3p, namely 3p23→3pter. In order to identify the origin of the additional segment, the parental chromosomes were studied.

The mother's cells revealed a three way translocation in which chromosomes 3, 11, and 18 were involved (fig 4). Our interpretation of this translocation was: one break in 3p23, one break in chromosome 11q25, and one break at 18q21·1. The detailed designation of this karyotype following the ISCN (1978) convention is 46,XX,t(3;11;18) (p23;q25;q21·1) (3qter → 3p23::18q21·1 → 18qter;11pter → 11q25::3p23 → 3pter;18pter → 18q21·1::11q25 → qter). Thus, the abnormal chromosome 11 segregated twice to gametes that on fertilisation gave rise to case 1 and case 2, whose karyotype is 46,XX(or XY), der 11,t(3;11;18)(p23;q25;q21·1) mat.

All other family members that have been studied were found to have normal karyotypes (see fig 1). Only one child (V.2) was a balanced carrier like the mother. The fact that the parents are second cousins and that the paternal grandparents have only two healthy children out of 12 pregnancies raised the possibility that the translocation is segregating in the family. However, the data suggest a *de novo* translocation in the mother. The fact that both grandfathers are dead excludes a final conclusion.

The same translocation was also present in the skin fibroblasts of the proband and his mother.

Discussion

The family described in this paper has two interesting aspects. The first is the partial trisomy for 3p in two sibs, resulting from malsegregation of a maternal translocation. Recently, at least three reviews of partial 3p trisomies have been published^{3 13 15} and we see no special need for an additional review. The clinical findings in both our cases seem to correspond very well to the documented cases. It is as yet not possible to classify the various cases according to the specific breakpoint in 3p. The breakpoint in our translocation was 3p23 and caused similar abnormalities to more proximal breakpoints. Monteiro and Ferrari⁵ give a detailed table summarising the clinical characteristics of partial 3p trisomy. Most of the features delineated in that table were found in our cases as well. We cannot comment on the preponderance of males in the reported cases, as we have one male and one female who seem to show the same degree of severity of symptoms. It has been suggested¹⁵ that there is a preponderance of males because of lethality of trisomy 3p in females. We cannot support this notion. de Grouchy and Turleau¹⁹ noted that life expectancy is short. Both our cases have already survived for over a year. Several other cases have been reported, the oldest being 11 years.¹⁶ Thus, it seems that more cases are needed before general conclusions can be drawn for use in genetic counselling.

The two balanced carriers of the complex translocation are healthy and normal and show no visible phenotypic abnormalities.

The second aspect posed by our family is the cytogenetic one. A complex three way translocation involving chromosomes 3, 11, and 18 is described. The mother who carries the translocation had six pregnancies and no known abortions were recorded. There are gaps of 4 and 5 years respectively between the third and fourth and fifth and sixth pregnancies. These gaps might indicate some degree of infertility, as no use of contraceptives was reported. Another observation worth mentioning is the fact that the two unbalanced children are the latest pregnancies. Whether this means decreased embryonic selection with increasing age, as suggested by Ayme and Lippman-Hand,²⁰ or just a random chance event is difficult to assess.

In spite of the complex translocation carried by the mother, four out of six pregnancies gave rise to normal or balanced carrier offspring. Fig 5 shows a suggested pachytene orientation in meiosis for the chromosomes involved in the translocation.

The table lists the expected gametes resulting from 3:3 meiotic segregation in the postulated pachytene sextavalent. Four different disjunctions will give rise

FIG 5 Pachytene orientation in meiosis of the three chromosome pairs involved in the complex translocation.

TABLE Expected karyotypes and phenotypes resulting from 3:3 disjunction of the pachytene sextavalent.

Partial karyotype of gamete	Expected zygote after fertilisation with normal paternal gamete	Phenotype
1 a b c	Normal	Normal
2 a' b' c'	Balanced carrier	Normal
3 a' b' c	Partial trisomy 18q Partial monosomy 3p	Lethal
4 a b' c'	Partial trisomy 3p Partial monosomy 18q	Lethal
5 a' b' c	Partial trisomy 18q Partial monosomy 11q	Abnormal, viable
6 a b c'	Partial trisomy 11q Partial monosomy 18q	Abnormal, viable
7 a b' c	Partial trisomy 3p Partial monosomy 11q	Abnormal, viable
8 a' b' c'	Partial trisomy 11q Partial monosomy 3q	Probably lethal

to eight types of gametes, of which only two will give rise to normal viable zygotes, and half of those will be balanced carriers (as found in the mother and in V.2).

The two abnormal children represent gamete No 7. Gamete No 5, which gives rise to partial trisomy 18 and monosomy 11q25, is expected to be viable if one considers that full trisomy 18 comes to term. The monosomy 11q25 is not expected to be lethal, as the two patients in the family should be monosomic for that segment as well. Similar consideration applies to gamete No 6, as monosomy 18q has been described in several cases. To the best of our knowledge no monosomy 3p has been described.

There are many more possible disjunctions resulting from 5:1 and 4:2 segregations. We consider it unnecessary to depict all these possibilities as it would be a purely academic exercise.

It would be of interest to know whether a male carrier of such a translocation would be fertile. It is known that impairment of meiosis varies between male and female carriers.²¹ If the translocation in the mother was not de novo, it could have been

inherited only through her fertile father. This together with the absence of any translocation carrier in the mother's sibships, seems to indicate a de novo event in a parental gamete or in the early zygote giving rise to the mother. It seems that one event has caused the three breaks giving rise to the complex translocation.

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