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DISTAL 14q TRISOMY SYNDROME IN TWO SIBLINGS: FURTHER DELINEATION OF ITS PHENOTYPE

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Summary We describe two siblings with distal 14q trisomy resulting from a maternal translocation t(5;14)(p15.33;q31.2): a male newborn infant who died at the age of 1 month and a prenatally diagnosed male fetus. They showed almost identical phenotypic abnormalities. Review of the literature suggests the occurrence of a distal 14q trisomy syndrome, which is clinically characterized by mental retardation, growth failure, frontal bossing, facial asymmetry, hypertelorism, sparse eyebrows and eyelashes, short prominent nose, cupid bow upperlip, micrognathia, and low-set and posteriorly rotated ears. It seems likely that triplication of the segment 14q32.1 → qter is critical for clinical manifestation of this syndrome.

Key Words chromosome 5, chromosome 14, distal 14q trisomy syndrome, prenatal diagnosis

INTRODUCTION

Distal trisomy 14q is less frequently seen than proximal 14q trisomy, which has been established as a distinct clinical entity (de Grouchy and Turleau, 1984). At least 19 cases with distal 14q trisomy have been reported so far. Although delineation of a distal 14q trisomy syndrome has been attempted (Turleau *et al.*, 1983; Sklower *et al.*, 1984), it still remains open whether or not a distal 14q trisomy is associated with a well-defined clinical syndrome. In this paper, we describe two additional siblings with distal 14q trisomy resulting from a maternal translocation t(5;14)(p15.33;q31.2). Comparison of the clinical features of the present cases with those of the previously reported cases indicates that distal 14q trisomy is a clinically recognizable syndrome.

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CASE REPORTS

Case 1. The patient, a male newborn infant, was the first child of healthy nonconsanguineous parents. The mother and father were 28 and 32 years old, respectively, at the time of the child's birth. There was no family history of spontaneous abortions, mental retardation or congenital anomalies. He was delivered by caesarean section at the 35th gestational week because of placenta previa. The birth weight was 1,495 g, and the body length was 38.5 cm. The Apgar scores were both 8 at 1 and 5 min of age. Physical examination showed a preterm, small-for-dates baby with various phenotypic abnormalities. He had an odd facial appearance, consisting of facial asymmetry (right-sided hypotrophy), frontal bossing, hypertelorism, cloudy left cornea, narrow right palpebral fissure, sparse eyebrows and eyelashes, short prominent nose, cupid bow upperlip, and micrognathia (Fig. 1). The ears were low-set and malformed, with prominent antihelices and atresia of both external auditory canals. There was pigeon breast, overlapping of fingers, clinodactyly of the 5th fingers, and prominent calcaneus. A small penis and severe muscular hypotonia were also noticed. Laboratory investigations including complete blood count, blood biochemistry and urinalysis yielded normal results. The baby failed to thrive and died of septicemia at the age of 1 month. Autopsy showed thymic hypoplasia and a patent foramen ovale but no other internal malformations.

Case 2. The mother became pregnant one and a half years after the death of case 1. Amniocentesis was carried out at the 17th gestational week, and chromosome analysis of an amniotic cell culture revealed an unbalanced chromosomal abnormality. The parents elected to terminate the pregnancy. This male fetus was

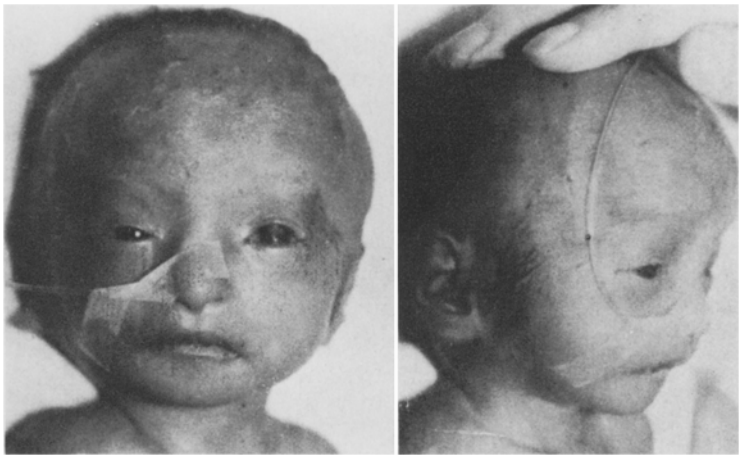


Fig. 1. Case 1 at the age of one month.

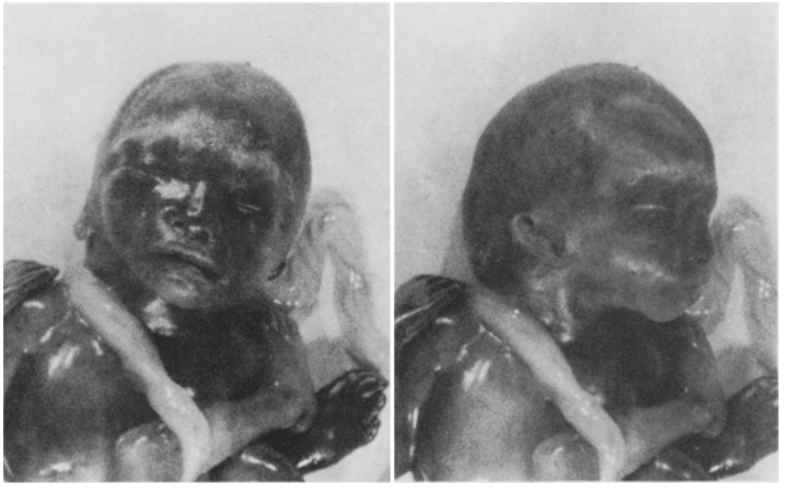


Fig. 2. Case 2 aborted at the 20th gestational week.

aborted at the 20th gestational week by prostaglandin induction. The crown-to-heel length was 23.8 cm, and the weight was 194 g. The phenotypic features were similar to those of case 1 except for absence of corneal opacity and atresia of the external auditory canals (Fig. 2). On the other hand, right pes equinovarus was seen in this fetal case. Autopsy did not show any internal malformation.

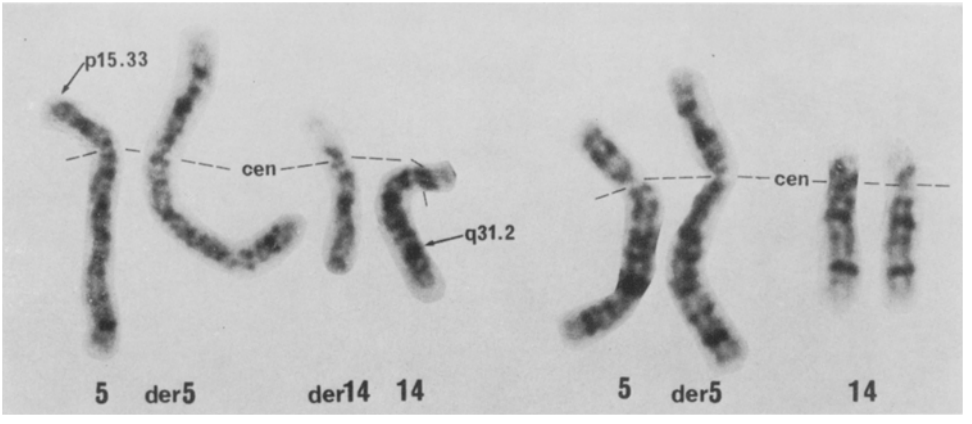
CYTOGENETIC FINDINGS

Cytogenetic analysis was performed on cultured peripheral blood lymphocytes of case 1 and the parents and on cultured amniotic cells and skin fibroblasts of case 2. Chromosomes were stained by GTG-banding. Prophasic cells in lymphocyte cultures were collected according to the method of Ikeuchi and Sasaki (1979).

Chromosome analysis of case 1 showed an extra amount of chromosome material on the short arm of chromosome 5. The father had normal chromosomes, while the mother was found to be carrying a balanced reciprocal translocation between chromosomes 5 and 14. The high-resolution banding study revealed the breakpoints at 5p15.33 and 14q31.2 (Fig. 3). The same karyotypic abnormality as seen in case 1 was detected in the cultured amniotic cells of case 2. This abnormality was subsequently confirmed on the fibroblast culture obtained from the skin of the aborted fetus. Karyotypes of both cases were designated as 46,XY,−5, +der(5),t(5;14)(p15.33;q31.2)mat.

DISCUSSION

The present cases had trisomy for 14q31.2→qter derived from an adjacent I segregation of the maternal reciprocal translocation, t(5;14)(p15.33;q31.2). Since



(A) (B)

Fig. 3. Partial karyotypes of the mother (A) and the case 2 (B). Arrows indicate breakpoints of the translocation.

the breakpoint is located in the terminal band of the short arm of chromosome 5, monosomy for 5p is negligible. Clinical features of the two cases were distinct and resembled each other. The phenotypic discordance in certain features between the two cases may be accounted for by the development of such abnormalities in late fetal life or the difficulty in assessing them in a mid-trimester fetus. As far as we are aware, our case 2 seems to be the second example of distal 14q trisomy which was diagnosed prenatally (Wahlström, 1974).

The majority of the previously reported cases with distal 14q trisomy resulted from parental balanced translocations or pericentric inversions. Four cases occurred *de novo*: a tandem duplication in 3 cases (Nikolis *et al.*, 1983; Orye *et al.*, 1983; Carr *et al.*, 1987) and an unbalanced translocation of the distal 14q segment onto the short arm of chromosome 10 in one case (Bridgman and Butler, 1980). Trisomic segments of the reported cases were varied, ranging from q22→qter to q32→qter. To make specific karyotype-phenotype comparisons on the basis of length of 14q, these cases were divided into three groups: 5 cases with trisomy for 14q22 or q23→qter (Pfeiffer *et al.*, 1973; Fryns *et al.*, 1977; Bridgman and Butler, 1980; Georgmaneanu *et al.*, 1981; Cohen *et al.*, 1983), 9 cases with trisomy for 14q24→qter (Wyandt *et al.*, 1977; Atkins and Patil, 1983; Nikolis *et al.*, 1983; Orye *et al.*, 1983; Romain *et al.*, 1983; Kaiser *et al.*, 1984; Markkanen *et al.*, 1984; Sklower *et al.*, 1984; Mikelsaar *et al.*, 1987), and 5 cases with trisomy for 14q31 or q32→qter (Trunca and Opitz, 1977; Turleau *et al.*, 1983; Sklower *et al.*, 1984; Carr *et al.*, 1987).

Clinical features of the three groups are summarized in Table 1. Intriguingly, the three groups have similar phenotypic features, except for incidence of early infant death and congenital heart disease. Common clinical features are growth retardation, mental retardation, microcephaly, facial asymmetry (this may be overlooked in many cases), frontal bossing, hypertelorism, sparse eyebrows and eyelashes, cupid

Table 1. Summary of clinical features of the distal 14q trisomy syndrome.

Trisomic segment (number of cases)	q22 or23→qter (n = 5)	q24→qter (n = 9)	q31 or 32→qter (n = 5)	Present cases 1	2	Total
Early infant death	60 % (3/5)	33 % (3/9)	0 % (0/5)	+	?	35 % (7/20)
Low birthweight	80 % (4/5)	67 % (6/9)	75 % (3/4)	+	?	74 % (14/19)
Growth retardation	80 % (4/5)	100 % (8/8)	100 % (5/5)	+	?	95 % (18/19)
Mental retardation	100 % (3/3)	100 % (7/7)	100 % (5/5)	?	?	100 % (15/15)
Hypotonia	75 % (3/4)	63 % (5/8)	75 % (3/4)	+	?	71 % (12/17)
Microcephaly	100 % (3/3)	66 % (4/7)	100 % (4/4)	?	?	79 % (11/14)
Facial asymmetry	100 % (3/3)	--- (0/0)	100 % (2/2)	+	+	100 % (7/7)
Frontal bossing	50 % (2/4)	75 % (6/8)	100 % (2/2)	+	+	75 % (12/16)
Hypertelorism	80 % (4/5)	88 % (7/8)	100 % (5/5)	+	+	95 % (19/20)
Sparse eyebrows and -lashes	--- (0/0)	100 % (4/4)	100 % (4/4)	+	?	100 % (9/9)
Prominent nose	67 % (2/3)	50 % (4/8)	75 % (3/4)	+	+	65 % (11/17)
Cupid bow upperlip	75 % (3/4)	100 % (9/9)	100 % (4/4)	+	+	95 % (18/19)
Micrognathia	100 % (3/3)	100 % (9/9)	80 % (4/5)	+	+	95 % (18/19)
Low-set and posteriorly rotated ears	100 % (4/4)	75 % (6/8)	100 % (5/5)	+	+	89 % (17/19)
Congenital heart disease	60 % (3/5)	25 % (2/8)	0 % (0/4)	+	-	32 % (6/19)
Ocular abnormalities	60 % (3/5)	78 % (7/9)	50 % (1/2)	+	?	71 % (12/17)
Finger and/or toe abnormalities	50 % (2/4)	75 % (6/8)	67 % (2/3)	+	+	71 % (12/17)
Genitourinary abnormalities	60 % (3/5)	43 % (3/7)	33 % (1/3)	+	+	53 % (9/17)

bow upperlip, micrognathia, and ear malformations. Although several of these are nonspecific features commonly seen in various chromosome aberrations, those such as facial asymmetry, sparse eyebrows and eyelashes, and cupid bow upperlip are rarely seen in other chromosomal syndromes (de Grouchy and Turleau, 1984; Schinzel, 1984). The constellation of such features permits us to recognize the distal 14q trisomy on a clinical basis alone. The full picture of the distal 14q trisomy syndrome in a case with trisomy for 14q32.1→qter (Turleau *et al.*, 1983) suggests that the triplication of the segment 14q32.2→qter suffices to cause the syndrome.

Finally, it should be noted that cases with 14 trisomy mosaicism have many clinical features in common with those of the distal 14q trisomy syndrome but not with those of the proximal 14q trisomy syndrome (de Grouchy and Turleau, 1984). We believe that 'epistasis' of genetic materials in the distal 14q segment over those in the proximal 14q segment may be operating in clinical manifestation of the 14 trisomy mosaicism.

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