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PARTIAL TRISOMIES 9 AND 4 RESULTING FROM MATERNAL TRANSLOCATION t(4; 9) (q25?; q13)

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Summary A female infant of partial trisomies 9 and 4 resulting from a maternal balanced translocation was described. The karyotype was designated as 47,XX,+der(9),t(4; 9) (q25?; q13)mat. Her phenotype was in accordance with the trisomy 9p syndrome, but the mental retardation and malformation pattern seemed much more pronounced. Moreover, she showed slowly progressive hydrocephaly, an unusual finding either in trisomy 9p or in partial trisomy 4q. A possible relationship of trisomy for 9q11→9q13 to the appearance of hydrocephaly was suggested. The cytogenetic findings in the present case provided a further evidence that the involvement of a chromosome 9 in reciprocal translocations may predispose to 3 : 1 meiotic disjunction.

INTRODUCTION

Since Rethoré *et al.* (1970, 1973) reported cases of trisomy for the short arm of chromosome 9 as a clinical syndrome, a large number of cases with this syndrome have been described in the literature. This syndrome, however, is cytogenetically a heterogenous entity, consisting of at least 5 types of trisomy 9p (Lurie *et al.*, 1976). About two thirds of the cases showed trisomy 9p associated with partial trisomy or monosomy for another chromosome, which is the result of unbalanced 2 : 2 or 3 : 1 disjunction of familial translocations. The associated segment in trisomy or monosomy is usually small or genetically inert to produce few or no phenotypic effects. The present paper describes a case of partial trisomies 9 and 4 resulting from a maternal translocation t(4; 9) (q25?; q13). The patient exhibited some malformations that could be ascribed to the partial trisomy 4, in addition to the cardinal features of the trisomy 9p syndrome.

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CASE REPORT

The patient, a 4-month-old female, was referred to us for evaluation of delayed development and unusual appearance. She was the product of the first pregnancy of a 36-year-old mother and an unrelated 31-year-old father. Family history was not contributory. The pregnancy was complicated by threatened abortion in the first trimester and crural edema in the last trimester. The delivery was made at term through cesarean section because of breech presentation and early rupture of the fetal membrane. The birth weight was 1,990 g, length 43.0 cm, and head circumference 30.0 cm. Apgar scores were 7 at 1 min. In the first week of life, indirect hyperbilirubinemia was treated with phototherapy. There was sucking difficulty with a poor weight gain, and she was subjected to repeated tube feedings.

Physical examinations at 4 months of age revealed that the body weight was 4,550 g, length 51.3 cm, and head circumference 32.5 cm. The craniofacial features of the patient included microcephaly; small and deeply set eyes with hypertelorism, narrow palpebral fissures, and antimongoloid slants; globulous nasal tip; micrognathia; downturned corners of the mouth; and low-set and protruding ears with deformed helices and antihelices (Fig. 1). Other abnormalities noticed were short neck with redundant nuchal skin folds; small umbilical hernia; sacral dimple; congenital dislocation of the left hip joint; small hands and feet with hypoplastic fingers and toes; proximally inserted thumbs; clinodactyly of the fingers *V*; dysplastic nails; talipes calcaneovalgus; and severe hypotonia. Ophthalmologic examination showed normal fundi and persistent pupillary membranes. No cardiac murmurs or abnormal heart sounds were heard.

The subsequent clinical course of the infant was marked by an episode with acute urinary tract infection at 5 months of age. Her somatic growth was slow. At 12 months, the body weight was 8,400 g, length 66.4 cm, and head circumference 42.5 cm. When last seen at 15 months, she remained to be a poor feeder, and still underwent tube feedings. The anterior fontanel was found to be widely open (5×5 cm). Profound psychomotor retardation was also present: she could not yet hold her head or show any definite reaction to her surroundings.

Full laboratory investigations were carried out at 12 months of age. X-ray examinations of the extremities showed bilateral hypoplasia of the middle phalanges of fingers V and the distal phalanges of all fingers and toes I and II; absence of the middle and distal phalanges of toes III, IV, and V; and two small ossification centers on the wrist. On the plain skull X-ray, there was platybasia and increased digital impressions over the parietal regions. Cranial computerized tomography revealed remarkable enlargement of the lateral and 3rd ventricles (Fig. 2). Radioisotope cisternography indicated that cerebrospinal fluid flow was almost intact, and a diagnosis of slowly progressive hydrocephaly was made. Intravenous pyelography disclosed a horseshoe kidney with normal ureteropelvic system. Chest roentgenogram and electrocardiogram were found to be normal.

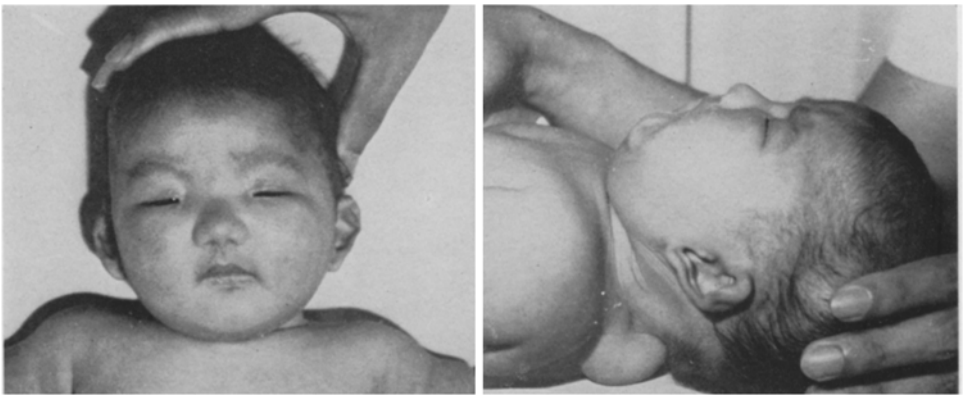


Fig. 1. The appearance of the patient at the age of 4 months.

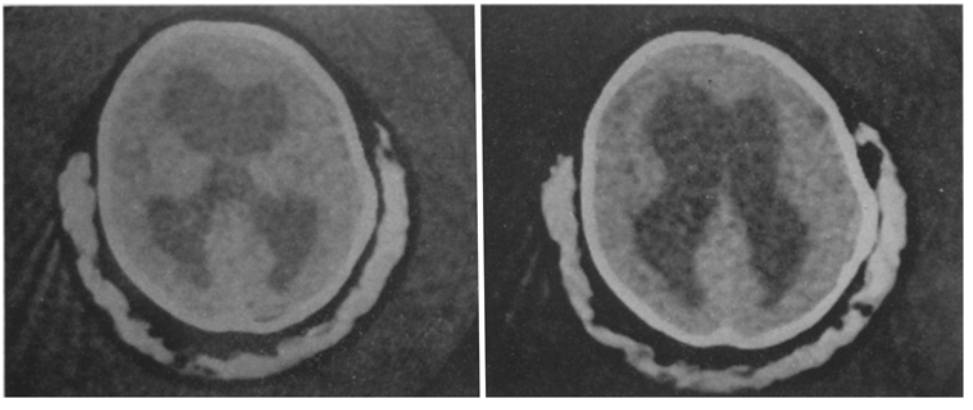


Fig. 2. CT scan of the patient, showing remarkable enlargement of the lateral and 3rd ventricles.

DERMATOGLYPHIC FINDINGS

The patient showed unusual dermatoglyphic findings. There were ten arches on the fingertips. Digital triradii b, c and d were absent on each palm. Both axial triradii were distally displaced (t″). The triradii a terminated at 1, and the t″ at 11 and 5′. A single flexion fold was observed on the fingers V. There was no simian crease on the palms or patterns on the thenar/I areas. Tibial arches were present on the hallucal areas. Dermatoglyphic findings of the parents were not remarkable.

CYTOGENETIC FINDINGS

Chromosome analysis using GTG, RHG and CBG was performed on meta-

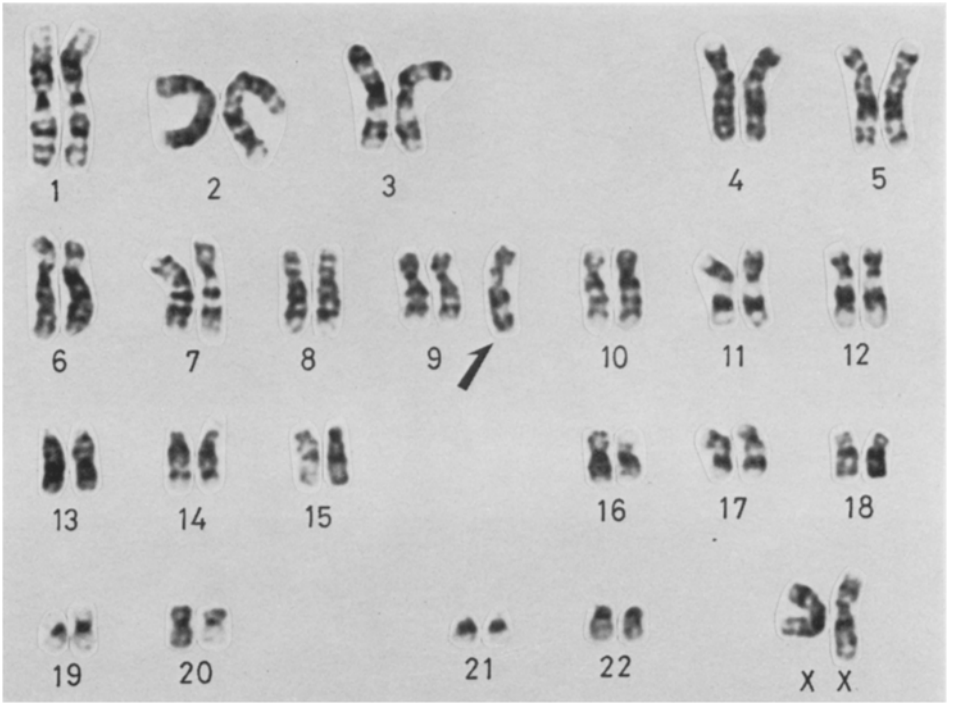
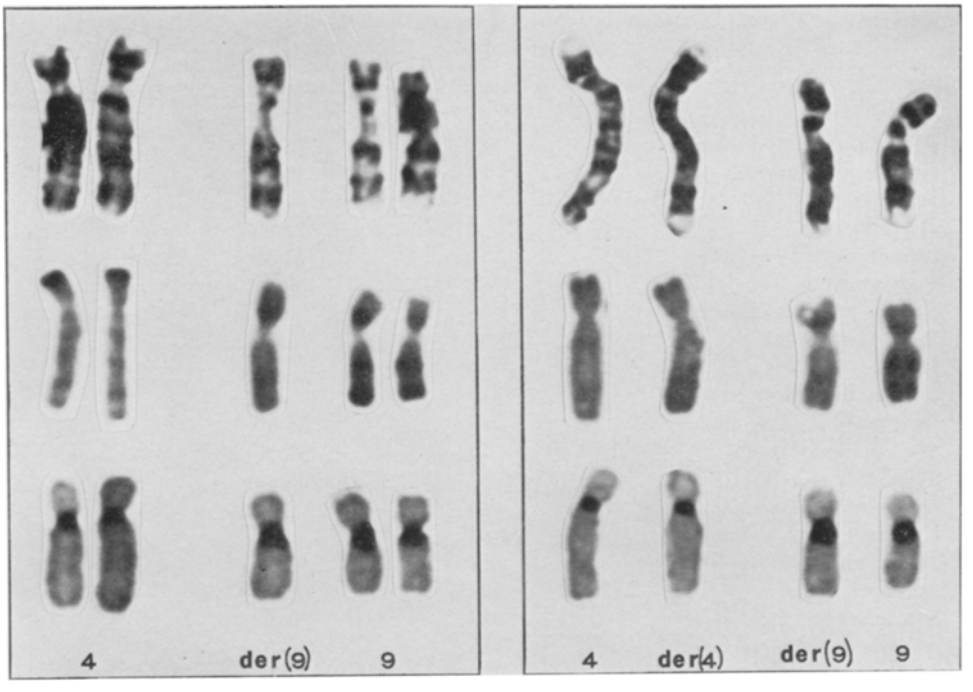


Fig. 3. Complete karyotype of the patient (G-banding). The arrow indicates the extra chromosome.

phases obtained from short-term lymphocytes cultures. The patient had a 47,XX chromosome constitution, in which a C-group-like chromosome was always additionally present (Fig. 3). Banding studies revealed that the short arm and the proximal portion of the long arm of the extra chromosome appeared to be equivalent to the short arm and constitutive heterochromatin of chromosome 9 (Fig. 4A). The banding karyotype of the father showed normal chromosomes. The mother, on the other hand, was found to carry a balanced translocation between the long arms of chromosomes 4 and 9. The breakpoints appeared to occur at bands 4q25 and 9q13 (Fig. 4B). The interpretation of the former breakpoint, however, was not conclusive in view of inadequate banding resolution of the 4q2 region. We believed that the rearranged chromosome 9 along with the normal homologue of the mother were transmitted to the patient. The karyotype of the patient was, therefore, designated as 47,XX,+der(9),t(4; 9) (q25?; q13)mat. She was in fact trisomic for both 9pter→9q13 and 4q25?→4qter.

DISCUSSION

Trisomy 9p is a well-defined clinical syndrome, which is characterized by the



A B

Fig. 4. Partial karyotypes of the patient (A) and mother (B). G-banding (top), R-banding (middle), and C-banding (bottom).

common occurrence of moderate mental retardation, unique dysmorphism of the face and hands, and dermatoglyphic abnormalities. The clinical picture of trisomy 9p remains unvaried even with the addition of 9q1 region to the trisomy, but once 9q2 or q3 region is involved, various internal malformations appear (Sutherland *et al.*, 1976). Partial trisomy 4q, though being associated with a number of phenotypic abnormalities, does not seem to represent any distinct clinical entities (Stella *et al.*, 1979; Fryns and van den Berghe 1980). Clinical features found in trisomy 9p or in partial trisomy 4q were summarized in Table 1. The phenotype of the patient was in accordance with the trisomy 9p syndrome, but her mental retardation and malformation pattern seemed much more pronounced than usual for this syndrome. It appeared that the associated trisomy for the distal 4q segment have contributed to these phenotypic modifications. Clinical features that could be ascribed to the partial trisomy 4q included narrow palpebral fissures, thumb abnormality, urinary tract malformation, skeletal anomalies, and umbilical hernia.

Another prominent finding of the patient was the presence of gross cerebral malformation, which was probably related to the profound mental retardation. The absence of central nervous system malformations is a rule either for partial trisomy 4q or for trisomy 9p. This kind of malformation, however, occurs frequently when

Table 1. Clinical features of the patient compared with reported cases of the trisomy 9p syndrome or of partial trisomy 4q.

	Trisomy 9p syndrome[a]	Partial trisomy 4q[b]	Present case
Psychomotor retardation	>80%	>80%	+
Growth retardation	>80	50-80	+
Microcephaly	>80	50-80	+
Hypertelorism	>80	50-80	+
Antimongoloid eye slant	>80	30-50	+
Enophthalmos	>80	30-50	+
Narrow palpebral fissures	<10	30-50	+
Wide nasal bridge	10-30	50-80	−
Globulous nose	>80	<10	+
Low-set or malformed ears	>80	>80	+
Downward slanting mouth	>80	30-50	+
Micrognathia	<10	30-50	+
Short neck	10-30	50-80	+
Hypoplasia of some phalanges	>80	<10	+
Clinodactyly of 5th fingers	>80	none	+
Thumb abnormalities	<10	50-80	+
Nail dysplasia	>80	none	+
Simian crease	>80	50-80	−
Absence or fusion of b and c triradii	>80	<10	+
Abnormal flexion folds of the digits	30-50	<10	+
Urinary tract malformations	<10	50-80	+
Congenital heart disease	<10	30-50	−
Congenital hip dislocation	<10	10-30	+
Umbilical hernia	<10	10-30	+
Cerebral malformations	<10	none	+
Cryptorchidism in males	<10	>80	/
Low birth weight	10-30	30-50	+

[a] This also includes cases of trisomy for 9pter→9q13.
[b] Findings are based on the review by Stella *et al.* (1979).

an individual is trisomic not only for the whole short arm but also for some regions of the long arm of chromosome 9. Indeed, 6 such cases have been documented in the literature. Cytogenetically, their breakpoints were at 9q13 (Dinno *et al.*, 1974; Gripenberg *et al.*, 1977), 9q21 (Baccichetti *et al.*, 1979), 9q22 (Howard-Peebles *et al.*, 1977), 9q24 (Schwanitz *et al.*, 1974), or 9q32 (Sutherland *et al.*, 1976). It is generally recognized that mental retardation in trisomy 9q− is much deeper than in trisomy 9p. This, together with the exclusive occurrence of brain malformations in trisomy 9q−, would suggest that triplication of certain regions of the long arm of chromosome 9 may have detrimental influences on the organogenesis of the central nervous system. Interestingly, 4 out of the 6 cases showed hydrocephaly (Dinno *et al.*, 1974; Schwanitz *et al.*, 1974; Howard-Peebles *et al.*, 1977: Baccichetti *et al.*, 1979). It would be, therefore, tempting to suppose that trisomy for 9q11→9q13 may be causally related to the appearance of hydrocephaly.

The abnormal karyotype of the patient was the result of meiotic 3 : 1 segregation of the maternal translocation. According to Lindenbaum and Bobrow (1975), 3 : 1 disjunction is rare and represents 6–25% of the total chromosomal imbalances caused by reciprocal translocations. There is increasing evidence to suggest that the involvement of an acrocentric chromosome or a chromosome 9 in the translocations predisposes to 3 : 1 disjunction (Jalbert and Sele, 1979). As far as we know, tertiary trisomy 9p or 9q− has been described in 20 families with reciprocal translocations. Eight cases out of them resulted from translocations between an acrocentric and a chromosome 9 (Rethoré *et al.*, 1973; Podruch and Weisskopf, 1974; Turleau *et al.*, 1974; Balicek *et al.*, 1975; Philippe *et al.*, 1975; Abe *et al.*, 1976; Lewandowski *et al.*, 1976; Habedank and Faust, 1978), and the remaining 12 cases had translocations between a nonacrocentric chromosome and a chromosome 9 (Rott *et al.*, 1971; Rethoré *et al.*, 1973; Rethoré *et al.*, 1974; Schwanitz *et al.*, 1974; Centerwall *et al.*, 1975; Lindenbaum and Bobrow, 1975; Mason *et al.*, 1975; Penchaszadeh and Coco, 1975; Stoll *et al.*, 1975; Sutherland *et al.*, 1976; Moirot *et al.*, 1977; Neu *et al.*, 1979). In the latter group, it should be noted that the following three features were shared by all of the cases: (1) the 3 : 1 disjunction was derived from a maternal translocation; (2) no unbalanced offspring due to 2 : 2 segregation have been ascertained in the same family; and (3) the derivative chromosome 9, which was always shorter than the other translocation chromosome, had a breakpoint on its long arms and retained more or less the heterochromatic region (9qh). This would lead us to suppose either that during oogenesis or in the early stage of pregnancy a selection factor may be operating to eliminate unbalanced gametes or conceptuses due to 2 : 2 segregation, or that the specific structural rearrangement of a chromosome 9 in reciprocal translocations may affect meiotic paring and favor 3 : 1 disjunction.

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