Partial trisomy D: a diagnostic and cytogenetic dilemma*

Summary. An 18-month-old proposita with psychomotor retardation and other congenital abnormalities is presented. Chromosomal analysis of both parents proved normal. However, the karyotype of the proposita contained 47 chromosomes in both lymphocytes and cultured fibroblasts. The marker chromosome proved to be a deleted No. 14 or 15. Comparison of the reported cases of partial trisomy D indicates that a definitive clinical syndrome is not apparent in either case.

With the institution of chromosome banding techniques, many new 'partial trisomy' syndromes have been identified (Lewandowski and Yunis, 1975). The majority of these cases result from clinically abnormal, chromosomally unbalanced segregants of reciprocal translocations. Therefore, karyotypic analysis allows the identification of the additional chromosomal material so that phenotypic-karyotypic correlations are possible. However, other instances of partial trisomy are the result of non-disjunction of apparently deleted chromosomes, leading to an extra abnormal marker chromosome.

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We wish to describe a child with psychomotor retardation and congenital anomalies possessing 47 chromosomes with partial trismy 'D'. Banding revealed that the marker chromosome was definitely not a No. 13 and its assignment to either No. 14 or 15 was difficult.

Case report and family history

The proposita is the only child of healthy, unrelated parents, the mother being 26 years old and the father 27. The mother had had one previous miscarriage. During the present pregnancy, she received hormone therapy because of vaginal bleeding in the second month. The proposita was born at term after a normal delivery and weighed 2700 g. Bilateral congenital dislocation of the hip was diagnosed shortly after birth.

The baby was referred to the Department of Human Genetics at 18 months of age because of psychomotor retardation, generalized hypotonia, seizures during the last two months, and additional congenital anomalies. On physical examination a left epicanthal fold and divergent strabismus of the right eye were observed (Fig. 1a). The ears were small with very small antehelices. Scars from the removal of preauricular skin tags were evident. The nares were anteverted; the palate was high and arched. A low hair line was observed on a short neck. A large cavernous haemangioma was present on the right forearm (Fig. 1b). The fingers and toes seemed shortened and somewhat large. Hypotonia was pronounced and head lag was present. Fundoscopy, audiometry, electroencephalogram, x-rays of skull and chest, and bone age, as well as haematological examination and urinary screening tests for mucopolysaccharidosis and amino acids were all within normal limits.

Cytogenetic studies

Chromosomes, from phytohaemagglutinin (PHA) stimulated peripheral lymphocytes, were studied in the proposita and her parents. In addition, cultured skin fibroblasts of the proposita were examined. The initiation, culture, and harvest of cells for cytogenetic evaluation were according to standard methods. G-banding patterns were achieved by the 'hot-plate' Giemsa pH 9 technique of Patil et al (1971).

The karyotypes of the parents were numerically and structurally normal. In both lymphocytes and fibroblasts, the proposita had a modal chromosome number of 47 with an extra small acrocentric chromosome, the same size and morphology as a G group element. This marker participated in satellite association with other acrocentrics in 40% of the metaphases. After G-banding (Fig. 2), it became apparent that the marker was not a member of Group G, but did fit the pattern of either a deleted No. 14 or 15. However, without the presence of the distal portion of the long arm, allowing distinction between these two chromosomes, precise identification of the marker was difficult. None the less, based on the proximity to the centromere and size of the proximal darkly staining wide band (14q21), we felt that this...
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Fig. 1. The proposita: (a) note right divergent strabismus and left epicanthal fold; (b) note preauricular skin tag and cavernous haemangioma.

Fig. 2. G-banded karyotype of the proposita. Arrow indicates extra 'G' group-like marker which is a partial No. 14.
marker was more likely to be a segment of chromosome No. 14 with the break point in the light band 14q22. If this interpretation is correct, the patient is partially trisomic for the majority of chromosome No. 14.

Discussion

Even among patients with identical complete autosomal trisomy syndromes, phenotypic variability sometimes exists. Such variability is much more pronounced in cases of partial trisomy. This problem is readily understood by considering the cytological basis for these conditions. All partial trisomies are predicated upon chromosomal breaks which may result in either translocations or deletions. Since all break points will not be identical, the resultant chromosomal imbalance will differ from patient to patient. Consequently, the phenotype of different partial trisomies involving the same chromosome may be highly variable. However, if the chromosome in question cannot be precisely identified and may, in fact, represent a segment of one of several chromosomes, the basis for clinical variability is considerably broadened.

Among the 8 cases of partial trisomy 14 reviewed by Raoul et al. (1975), the most consistent clinical findings include psychomotor as well as growth retardation and microphthalmia. Other malformations such as microcephalus, ptosis, high arched or cleft palate, a peculiarly shaped mouth, prominent nose, low set ears, congenital heart disease, and different limb anomalies were observed in variable proportions of the patients. Of these cases, 7 resulted from translocation malsegregation and one (Muldal et al., 1973) was sporadic, as in the presently reported case.

Eight cases of partial trisomy 15, yielding chromosomal markers similar to that observed in our case, have been reported (Cohen et al., 1975; Crandall et al., 1973; Magenis et al., 1972; Parker and Alfi, 1972; Rethore et al., 1973; Webb et al., 1971). The only constant feature was moderate to severe mental retardation. Other variable findings included strabismus, antimongoloid slant, seizures, hypotonia, hyperactivity, and skeletal deformities. Most authors felt that these signs were not specific enough to constitute a well-delineated clinical syndrome. An additional case, partially trisomic for the distal portion of 15q (Fujimoto et al., 1974) manifested psychomotor retardation, microcephalus, seizures, cataracts, low set ears, micrognathia, hearing defect, and long tapering fingers. This phenotype differs somewhat from those patients with partial trisomy for the proximal part of 15q.

The cytogenetic evolution of this type of aberration involves at least two events: one, leading to the inclusion of the extra marker chromosome, i.e. nondisjunction, and the second giving rise to loss of the distal segment of the long arm of the marker, i.e. deletion. In most cases, the apparent deletion occurs as an integral part of a translocation, with the missing segment located on another chromosome. In a minority of cases a direct loss of chromatin material seems to have occurred. Since in our family both parental karyotypes were normal, with no evidence of translocation, a deletion seems most feasible. Furthermore, since mosaicism was not observed in either tissue examined, it may be further assumed that nondisjunction of the deleted marker occurred before fertilization, yielding an unbalanced parental gamete, which included the marker chromosome. In neither partial trisomy D-syndrome (14 or 15), yielding extra G-like marker chromosomes, does a definite clinical basis exist upon which a firm diagnosis can be made. The cytogenetic classification of these markers may also be difficult if the banding is any less than optimum. The patient described here had several clinical features compatible with the reported cases of partial trisomy 14, though the fit was by no means complete. No similarity at all exists between our case and those of partial trisomy 15. Therefore, it is only through the collection of a large number of cases which are described in detail, both clinically and cytogenetically, that answers to the diagnostic dilemma presented by such patients may be forthcoming.

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REFERENCES


Larsen syndrome in two generations of an Italian family

Summary. This paper describes a familial case of Larsen syndrome. Typical anomalies were present in the propositus and 2 of his 6 daughters. In addition, all patients had progressive deafness and the 2 daughters had cleft palate. The certain exclusion of any consanguinity between the couple, suggests, in this instance, the dominant mode of transmission of the syndrome.

The association of multiple congenital joint dislocations with characteristic facies is known as Larsen syndrome (Larsen, Schottstaedt, and Bost, 1950). The main clinical findings include: flattened face with depressed nasal bridge, anterior dislocation of the tibia, bilateral dislocation of hips and elbows, and deformities of feet and hands. Mental development as well as the result of a number of laboratory studies are normal. To date, more than 20 instances have been reported, some of them having minor variations of the classical picture (Lee, 1973).

We have studied a family from Southern Italy in which 2 children and their father were affected. This is, to our knowledge, the only severe male case known to have transmitted the full syndrome to his children.

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The pedigree of the family is shown in Fig. 1. The propositus (III.8) was a 54-year-old man, height 135 cm. He was the last of 4 sibs, the product of a consanguineous mating. None of his sibs had any deformity; however, one member of the kindred was affected by deafness (I.5) and another one by progressive blindness and deafness (III.1). Our patient married a normal woman who certainly could not be consanguineous, because she came from another city, about 400 km away. They had 6 children, all females, and the last two, 12 years and 7 years of age, respectively, had the same deformities as their father (Fig. 2).

Briefly, they all presented the complete picture of Larsen syndrome: flattened face with hypertelorism, strabismus, antimongoloid palpebral fissures, low set ears, scapho-oxycephaly; bilateral joint dislocations of hips, elbows, knees, and deformities of feet and hands. In addition, there was progressive deafness and cleft palate in the two daughters. Radiological examinations showed the typical congenital joint dislocations of the hips, knees, elbows, as well as abnormalities of the skull (scapho-oxycephaly), synostosis of some tarsal bones, and metacarpophalangeal subluxations. Biochemical data and chromosome analyses were normal. Mental development was normal.

Discussion

Our observations are consistent with a diagnosis of Larsen syndrome: in fact, such diagnosis may be posed whenever there are at least two main features—that is characteristic flattened face and congenital joint dislocation (Silverman, 1972). Though having the full-blown picture, the severity was nevertheless different among the three subjects: while the propositus and his older daughter were able to walk, but with some difficulty, the other daughter, who was 7 years old, was unable even to stand. This is consistent with the well-known variability of expressivity of the gene (Latta al, 1971).

As regards the mode of inheritance of the syndrome, most observations are consistent with auto-

Fig. 1.
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