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Note added in proof

Since submission of this paper five cases of pure, or almost pure, partial trisomy of 12q24 have been reported.[18–20] The many features common to these and to the three cases of pure partial trisomy described above support the suggestion in the concluding paragraph that pure trisomy of this region of chromosome 12 results in an identifiable clinical syndrome.

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Unilateral radial aplasia and trisomy 22 mosaicism

SUMMARY A child with unilateral radial aplasia, asymmetry, other malformations, and severe physical and mental retardation is reported. In blood and bone marrow cultures a low mosaicism for trisomy 22 was found. In a few cells a chromosome 22 was missing. The importance of early cytogenetic analysis on large numbers of cells is emphasised, especially in cases of asymmetry where mosaicism is suspected.

Radial dysplasia is a relatively common limb malformation which has been associated with major anomalies in various systems, mostly genitourinary, skeletal, gastrointestinal, and cardiac. It may occur within a definite syndrome, for example, thrombocytopenia and absent radius (TAR), Holt-Oram syndrome, Fanconi's anaemia, and VATERL association, and it has also been reported in chromosomal disorders like trisomy 13 and 18.[1]

We describe a child with total unilateral radial aplasia associated with a clustering of defects on the same side, in whom trisomy 22 mosaicism was demonstrated.

Case report

A 2900 g female child was born after a normal pregnancy and delivery to non-consanguineous parents of Arabic origin. The 25-year-old mother, the 36-year-old father, and the four other children were healthy. There was no history of any congenital anomaly in the family.

A clustering of malformations was evident on the left side including a small palpebral fissure with slight ptosis, hypotrophy of the cheek, a low set ear with abnormal configuration of the helix, and mild stenosis of the external auditory canal. Total left radial aplasia with absent thumb was present (fig 1). The left forearm, hand, and the four medial fingers were smaller than those on the right side and there was colateral clinodactyly of the little finger with only one transverse crease on the left.

Repeated blood counts, including platelet and

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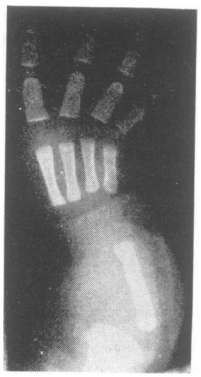

FIG 1 *Radial aplasia of the left arm.*

coagulation tests, were normal. *X*-ray showed hypoplasia of the middle phalanx of the little finger and total left radial aplasia. Computerised tomography of the skull and *x*-ray of the spine and chest were normal. The intravenous pyelogram revealed a normal right kidney. On the left side a non-functioning kidney was seen. The renal scan showed an ectopic left kidney in the pelvis. At the age of 2 years the child was severely retarded physically and mentally (fig 2).

CYTOGENETIC STUDIES

Chromosomes from phytohaemagglutinin (PHA) stimulated peripheral blood lymphocytes were studied in the proband and her parents shortly after the child's birth. The chromosomes were identified by trypsin-Giemsa banding (GTG) and the ASG technique. Heterochromatic polymorphism was evaluated by the C banding technique (CBG) and the nucleolar organiser regions (NOR) were studied by the technique of Tantravahi *et al.*[2]

Both parents had a normal karyotype. In the proband a low mosaicism was detected (46,XX/47,XX,+22) in 10 of the 100 cells studied (fig 3). Two cells (2%) were 45,XX,−22. Random loss could have been inferred but a very low mosaicism of a monosomic line was also acceptable because

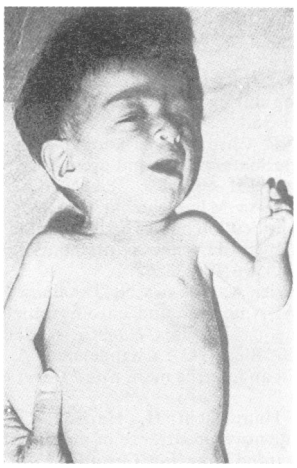

FIG 2 *The patient when 2 years old, weighing 3600 g, severely retarded physically and mentally.*

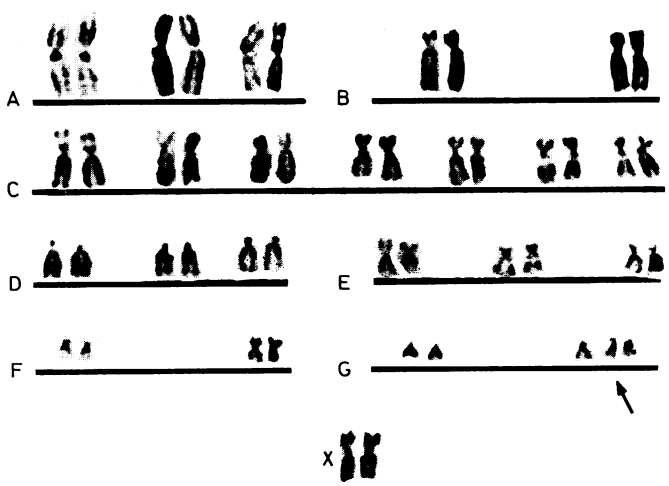

FIG 3 *G banded karyotype of the proband showing trisomy 22.*

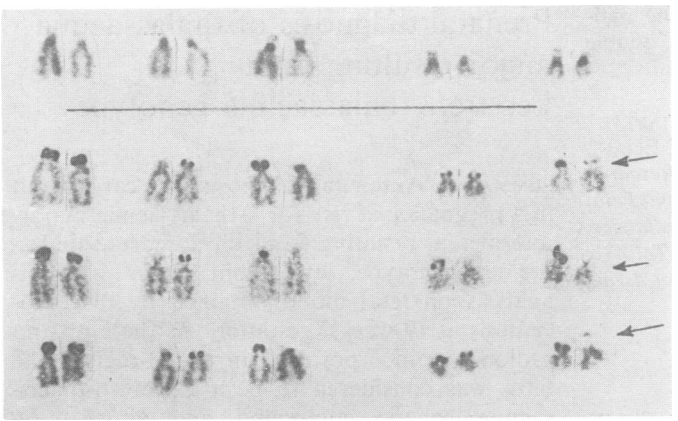

FIG 4 *C banding (upper line) and Ag staining of D and G group chromosomes of the mother. Note the enlarged heterochromatin and absent NOR in one chromosome 22.*

random losses were not frequent and only a 45,XX, −C cell was detected in addition.

A variant chromosome 22 with increased heterochromatin and a moderately long stalk, always without NOR activity, was detected in the mother and the proband (fig 4).

When the child was 3 months old, lymphocytes cultured with PHA for 48, 72, and 96 hours revealed trisomy 22 mosaicism in 5% (four of 80) of the cells studied. One cell was 45,XX,−G. No significant differences in the incidence of trisomic cells were found in cultures with different incubation times.

On the same occasion a direct preparation of a bone marrow aspirate showed trisomy 22 in 10% (two of 20) of the dividing cells. A high incidence of polyploids (20%) was noted. Cultures of the infant's skin biopsies twice failed to grow.

Discussion

Since the availability of new staining techniques for chromosome studies, it has been possible to delineate a trisomy 22 syndrome with a distinct phenotype.[3] All the clinical features are not to be expected in cases of mosaicism. Mollica *et al*[4] have recently documented a child with most elements of this syndrome, trisomy 22 being found in nearly 70% of the cells. On the other hand, three additional cases of trisomy 22 mosaicism have been described in whom the phenotype was different from that of the complete trisomy 22 syndrome. Two of those children had a Turner-like phenotype.[5 6] The other one, reported by Purvis-Smith *et al*,[7] had defects of limbs and face very similar to those described in our child. The additional clinical findings in our patient, for example, severe mental and growth retardation, ear malformations, antimongoloid slant of the eyes, micrognathia, frontal bossing, and short neck are typical of the trisomy 22 syndrome.

The low mosaicism found in the blood and bone marrow of the proband, with a normal karyotype in both parents, leads us to conclude that the aneuploidy was a post-meiotic non-disjunctional event.

The polymorphism of chromosome 22 might have favoured such a non-disjunction either by the relatively large heterochromatic block extending both to the short and the long arm (fig 3), or by the stalk lacking NOR activity (fig 4). Sometimes heteromorphism in a chromosome pair is accompanied by complete or mosaic trisomy of the same chromosome, especially so for trisomy 21 and trisomy 9.

Variants of chromosome 22 have been previously reported in association with cases of trisomy 22.[8] Interestingly, Trabalza *et al*[9] reported a malformed child with a 46,XY,22p+ karyotype, the malformations being characteristic of trisomy 22, although this trisomy was not detected. The 22p+ chromosome was found in the normal mother and the normal maternal grandfather.

To detect mosaicism it is important to study as many tissues as possible, and these studies have to be performed early in infancy since the abnormal line may disappear with age.[10] Detailed chromosomal analysis is especially needed in patients with clustering of unilateral malformations and asymmetry who may be mosaics.[1 7 11–13] Schuler *et al*[13] found a significant difference in the incidence of trisomic cells from skin cultures taken from one side or the other of the body, being much higher in the left side with a cluster of malformations.

In our patient some cells with a missing chromosome 22 were found. A triple mosaicism may be suspected, 45,XX,−22/46,XX/47,XX,+22, the

monosomic line accounting for some of the malformations, as reported in patients with double aneuploidy of chromosome 18.[1 11 1]

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Prenatal diagnosis of thalassaemia major resulting from Lepore/β-thalassaemia genotype

SUMMARY Antenatal diagnosis was carried out in a pregnancy at risk for β-thalassaemia major/intermedia, resulting from the Lepore/β-thalassaemia genotype, by globin chain synthesis analysis on fetal blood obtained by placentocentesis at 19 weeks' gestation. As there was no radioactive incorporation in the β-region, the fetus was considered to be a Lepore/β-thalassaemia genetic compound and aborted on parental request. After abortion, cord blood analysis confirmed the absence of β-chain radioactivity.

In the last few years prenatal diagnosis of homozygous β^0- or β^+-thalassaemias and sickle cell anaemia by globin chain synthesis analysis on fetal reticulocytes has been shown to be feasible and accurate.[1–3]

Besides homozygous β^0- or β^+-thalassaemia, clinical findings consistent with thalassaemia major,[4–6] or less frequently with thalassaemia intermedia,[6 7] have been associated with the Lepore/β^0- or β^+- thalassaemia genotypes.

In this paper we report the results of antenatal diagnosis carried out in a couple at risk for β-thalassaemia major/intermedia resulting from the Lepore/β-thalassaemia genotype.

Subjects and methods

A couple in which the father was a Lepore heterozygote and the mother a high Hb A_2 β-thalassaemia carrier presented at our Genetic Service for counselling, when the mother was at 15 weeks' gestation.

The father, who belonged to a family of Italian extraction (from Naples), showed thalassaemia-like red cell indices and an Hb electrophoretic pattern characterised by A+A_2+F+, a variant moving less anodically than Hb A. This variant migrates on cellulose acetate electrophoresis, pH 8·4, slightly faster than Hb S and does not separate from Hb A in citrate agar electrophoresis, pH 6·0. Haemoglobin A_2 was 2·71%, Hb F 1·98%, and the variant was 8·5% of the total haemoglobin concentration.

Structural studies performed by Professor Tentori (Laboratorio di Patologia non Infettiva, Istituto

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