Trisomy 18 syndrome with an unusual karyotype: possible double isochromosome

SUMMARY Chromosome analysis of an infant with characteristic features of trisomy 18 is presented. The chromosome complement contained a modal count of 47 but there was only one No. 18. In addition, there were two metacentric chromosomes of different sizes. The two metacentric chromosomes were identified by G- and C-banding to be possible isochromosomes of the long and short arms of a No. 18 chromosome.

Trisomy 18 (Edwards' syndrome) is a clinically recognisable syndrome with an incidence in newborns of 0-0·1% (Jacobs et al., 1974). In most instances, it results from nondisjunction in a maternal or paternal gamete producing three normal No. 18 chromosomes in the zygote. Muller et al. (1972) described a case with the phenotype of trisomy 18 which had only one No. 18 chromosome and two metacentric chromosomes of different sizes. After autoradiography, the larger of the two was interpreted as being composed of two long arms of chromosome No. 18. The smaller metacentric chromosome was assumed to be equivalent to two short arms of chromosome No. 18. A similar case is presented here in which G and C banding were used to confirm the identity of the isochromosomes involved.

Case report

CLINICAL FINDINGS

The proposita (Fig. 1) was first seen as a 7-day-old infant born to a 23-year-old mother and a 28-year-old father who were not related. She was the product of a second pregnancy, the first having ended in spontaneous abortion. Delivery followed a term pregnancy which was complicated by the cord being wrapped around the neck. Crying was delayed because increased mucus and respiratory distress required administration of oxygen for approximately 10 hours after birth. Birthweight was 2727 g and body length was 49·5 cm. Head circumference was 34 cm and chest 30 cm. The baby had difficulty feeding during the first 5 days.

PHYSICAL EXAMINATION AT BIRTH

Physical examination revealed a 'staring appearance', low set ears, very small mouth, micrognathia, and short neck. There was a poor Moro's reflex, weak cry, no rooting reflex, poor grasp, and fair sucking instinct. Genitalia were small with gaping minor and major labia.

Extremities revealed rockerbottom feet and limited abduction at both hip joints (questionable subluxation). There was an overlapping of the forefinger and ring finger over the middle finger and a short dorsoflexed big toe. No simian lines were present. A faint systolic murmur was heard at the pulmonary area and borderline cardiomegaly was seen on x-ray examination.

Laboratory tests revealed a haemoglobin of 16·4 g/dl, bilirubin of 114·6 mmol/l (6·7 mg/100 ml) total and 3·42 mmol/l (0·2 mg/100 ml) direct, sodium of 147 mmol/l, and potassium of 3·1 mmol/l. Urinalysis results were normal except for 3 to 4 RBC/hpf.

SUBSEQUENT PHYSICAL DATA

The patient was seen at 1 year, at which time the karyotypes were repeated and photographs taken. On her most recent visit at the age of 17½ months, the patient was doing remarkably well. Weight at this time was 6556 g, length 73·0 cm, and head circumference 44·6 cm. All formula feedings were by the gavage route but solids were taken well from a spoon. Vision and
Fig. 1  Photographs of the proposita at 1 year of age showing features compatible with trisomy 18 syndrome.

Fig. 2  Complete karyotype of the proposita. The arrows indicate the two abnormal chromosomes.
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Fig. 3  Partial karyotypes of three additional cells (a, b, and c) with the normal No. 18, the isochromosome of the short arms, and the isochromosome of the long arms.

hearing were apparently present. She was extremely hypotonic and reached randomly for objects. She could raise her head well when prone but could not lift it when raised from the supine position. She was able to roll over one way but a sitting position was only a slump forward lying on her arms. She could smile and laugh. Strabismus and a high palate were also apparent at this time.

She was being given Lanoxin for support of a borderline cardiovascular compensation. Cardiomegaly was present on x-ray film and an atrioventricular canal defect was thought to be present.

CYTOGENETIC STUDIES
Chromosomal analyses of phytohaemagglutinin stimulated peripheral blood lymphocytes from whole blood of the proposita and both parents were done. The proposita was studied at 7 days and again at 1 year of age with identical results. Preparations shown here were from the latter analysis. Giemsa bands were induced by trypsin treatment (Larson et al., 1977) and C-bands were developed with standard procedures.

Study of the baby's chromosomes revealed a modal count of 47 in 84 cells analysed. Only one structurally normal No. 18 chromosome was identified. In addition, there were two metacentric chromosomes of unequal sizes. One was the size of a C group and the other smaller than the F group. Giemsa banding identified the larger of the two as the equivalent of two long arms of No. 18. The smaller metacentric had no distinct bands but was of similar size and staining quality to the short arms of the normal No. 18. It was interpreted as being composed of two short arms of chromosome 18 (Fig. 2 and 3). C-bands revealed one centromere in each metacentric chromosome that was approximately of equal size to that of the normal No. 18. Karyotypes of both parents were normal.

Discussion
The proposita had clinical features common in patients with trisomy 18 syndrome. These included low set ears, small mouth, abnormal genitalia, rocker-bottom feet, limited hip abduction, the characteristic flexion abnormality of the fingers, a short dorsiflexed big toe, and cardiac anomalies. Her karyotype, however, revealed 47 chromosomes with only one chromosome 18 and two metacentric chromosomes of different sizes. By G- and C-band analysis these metacentrics were interpreted to be isochromosomes of the long and short arms of No. 18. The presence of the features of the trisomy 18 syndrome can thus be explained by the genetic equivalent of three No. 18 chromosomes.

Reports of isochromosomes of both arms are extremely uncommon. In addition to the Muller et al. (1972) report, one other instance was a case described by Sinha et al. (1971) in which isochromosomes of both arms of a C group chromosome were present, but this occurred as a mosaic in 8 to 10% of the cells with a normal 46,XX cell line. Double isochromosomes of an autosome could probably result in viable birth of a non-mosaic in three chromosomes of the human complement. These would be the three in which trisomy is associated with live birth, Nos. 13, 18, and 21. Thus far it has only been reported in No. 18.

Generally the reports on isochromosomes involve only one arm. Mukerjee and Burdette (1966) described an extra metacentric chromosome with satellites on both ends which was interpreted as an isochromosome of the short arms on a No. 21 chromosome. Several reports of a supernumerary presumptive isochromosome of the short arms of chromosome No. 18 have made possible the description of an associated syndrome (Condron et al., 1974). Borgaonkar (1975) has catalogued a few cases of isochromosome or translocation of the long arms of Nos. 13 and 21 as well as the short arms of No. 18. Isochromosomes of the long arm of No. 17 are reported to be associated with malignancies, particularly myeloid leukaemias (Engel et al., 1975; Mitelman et al., 1975).

The origin of the metacentrics remains an intriguing and unresolved subject as the banding analyses do not give high enough resolution in the centromere area to pinpoint the break points. Muller et al., (1972) considered two possibilities for the origin of the abnormal chromosomes. First, isochromosomes may arise as a misdivision of the centromere with both products being passed on to the same gamete of
a parent. The products would then be true isochromosomes by Darlington's (1939) definition. Secondly, a reciprocal translocation may have occurred as a result of breaks at or near the centromere during the first division of meiosis between two No. 18 chromosomes followed by nondisjunction. In a recent report (Salamanca-Gómez, and Armendares, 1975) an 'isochromosome' of the long arm of No. 17 appears to be caused by this type of event. A marker indicated the non-sister origin of each arm.

Transverse division of one centromere seems more likely than breakage and reunion at appropriate positions between two No. 18 chromosomes. With support of the G and C band analysis, we favour isochromosome formation as the mechanism of formation of the two metacentric chromosomes in this report.

The authors gratefully acknowledge Dr William C. Rosen for referral of the patient and providing physical data and photographs.

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Partial 18 trisomy (with 47 chromosomes) resulting from a familial maternal translocation

**Summary** A newborn female infant presented with the classical picture of 18 trisomy syndrome. Her karyotype was 47,XX,+der(18)(12;18)(q24; q21)mat. The mother was a balanced reciprocal translocation carrier and so too was one of the two maternal uncles of the proposita, indicating that the translocation was already present in one of the grandparents who were not available for examination. This family suggests that triplication of the distal part of the long arm of chromosome 18 is not necessary to produce Edwards' syndrome.

Tertiary trisomy resulting in partial trisomy 18 in a child of a balanced D/E translocation carrier mother has been described by Gleissner et al. (1970), but at that time the break points were not defined.

**Fig. 1 Pedigree.**

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