

A child trisomic for the distal part of chromosome 14q

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SUMMARY A child is described with multiple congenital abnormalities including microcephaly, odd facies, Fallot's tetralogy, and absent parathyroids. These were associated with partial trisomy for the distal half of the long arm of chromosome 14, the extra segment being translocated to the short arms of No 10. The main clinical problems were those related to the congenital heart disease and hypocalcaemia.

Recent developments in cytogenetic technology have provided far more information about the substructural characteristics of individual chromosomes.¹ This in turn has produced a rapid expansion of new chromosome syndromes now recognised by virtue of the precision with which short segments of chromosomes can be identified.² Nevertheless, in most cases absolute evaluation has been straightforward because of the presence of a familial translocation. There remain however a number of cases, especially those with small duplications, that can only be identified with certainty if the banding sequence of the additional segment is distinctive. The present case is such an example and appears to be trisomic for the distal part of the long arm of chromosome 14.

Case report

This baby girl was born to a 29-year-old Jewish multigravida who had had one previous normal pregnancy and one miscarriage. The pregnancy had progressed satisfactorily until the 34th week, when spontaneous rupture of the membranes occurred, followed by premature labour and the normal delivery of a liveborn infant weighing 2 kg. The Apgar scores were 7 and 9. Examination showed a preterm, small-for-dates baby, with a gestational age of 35 weeks (Dubowitz criteria). She had an odd facial appearance with low set ears, wide nasal bridge, a narrow left palpebral fissure, and ptosis of the left lid, but the eyes were normal. The upper lip

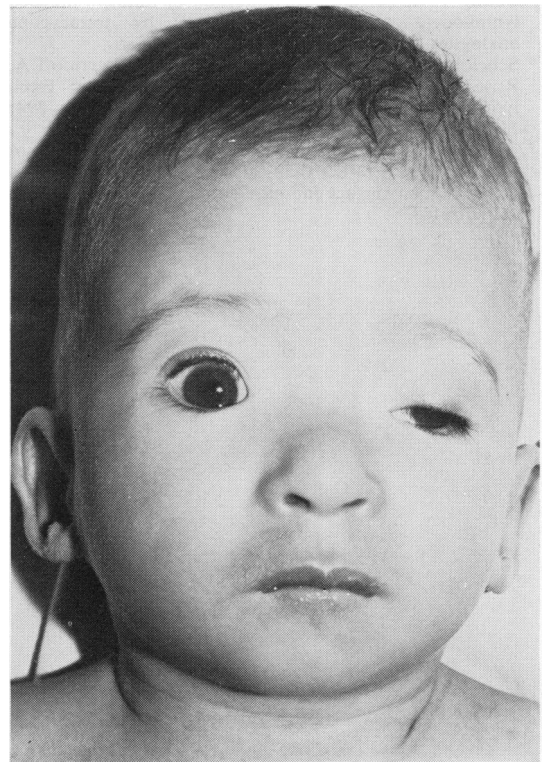


Fig. 1 Patient aged 4½ months. Note narrow left palpebral fissure, ptosis, and protruding upper lip.

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was very prominent (Fig. 1). There were no other external abnormalities except for widely spaced nipples.

The dermatoglyphic features were unremarkable.

All digits had ulnar loops except for R2 and R4 which had whorls. All palmar triradii were normal in position with D-line exits into the 4th interspaces producing a Cummin's main line index of 6 on each hand. Large hallucal loops into the first interspaces were present associated with a triradius at position 'f'.

Initial progress was satisfactory but a cardiac murmur became apparent on day 7. A chest x-ray showed oligoemic lung fields and heart size at the upper limit of normal, consistent with a diagnosis of congenital heart disease, but the electrocardiograph was normal for a neonate. A symptomatic low blood calcium level ranging between 1.78 and 2.25 mmol/l (7.12 and 9.0 mg/100 ml) was noticed at this time and treatment with calcium gluconate was started. Results of all other investigations—such as viral studies, Wassermann reaction, immunoglobulins, urinary chromatography, and skull x-ray—were normal.

On day 16 the infant became tachypnoeic, pyrexial, and started to grunt. A full screen for infection was performed and treatment with antibiotics started. During the next 24 hours her condition deteriorated and she became cyanosed. She was transferred to a specialist cardiac unit where further investigations, including cardiac catheterisation and angiography, showed a classical tetralogy of Fallot. Her condition stabilised and she was returned to our care, surgery being contemplated when she had grown.

She did well and gained weight until the beginning of the 5th week, when her condition again deteriorated. She became irritable and developed episodes of twitching in her left arm and leg. This responded to valium and phenobarbitone. Investigations showed no evidence of infection. An electroencephalogram,

although showing no positive abnormalities, showed less activity on the right side and she was found to have a calcium level of 1.45 mmol/l (5.8 mg/100 ml), a phosphate level of 3.48 mmol/l (10.8 mg/100 ml), and a magnesium level of 0.86 mmol/l (2.1 mg/100 ml). The alkaline phosphatase level was 501 KA units. She was given expressed breast milk and calcium gluconate orally, but these failed to correct the calcium/phosphate ratio. She was then started on dihydrotachysterol at a dose of 0.25 mg twice daily, maintaining the calcium and phosphate levels within the normal range and producing a fall in the alkaline phosphatase level (Fig. 2).

Her condition improved and she was discharged home at 10 weeks, weighing 3.42 kg. During the next few weeks she became difficult to feed and started to have fits and cyanotic attacks with increased frequency.

Apart from less active left limb movements, her general development was progressing satisfactorily and was up to that of her chronological age, although her head circumference had shown a steady fall away to below the 3rd centile. She was readmitted at 20 weeks, weighing 4.03 kg, her condition having further deteriorated after an upper respiratory infection. In view of the increasing cyanotic attacks she was referred back to the Brompton Hospital where a Waterston anastomosis was performed. The postoperative course was uneventful but, on the 10th day at the hospital, she was found in cardiorespiratory arrest in her cot. Attempts to resuscitate her were unsuccessful.

Necropsy examination showed pronounced oedema of both lungs. The brain was macroscopically normal, apart from convolutions of the cerebrum

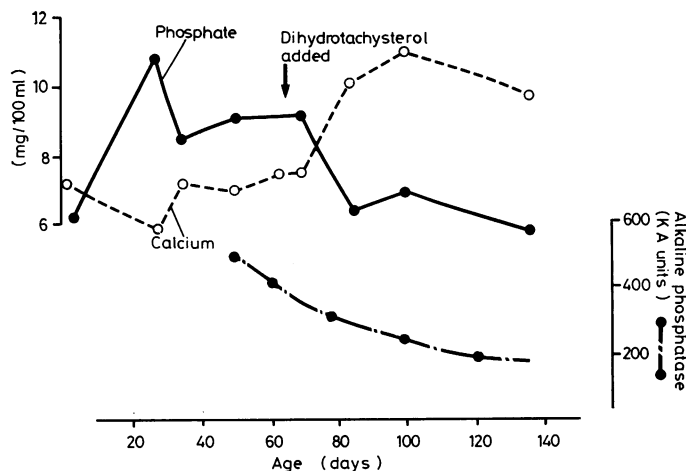


Fig. 2 Calcium, phosphate, and alkaline phosphatase levels before and after treatment.

Conversion: traditional units to SI—
Phosphate: 1 mg/100 ml \approx 0.323 mmol/l. Calcium: 1 mg/100 ml \approx 0.25 mmol/l.

which showed some flattening and immature development. The heart showed solitus, concordant double outlet right ventricle, pulmonary stenosis, ventricular septal defect, and patent foramen ovale.

The thymus weighed 9 g, but the parathyroids could not be found despite cross-sectioning the trachea and thyroid gland at different levels.

Cytogenetics. Standard chromosome preparations were obtained from short-term lymphocyte cultures from the patient and her parents. Giemsa banding was carried out using the trypsin method previously described.³ The patient's karyotype contained 46 chromosomes with normal homologous pairs except for No 10, one of which has extended short arms. The additional segment which displaced the 10p telomere had a distinctive G-banding pattern, very similar to the distal half of the long arm of No 14, from band q22 to qter (Fig. 3). The child was therefore trisomic for this segment of 14q—that is 46XX, 10p + (10 qter - 10p 14 :: 14q 22-14 qter).

The karyotypes of both parents were normal (mother = 46,XX; father = 46,XY).

Discussion

As both parents had normal karyotypes it was not possible to confirm the identity of the additional segment. However, the banding sequence, with two distinctive and clearly defined bands, eliminates virtually all chromosomes in the karyotypes as candidates if one assumes that the segment involved represents the terminal zone of one of them. A close inspection shows that only No 14 has a narrow dense band distal to the narrow pale band, the bands being generally much wider or with different interband distances and band order in other possible chromosomes (for example 1q, 3p, 5q, 6p, 8q, 10q, or 18q). In fact this 10p + chromosome with the additional segment has a banding sequence very similar to the

corresponding chromosome in the mother of a patient trisomic for the proximal half of 14q described by Raoul *et al.*⁴ In that case the mother was the carrier of a balanced translocation of the type t (10:14) (p15.2, q22).

Except for one mosaic patient, complete trisomy for chromosome 14 has not been described in a liveborn infant but it does occur in some spontaneously-aborted fetuses.⁵ Most known instances of partial trisomy 14 involve the proximal segment down to and including band q23. The total length of the segment varied and only 5 cases reviewed by Wyandt *et al.*⁶ appeared to be identical although the clinical manifestations were still somewhat variable. Nevertheless, the range of abnormalities—generalised retardation, microcephaly, microphthalmia, hypotelorism, large mouth with lips turned down at the corners, prominent nose, high arched or cleft palate, and deformities of the extremities—contrasted quite well with the clinical features of the three known trisomies for the distal half of No 14. In these cases, the main anomalies were antimongoloid slant, defects of the great vessels and heart, unusual mouth with protruding upper lip, and a high forehead typified by the case described by Luzatti (L Luzatti, 1977, personal communication to Wyandt *et al.*).

The unusual facial appearance of our patient was largely due to the unequal size of the palpebral fissures with ptosis of the left lid, but the upper lip did protrude as in other cases although the forehead was not remarkable. However the presence of a major congenital heart and great vessel abnormality in the form of Fallot's tetralogy is a more striking similarity, while absence of parathyroids has not been described previously. The hypocalcaemia was clearly related to the absence of parathyroids.

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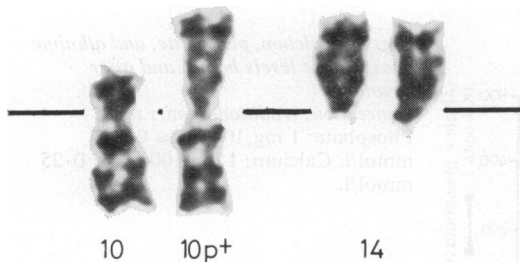


Fig. 3 Partial karyotype showing trisomy for the distal part of the long arm of chromosome 14 due to a *de novo* 10|14 interchange.

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