Multiple congenital defects associated with trisomy for the short arm of chromosome 4

Summary. The clinical and cytogenetic findings of a female infant with multiple congenital anomalies and trisomy for the short arm of chromosome 4 (46,XX,21p+) are described. The abnormal chromosome was inherited from the father who had a balanced translocation between the short arm of chromosome 4 and the short arm of chromosome 21. Clinical features are compared with those of one definite and one probable previously described case of trisomy for the short arm of chromosome 4. It is suggested that a clinical syndrome associated with +4p eventually may be identified.

Cases of trisomy for the short arm of a B-group chromosome have been described previously. In several instances the chromosome involved was identified as a No. 5 by Lejeune et al (1965), Laurent and Robert (1966), de Capoa et al (1967), and Noël, Quack, and Thiriet (1968). These patients had no severe physical anomalies, but they were all mentally retarded. Schinzel and Schmid (1972) described a patient who was trisomic for the short arm of No. 4, and Gustavson et al (1964) described a patient with trisomy for the short arm of an unidentified B-group chromosome; both cases had severe physical anomalies. We present a further case of trisomy for the short arm of chromosome 4.

Case report

The proposita, a female, was born to a 24-year-old woman and her 27-year-old husband. The mother's only previous pregnancy, three years before, was complicated by hypertension and had terminated in the birth of a stillborn male (1600 g); no necropsy was performed.

Following a threatened abortion at the end of the first trimester, the pregnancy was uneventful and terminated spontaneously at 39 weeks in the birth of a female infant (1700 g). The 1 minute Apgar score was 5 and rose to 9 after 10 minutes. Routine examination revealed 'unusual' facies, respiratory distress, and an imperforate anus. On transfer to the Sheffield Children's Hospital the infant was found to be cyanosed and hypothermic (35°C).

The abnormal facies (Fig. 1a) were characterized by narrow palpebral fissures, bilateral microphthalmia, and a bulbous nose with a depressed root. The palpebral fissures had a slight antimongoloid slant and microphthalmia was more severe on the right. The philtrum was long and the upper lip protruded. The neck was short and the hair line low. The ears were moderately low set but, apart from a small nodule below the antitragus on the left, appeared to be of normal morphology. Mild micrognathia was present; the buccal cavity was small with a short thick tongue and there was an intact, high arched palate. Neither microcephaly nor hypertelorism were observed but measurements relevant to these features were not recorded.

The fingers were held tightly flexed but could be extended. At rest the index finger usually overlapped the thumb while the third and the fifth digits often overlapped the ring finger. Both hips were in marked flexion and adduction and could neither be extended nor abducted. There was bilateral postural valgus deformity of the feet but they were not rockerbottomed.

Normal female genitalia were found but no anus was seen. Meconium appeared through a pin hole orifice in the midline of the perineum between the vaginal introitus and the normal anal position.

Apart from a soft ejection systolic murmur at the left sternal edge, the further systemic examination was unremarkable.

Radiology of the chest revealed cardiomegaly and oligo-}

genic lung fields. Films of the hip joints and pelvis

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showed no signs of dislocation of the hip or abnormality of the pelvis.

The plasma glucose was less than 10 mg/100 ml.

An electrocardiograph showed sinus rhythm.

Dermatoglyphics (Table I) were unremarkable apart from a high dermal ridge count.

At the age of 3 months the patient died in congestive cardiac failure. At necropsy the external appearance was that of a small-for-age female infant. The crown-rump measurement was 36 cm, crown-heel measurement 53 cm, and weight 3175 g. The facies were as described above but in addition left dacryocystitis was present. Examination of the heart revealed cardiomegaly due to left ventricular hypertrophy (LV thickness 1 cm). The left atrium was dilated and an atrial septal defect, 1 cm in diameter, was present. The right ventricle and infundibulum were hypoplastic and the tricuspid valves appeared rudimentary. Dissection of the hips was not undertaken and the further examination was unremarkable.

Cytogenetic studies

Thirty cells were counted from the proposita’s lymphocyte chromosome preparations stained with
lacto-orcein. All had 46 chromosomes. Only three members of the G-group were present (Fig. 2) and there was an extra chromosome in group 16. No other chromosome abnormality was found.

Lymphocyte and fibroblast culture preparations of the father showed 46 chromosomes. As in the proposita, there was a missing G-group chromosome and an extra chromosome resembling No. 16 (Fig. 2). There were only three morphologically normal B-group chromosomes and a marker chromosome, a large acrocentric, the long arm of which was the length of the long arm of a B-group chromosome. A B/G translocation was considered likely.

The mother and the paternal grandparents had normal chromosome complements.

The acrocentric marker chromosome found in the father's karyotype was seen to be in association with the normal acrocentric chromosomes. The associations were scored in 50 cells (Cohen and Shaw, 1967/1968) and the marker was found to associate 12 times. The normal B-group chromosome did not associate. Therefore the tendency to associate exhibited by this marker chromosome indicated that at least the terminal part of the short arm of the involved G-group chromosome was present in the marker.

Lymphocyte preparations of the proposita and fibroblast preparations of the father were banded with 0.25% trypsin and stained with Leishman's (Seabright, 1971). The banded karyotype of the proposita and her father showed the missing G-group chromosome to be a No. 21. The father's missing B-group chromosome was a No. 4 (Fig. 3). All other chromosomes banded normally. The short arm of the large acrocentric found in the father was satellited giving the appearance of the short arm of a No. 21; further evidence for a reciprocal translocation.

The abnormal metacentric chromosome had two dark bands, one of which was derived from the short arm of a No. 4 chromosome (4p15). The second band was either from the long arm of a 4 chromosome (4q13) or from the long arm of a 21 chromosome (21q21). In the 4 chromosome, the break was either in 4p14 or in the paracentric area. Similarly in the 21 chromosome, the break was in 21q22 or in the centric area.

If the unidentified band is 21q21 then the proposita was trisomic for the short arm of chromosome 4 and monosomic for the short arm of chromosome 21. If however the band is 4q13 then she was trisomic for the region of chromosome 4 up to 4q13 and monosomic for chromosome 21 up to band 21q21.

Discussion

The clinical features of the patients described by Schinzel and Schmid (1972; see Fig. 1b) and Gustavson et al (1964) are compared with the

Fig. 2. Partial karyotypes (orcein stained) of the proposita (line a) and her father (line b).
present case of trisomy for the short arm of chromosome 4 in Table II.

Because of the difficulty in our case of establishing the exact nature of the translocation, some clinical features may be due to abnormalities other than the +4p. The patient of Schinzel and Schmid was monosomic for part of the long arm of chromosome 18 as well as trisomic for the short arm of chromosome 4. This monosomy must have contributed additional clinical features to those associated with pure +4p.

Gustavson's patient was only described as being trisomic for the short arm of a B chromosome, the break points on the B and G chromosomes involved were also not identified.

These cytological differences complicate the evaluation of the clinical features (Table II) as a recognizable clinical syndrome. The features in common in the three cases may be thought of as due to trisomy for 4p rather than the other monosomies and possible trisomies.

Schinzel and Schmid emphasized the combination of narrow palpebral fissures, bulbous nose, ear defect, and deformity of the fingers, feet, and pelvis. We would suggest that eye deformity, macrognathia, low hair line, long philtrum, and a high dermal ridge count be added to the list of features which may form the basis of a new clinical syndrome associated with trisomy for the short arm of chromosome 4.

The authors wish to thank Dr R. J. M. Bell, paediatrician, for referring the patient, Dr Eunice Howard for the necropsy findings, Dr Doreen C. B. Colver for her help in examining the patient, and Mrs Diana J. Curtis for the banded karyotype of the proposita. We are indebted to
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TABLE II

DETAILS OF THE CLINICAL FEATURES OF TWO PROVEN AND ONE POSSIBLE CASE OF +4p

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Present Case</th>
<th>Schinzel and Schmid (1972)</th>
<th>Gustavson et al (1964)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Narrow palpebral fissures</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypertelorism</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Ocular abnormality</td>
<td>Microphthalmia</td>
<td>-</td>
<td>Iris colobomata</td>
</tr>
<tr>
<td>Depressed root to nose</td>
<td>+</td>
<td>+</td>
<td>Not stated</td>
</tr>
<tr>
<td>Bulbous nose</td>
<td>+</td>
<td>+</td>
<td>Not stated</td>
</tr>
<tr>
<td>Long philtrum</td>
<td>+</td>
<td>+/-</td>
<td>Not stated</td>
</tr>
<tr>
<td>Micrognathia</td>
<td>+/-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Macroglossia</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Short neck</td>
<td>+/-</td>
<td>+</td>
<td>Not stated</td>
</tr>
<tr>
<td>Ear abnormality</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Low hair line</td>
<td>+</td>
<td>+</td>
<td>Not stated</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>-</td>
<td>+/-</td>
<td>Hydrocephalus</td>
</tr>
<tr>
<td>Digital anomalies</td>
<td>Characteristic posture of fingers</td>
<td>Long fingers and toes; characteristic posture of fingers; flexion contractures</td>
<td>Long fingers and toes</td>
</tr>
<tr>
<td>Pelvic deformity</td>
<td>Fixed flexion—adduction</td>
<td>Abnormal configuration; dislocated hips</td>
<td>-</td>
</tr>
<tr>
<td>Foot deformity</td>
<td>Valgus deformity</td>
<td>Calcaneal deformity; prominent heels; plantar flexion impossible</td>
<td>Not stated</td>
</tr>
<tr>
<td>Heart defect</td>
<td>+</td>
<td>'Left ventricular hypertrophy'</td>
<td>-</td>
</tr>
<tr>
<td>Alimentary tract deformity</td>
<td>Anal atresia of membranous type</td>
<td>-</td>
<td>Anal atresia of membranous type</td>
</tr>
<tr>
<td>Dermal ridge count (fingers)</td>
<td>High</td>
<td>High</td>
<td>Not stated</td>
</tr>
<tr>
<td>Low birth weight for maturity</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Additional features</td>
<td>-</td>
<td>Elbows not completely extendable</td>
<td>Sagittal suture synostosis; lumbar scoliosis; hydronephrosis</td>
</tr>
</tbody>
</table>

+ = present; - = absent.

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