Trisomy 16p in a liveborn infant and a review of partial and full trisomy 16

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SUMMARY An abnormal female infant, who survived for 10 months with almost complete trisomy 16p and monosomy of sub-band 21q22.3, is described. The chromosome anomaly was the result of an unbalanced segregation of a maternal balanced translocation t(16;21)(p11;q22.3). The partial monosomy was considered to have had little or no adverse phenotypic effect. Cases with trisomy of chromosome 16 material are reviewed. It appears that while full trisomy 16 always results in early spontaneous abortion, trisomy 16p or 16q may be compatible with limited postnatal survival.

Trisomy 16, unreported in liveborn cases investigated with banding techniques, has often been shown to be the most common trisomy in surveys of spontaneous abortuses (Carr, 1967; Arakaki and Waxman, 1970a; Kajii et al., 1973; Bouë et al., 1975; McConnell and Carr, 1975; Creasy et al., 1976; Lauritsen, 1976). It has been suggested that its lethality is the result of the additional short arm material (Schmickel et al., 1975). We describe here what we consider to be a unique case of almost complete trisomy 16p in a girl who lived for 10 months, and we review cases with trisomy of chromosome 16 material.

Case history

The proposita (Fig. 1, III.2) was born at term by caesarian section because of fetal distress. She was the second born infant of a 23-year-old mother (now gravida 3, para 3) and a 30-year-old father.

At birth the proposita weighed 2125 g, with a head circumference of 31 cm, and no physical signs of prematurity. Her Apgar score was 6 at 1 minute, 8 at 5 minutes, and 9 at 10 minutes. The extremities of her body were blue and respiratory effort was slow and irregular. Oxygen was administered.

On examination, the baby had odd facies with upward slanting palpebral fissures, asymmetrical ears, a hypoplastic mandible, and tongue-tie (Fig. 2 and 3). There was proximal insertion of the thumbs, which were hypoplastic (Fig. 4) and adducted under the fingers during fistling (Fig. 5). The index fingers overlapped the middle fingers (Fig. 5), and there was a simian crease on the left hand. Dorsiflexion of the big toes was noted. She had a systolic murmur, loudest at the left sternal border, which was not characterised further. There were only 2 blood vessels in the umbilical cord.

Full radiological examination showed no further abnormality, except for a pelvis that was small in relation to the chronological age. An intravenous pyelogram showed no abnormality. Her electrocardiogram showed slight right axis deviation. Routine

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Fig. 1 Pedigree of family.
laboratory investigations of the complete blood cell count, red cell osmotic fragility, Hb electrophoresis, serum electrolytes, serum folate, and urine sugars, creatinine, amino acids, and mucopolysaccharides were all within normal limits. On one occasion pathogenic Esch. coli 0114 was cultured from a rectal swab, but was not subsequently reisolated. No other bacterial or viral pathogens were isolated.

During the first week of life the condition of the baby was poor, complicated by a moderate degree of...
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respiratory distress and mild hypoglycaemia (blood glucose levels varied between 1.1 and 1.7 mmol/l), jaundice (serum bilirubin levels varied between 147 and 172 µmol/l), and hypocalcaemia (serum calcium levels varied between 1.26 and 1.86 mmol/l). At 7 days she had a series of convulsions, each lasting between 30 seconds and 1½ minutes. Calcium gluconate was administered and the attacks did not recur. She was initially fed through a nasogastric tube and, though there was intermittent vomiting, her condition began to improve, so that at 1 month of age she began to feed from the bottle and gradually gained weight. At 7 weeks she was found apnoeic and cyanotic, but recovered after suction of the oropharynx. She remained in hospital for 3 months, by which time she was feeding well despite her developmental retardation (weight 3250 g). The child died unexpectedly at home at the age of 10 months.

Necropsy showed no internal congenital malformation, and death was attributed to 'bronchiolitis (sudden death in infancy syndrome)'.

Cytogenetic studies

Chromosome preparations were made from peripheral blood using standard techniques (Moorhead et al., 1960), and GTG banded (Paris Conference, 1971, Supplement, 1975) with a method modified from Seabright (1971). On examination each metaphase spread from the proposita (III.2) had a count of 46 with one chromosome 21 having a long arm nearly twice the length of that of its homologue. Analysis of chromosome preparations from the mother (II.2) showed the presence of a balanced translocation in which the short arm of one chromosome 16 was exchanged with the end of the long arm of one chromosome 21 (Fig. 6). The interchange points appeared to be close to the centromere of chromosome 16 within band 16p11, and at the junction of sub-bands 21q22.2 and 21q22.3 of chromosome 21 (Fig. 7). The karyotype of the mother was therefore designated 46,XX,t(16;21)(p11;q22.3) (Paris Conference, 1971), and that of the proposita was interpreted as 46,XX,der(21),t(16;21)(p11;q22.3)mat.

Fig. 6 GTG-banded karyotype of the mother (II.2) of the proposita showing the reciprocal translocation between chromosomes 16 and 21 (arrows).
The proposita was thus trisomic for almost the whole short arm of chromosome 16, and monosomic for sub-band 21q22.3 of chromosome 21.

The karyotypes of the father (I.1) and the maternal grandmother (I.2) of the proposita were normal. After ascertainment, the third pregnancy of the mother of the proposita was monitored. Amniocentesis, followed by cell culture and chromosome analysis, showed the presence of a chromosomally normal female fetus (III.3). This result was confirmed with a lymphocyte culture after the birth of a phenotypically normal female infant.

The brother (III.1) and the maternal grandfather (I.1) of the proposita were both phenotypically normal but were unavailable for cytogenetic investigation.

**Discussion**

It is well established that trisomy 16 is found in at least 5% of all spontaneous abortuses (Arakaki and Waxman, 1970a; Boué et al., 1975; Creasy et al., 1976; Lauritsen, 1976), which account for 15% of clinically recognisable pregnancies (Reid et al., 1972). This prevalence of trisomy 16 in abortuses, compared with its complete absence from surveys of perinatal and neonatal deaths and stillbirths (Bauld et al., 1974; Machin and Crolla, 1974), and from extensive surveys of newborn infants (reviewed by Hamerton et al., 1975), suggests that trisomy 16 invariably has a lethal effect early in pregnancy. No trisomy 16 conceptus has been reported expelled with a gestation (from first day of LMP to day of abortion minus 2 weeks) greater than 16 weeks, the average gestational age being approximately 10 weeks. These abortuses showed either abnormal or arrested development, the most common phenotypes being severely disorganised embryos, intact empty sacs, and ruptured sacs without cord stumps (Arakaki and Waxman, 1970a;b; Hamerton, 1971; Creasy et al., 1976; Lauritsen, 1976). Only a few macroscopically normal trisomy 16 embryos have been described, the largest of which was 10 mm long (Clendenin and Benirschke, 1963; Creasy et al., 1976; M. Seabright, 1977, personal communication). Trisomy 16 mosaicism has occasionally also been reported in spontaneous abortuses (Arakaki and Waxman 1970a; Ikeuchi and Sasaki, 1975; Creasy et al., 1976).

However, putative reports of full trisomy 16 have been made in abnormal adults (Lewis et al., 1963; Melnyk et al., 1967), and in a case of neonatal death (Taylor, 1971). Reputedly, trisomy 16 mosaicism has been found in living individuals (Schmidt et al., 1963; Backus and Darien, 1968; Arakaki and Waxman, 1969), and in an infant who died in the neonatal period (Konstantinova, cited in Borgaonker and Bolling, 1977). In these cases, chromosomes were identified without the aid of banding techniques. It is probably significant, therefore, that rearrangements involving group or X chromosomes can result in chromosomes indistinguishable from chromosome 16 with conventional staining techniques. Some cases of partial trisomy 9, an abnormality associated with multiple congenital malformations compatible with postnatal survival, can be included in this category (Mason et al., 1975; Penchaszadeh and Coco, 1975; P. J. Gregory, S. H. Roberts, and D. P. Duckett, 1977, unpublished data). These reports of full or mosaic trisomy 16 in liveborn individuals should therefore be regarded with some scepticism.

Trisomy of 16p material (Hamerton, 1971; Hasegawa et al., 1973) and of 16q material (Kim et al., 1974) has also been implicated in spontaneous abortions. Similarly, in the present case, there is the possibility that the 3 spontaneous abortuses of the maternal grandmother (I.2) were trisomic for 16p as a result of an unbalanced segregation in the maternal grandfather (I.1).

However, there are a few reports, in addition to the child described here, of postnatal survival in infants with trisomy of 16p or 16q material (Table). All these cases had multiple congenital abnormalities, coupled with a birthweight below 2500 g, and with one exception (Stern and Murch, 1975) they were dead within 1 year. A few similarities can be seen between...
the present case and the previously reported cases with trisomy of 16p material (Table: 1, 2, 3, and 4). These common features include a hypoplastic mandible and abnormalities of the auricles (Pergament et al., 1970; Schmickel et al., 1975; Stern and Murch, 1975), flexion deformities of the fingers (Schmickel et al., 1975; Stern and Murch, 1975), and dorsiflexion of the big toes and a single umbilical artery (Stern and Murch, 1975). The 3 cases previously reported were males with cryptorchidism. Phenotypic discrepancies may be explained by the almost complete trisomy of 16p in the present case, compared with the more partial trisomy 16p in the other reports, and by the other chromosomal imbalances, resulting from the attendant rearrangements, which differ in each instance.

The proposita described here was monosomic for the terminal sub-band 21q22.3 of chromosome 21. Lejeune et al. (1964) first postulated that partial monosomy of the chromosome responsible for Down's syndrome would result in a phenotype in some respects antithetical to mongolism. Cases with 'anti-mongolism' (Reisman et al., 1966) and 21q deletion comprise the G-deletion syndrome 1 of Warren and Rimoin (1970), reviewed by Gericke et al., (1975). Some abnormalities, including developmental retar-

Table: Comparison of liveborn cases with partial trisomy 16

<table>
<thead>
<tr>
<th>Author</th>
<th>Cytogenetic findings</th>
<th>Pregnancy (wk)</th>
<th>Birthweight (g)</th>
<th>Length of life (months)</th>
<th>Facies</th>
<th>Other clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Present case</td>
<td>46,XX,der(21)(x;16;21)(p11;q222.3)mat:</td>
<td>38</td>
<td>7125</td>
<td>10</td>
<td>Asymmetry of ears; upward slanting palpebral fissures; hypoplastic mandible</td>
<td>Thumbs proximally inserted, hypoplastic, and adducted under fingers during fistng; index fingers overlapped 3rd fingers; simian crease on left hand; dorsiflexion of big toes; small pelvis; single umbilical artery</td>
</tr>
<tr>
<td>(2) Stere and Murch (1975)</td>
<td>47,XY,der(18)(x;16;18)(p12;q11)mat: partial trisomy 16p(distant); trisomy 18p; partial trisomy 18q(proximal)</td>
<td>35</td>
<td>1700</td>
<td>Alive at 3 years</td>
<td>Microcephalic; small palpebral fissures; auricles low-set and malformed; hypoplastic mandible</td>
<td>Cleft soft palate; index fingers overlapped 3rd, and 5th overlapped 4th fingers; rocker-bottom feet; dorsiflexion of big toes; pseudohermaphroditism; bilateral cryptorchidism; single umbilical artery; child grossly retarded and static at 3 years</td>
</tr>
<tr>
<td>(3) Pergament et al. (1970)</td>
<td>76% of cells were 46,XY,16;+;r(16); partial monosomy 16p and q; 17% of cells were 45,XY,16; partial monosomy 16p</td>
<td>40</td>
<td>1800</td>
<td>7.5 months</td>
<td>Hypertelorism; epicanthic folds; low-set ears; beak-shaped nose; hypoplastic mandible</td>
<td>Silt-like openings of the external auditory canals; 5th toes overlapped 4th toes; hypoparathyroidism; bilateral cryptorchidism; general demineralisation of skeleton</td>
</tr>
<tr>
<td>(4) Schmickel et al. (1975)</td>
<td>47,XY,der(16)(x;15p;+;16p;mat:;trisomy 16q; probable partial trisomy 16p (proximal)</td>
<td>40</td>
<td>1860</td>
<td>7 weeks</td>
<td>Asymmetry of skull; small palpebral fissures with antimongoloid slants; small round ears with little cartilage; hypoplastic mandible</td>
<td>Clinoanodactyly of 2nd and 5th fingers; metatarsus adductus deformity; retarded calcanus; fusion of sacral vertebral bodies; systolic murmur due to ventricular septal defect; bilateral cryptorchidism</td>
</tr>
<tr>
<td>(5) Eriksson et al. (1971)</td>
<td>46,XY.der(18)(x;16;18q1q2)mat: partial trisomy 16q(distant); partial monosomy 18q(distant)</td>
<td>38</td>
<td>2270</td>
<td>14 days</td>
<td>Hypertelorism; low-set, malformed ears; slight proptalmia</td>
<td>Bilateral clinoanodactyly; grossly malformed heart and persistent ductus arteriosus; incisural and cerebellar herniation of brain; single umbilical artery</td>
</tr>
<tr>
<td>(6) Francke (1972)</td>
<td>46,XX,der(22)(x;16;22q2q4)mat: partial trisomy 16q(distant)</td>
<td>Premature</td>
<td>Low</td>
<td>Died during first year</td>
<td>Prominent forehead; flat nasal bridge</td>
<td>Large persistent ductus arteriosus; generalised hypotonia</td>
</tr>
<tr>
<td>(7) Machin and Crolla (1974)</td>
<td>46,XX,der(21)(x;16;18q1q21:p11:mat: partial trisomy 16q(distant)</td>
<td>38</td>
<td>2054</td>
<td>Died in neonatal period</td>
<td>Not stated</td>
<td>Multiple malformations</td>
</tr>
</tbody>
</table>

Two further cases of unbalanced segregation of translocations involving chromosome 16, 47,XX,+,der(14)(x;14;16q11q24)mat (Young et al., 1976), and 46,XX,der(9)(x;9;16p2q2)mat (Alfi et al., 1973), were not included because the translocations were only presumed to be reciprocal resulting in trisomy of the 16q telomere.
dation and a hypoplastic mandible, which have been commonly found as part of this syndrome, were present in the proposita. However, the manifestation of Down's syndrome is now considered to be dependent only on the trisomy of sub-band 21q22.1 (Habedank and Kampe, 1975; Sinet et al., 1976). Further, Lewandowski and Yunis (1975) suggest that this sub-band must be deleted for the clinical features of G-deletion syndrome 1 to occur. It is therefore probable, in this case, that the monosomy of 21q22.3 had little or no deleterious effect, and that the phenotypic abnormalities could be exclusively attributed to the trisomy of 16p. This view is reinforced by the report of a family in which 6 phenotypically normal members were monosomic for all but the most proximal part of band 21q22 (Habedank and Kampe, 1975).

In conclusion, there are as yet insufficient data to delineate a phenotype for trisomy 16p. It is difficult to distinguish the effects of trisomy 16p material from those of the other chromosomal imbalances in the previously reported cases. However, it is evident that, in contrast to the suggestion of Schmickel et al. (1975), trisomy 16p does not inevitably lead to spontaneous abortion. Both trisomy 16p and 16q cause congenital abnormalities, but these may be consistent with intrauterine life and a limited degree of postnatal survival. Moreover, since full trisomy 16 is apparently incompatible with all but the most rudimentary development, it must be the combined effects of the additional short and long arms that impart such lethality to this condition.

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