Case Reports


Antenatal diagnosis of trisomy 13 with unexpected increase in alpha-feto protein

Summary. A 24-year-old woman who had previously given birth to an infant with Down's syndrome was shown by chromosomal analysis of the liquor amnii to be carrying an infant with trisomy D. Routine examination of serum and liquor alpha-feto protein (AFP) in the antenatal period showed unexpected high levels of both, consistent with a neural tube defect. The fetus, however, did not have evidence of a neural tube defect but had scalp defects which were presumed to have allowed the leakage of AFP from the fetus into the liquor amnii and hence into the maternal serum.

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This 24-year-old woman had her first infant, a female, with classical Down's syndrome, in 1971. At that time she was 20 years old and her husband 24 years old. The infant's karyotype was 46, XX + 21 and mother and father had normal karyotypes. A second pregnancy in 1972 was terminated at nine weeks on psychiatric grounds. She became pregnant for the third time in September 1974 and was referred for amniocentesis on 15 January 1975. She was in good general health. Her blood group was Rhesus positive and she had no history of hepatitis or thyroid disease. Subsequent screening for thyroid antibodies was negative, and her serum complement was normal as were her immunoglobulins. There was no family history of aneuploidy in her relatives or in those of her husband.

Liquor amnii was obtained without difficulty and unexpectedly showed an increased AFP level of 70 μg/ml (radioimmunoassay technique; normal upper limits 40 to 45 μg/ml). A simultaneous check at another laboratory by a different method (single radial immunodiffusion) confirmed the raised level. Cytogenetic studies on the liquor specimen showed the presence of a fetus with trisomy D abnormality. The mother was therefore offered termination, and this was performed at 20 weeks' gestation. A further specimen of liquor obtained before induction, and while the fetus was still alive, showed that the AFP was still raised, 68 μg/ml in the liquor; 187 ng/ml in the serum.

Fig. 1.

Necropsy

External features. The fetus was female, weighing 240 g (Fig. 1). At the vertex of the skull there was an area of translucent, very thin skin, approximately 3 × 1 cm, the histological appearance of which is shown in Fig. 2.

There was a similar smaller defect near the posterior fontanelle. There was micrognathia, low set ears, a cleft palate, and polydactyly.

CNS. The brain weighed 40 g and showed no gross abnormality. The optic and olfactory nerves were normal.

Thorax. There was anomalous venous drainage with a small high ventricular septal defect.

Abdomen. A Meckel's diverticulum was present. The uterus was bicornuate with a single cervix. The right umbilical artery was absent. All other organs appeared normal on macroscopical and microscopical examination.

The position of the scalp defects and their characteristics were similar to those previously described in infants with trisomy 13. Subsequent fibroblast culture from the fetus confirmed trisomy 13. One month after
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**Delivery**

The antennal diagnosis of fetal aneuploidies is well documented (Ferguson-Smith et al, 1971) and amniocentesis would normally be recommended when a previous sib has been shown to have a chromosomal anomaly, particularly a trisomy 21. Hamerton, Giannelli, and Polani (1965) and others have reported the recurrence of trisomy 21 in more than one member of a family and this is very likely to occur where mother or father are shown to have a D/G translocation. Two different trisomies in successive sibsin a family have been reported only rarely (Laurence, Gregory, and Sharp, 1974; Butler et al, 1973) and it has been suggested that this sequence of events may occur more frequently than reported because of a high fetal loss with trisomy 13. Certainly there is a wide discrepancy between the reported incidence of trisomy 21, 1.5/1000, and trisomy 13, approximately 1/14,500. Trisomic aneuploidies occur as a result of meiotic non-disjunction and genes predisposing to non-disjunction are present in some animals and possibly in the human. Late maternal age appears to be a factor, more so in Down's syndrome than in the other trisomies. Minor structural abnormalities of the chromosomes; delay in the disappearance of the nucleolus; autoimmune thyroid disease; and virus infections have also been incriminated but did not appear to be present in this case. The high frequency of trisomy 21 suggests a special relation of the small acrocentric chromosomes to the protein spindle at meiosis.

The unexpected AFP values obtained both in serum and liquor seem to be explained by the presence of the fetal scalp defects. AFP, the prime plasma protein of the fetus during early intrauterine life, has been shown to be significantly raised in the amniotic fluid in cases of neural tube abnormality. It enters the liquor amnii, and hence the maternal serum, by diffusion through the membrane covering the meningomyelocele or directly where there is no covering. The serum level of AFP is also raised in a variety of other conditions, particularly in patients with hepato-cellular carcinoma and teratoblastoma, but none of these was present in this mother. The scalp defects as described in the fetus allowed only thin membranes to separate the cerebrospinal fluid from the liquor, and diffusion would be possible in the same way as with the membrane covering a meningomyelocele.

Scalp defects are not uncommon in trisomy 13 but they are rare congenital abnormalities (Conway and Johnson, 1956). There are no incidence figures quoted but they have been reported in infants without other serious associated abnormalities. For that reason they could, on occasions, produce a false positive result in the antenatal detection of neural tube defects. Cytogenetic studies would distinguish those fetuses with scalp defects and trisomic abnormalities but there seems to be no easy way of detecting the others antenatally. Very large scalp defects have been reported to be associated with a mortality rate of 20% (Cutlip et al, 1967), but some of these have probably been in association with unrecognized chromosomal anomalies. The size of the defect is probably not critical but the thickness of the membrane obviously is an important factor.

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Discordance for Cornelia de Lange syndrome in twins*

**Summary.** A male infant, the first-born of twins, with features of Cornelia de Lange syndrome is described. His normal twin was discordant for 3 of the 14 blood loci tested. Chromosomes from the affected infant appeared normal. Though the aetiological basis for the Cornelia de Lange syndrome remains obscure, most authorities accept genetic rather than environmental causation. The present findings of discordance for Cornelia de Lange syndrome in twins support this view but do not clarify the mode of inheritance.

Nearly 300 cases of the Cornelia de Lange syndrome have been reported; they include at least two sets of twins (Choo and Bianchi, 1965; Opitz et al., 1965). In these 2 cases, the twins were concordant for the syndrome and were presumably monozygotic. Two additional sets of twins, one concordant and one discordant for Cornelia de Lange syndrome, are known to the authors but have not been published with confirmatory data. It is the opinion of the authors and others (Motl and Opitz, 1971) that twins reported by Kroth do not clearly have the Cornelia de Lange syndrome.

The observation of twins discordant for the Cornelia de Lange syndrome forms the basis of the present report.

**Case report**

The parents, both normal 21-year-old Caucasians, have no known common ancestors. Their first child is a normal male; their second pregnancy was terminated by elective abortion. No relatives are known to have chromosome abnormalities, skeletal malformations, mental retardation, or features of the Cornelia de Lange syndrome.

Three months before the third pregnancy the mother underwent abdominal surgery to correct a stenotic ureter adjacent to the right renal pelvis. Five months later she had a urinary tract infection which was treated with hexamine mandelate for two weeks. Apart from this treatment and dietary supplements of iron and vitamins, no other drugs were taken during pregnancy. The mother denies any other illness during pregnancy.

The pregnancy was terminated in the thirty-ninth week by caesarian section after prolonged rupture of the amniotic membranes and fetal bradycardia. Twins were not suspected before delivery.

_Ta._ C. weighed 950 g, had a head circumference of 24.8 cm, and a length of 36.2 cm. A diagnosis of the Cornelia de Lange syndrome was made on the basis of: microbrachycephaly, general hirsutism, synphysis, long eyelashes, elongated philtrum, small nose with anteverted nostrils, ‘carp-like mouth’, microtia of the upper extremities, with each forearm terminating in a single digit, soft tissue limitation at the elbow, cardiac murmur, poorly differentiated genitalia, with hypoplastic foreskin, chordae, and incompletely descended testes, and cutaneous syndactyly of the right first and second toes (Fig. 1 and 2).

Radiological evaluation showed microcephaly, bell-shaped rib cage, malformed radius with absent ulna bilaterally, absent carpal bones on the left, and two unidentifiable carpal bones on the right.

The infant’s respirations were depressed immediately after birth but improved spontaneously over the first hour of life. Apnoeic episodes, cyanosis with feeding, and hypothermia recurred intermittently until death during an apnoeic episode at 34 hours of age.

At necropsy, the cusps of the pulmonary valve were thickened, a finding of uncertain importance. No gross or microscopical abnormalities other than those noted clinically were detected.

_Ta._ C. (HH 72-23077), the second born twin, weighed

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