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Kleeblattschädel anomaly and partial trisomy for chromosome 13 (47,XY,+der(13),t(3,13)(q24; q14)

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This paper reports a case of partial trisomy involving the proximal segment of the long arm of chromosome 13. Kleeblattschädel anomaly was one of the many anomalies found in conjunction with this syndrome. The cytogenetic classification of the extra partial chromosome was based on trypsin-giemsa banding patterns and a paternal translocation involving chromosomes 3 and 13.

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Whereas trisomy 13 is characterized by a definite set of clinical symptoms (Patau et al. 1960), the rarer partial trisomy 13 is less well defined, and its clinical symptomatology varies with the length of the trisomic segment involved. We report a patient with Kleeblattschädel anomaly having an extra G-like chromosome and displaying nonspecific clinical features which made syndrome classification difficult. Through banding patterns and the discovery of a parental translocation, the exact cytogenetic classification of the extra chromosome as a partial #13 was possible. To the best of our knowledge, this is the first time that Kleeblattschädel anomaly has been noted in a patient with partial trisomy 13.

Case Report

The proband was a white male infant born to a 21-year-old mother and a 21-year-old father. The pregnancy was uncomplicated except for some minimal vaginal bleeding 1 week prior to delivery. Labor started spontaneously at 37 weeks of gestation. Delivery was by cesarean section because of fetal distress. The birth weight was 2.1 kg, birth length 43 cm, and head circumference 31 cm. The APGAR score was 9 at 1 min and 10 at 5 min after delivery. Only two vessels were noted in the umbilical cord. The child had lanugo hair over his shoulders and back. A small sacral myelomeningocele and somewhat a trilobed-appearing skull with synostosis of the right coroneal suture were noted.

X-rays showed the heart and mediastinum to be normal. The computerized tomography of the brain was rather limited due to the bizarre shape of the skull (Fig. 1). The skull was dolichocephalic in shape (Kleeblattschädel anomaly). Abnormalities included were: marked dilatation of lateral ventricles; questionable cyst-like deformity;

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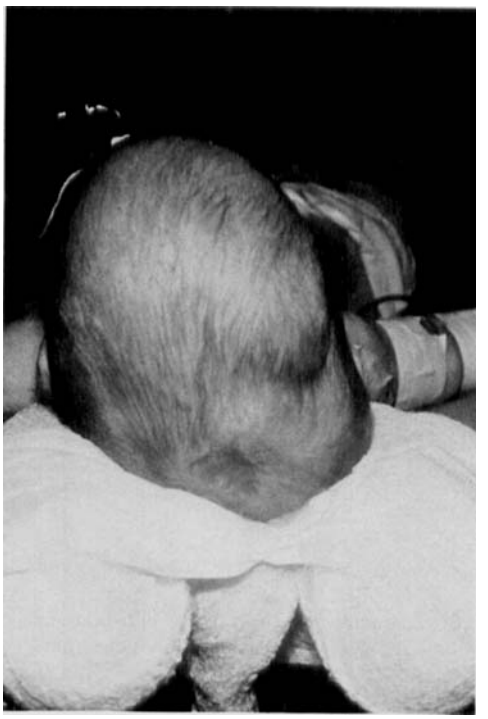

Fig. 1. Skull of proband showing trilobed appearance.

poorly defined third ventricle; sunken right orbit; and some atrophy in the hemispheric area.

During the child's initial hospital course the myelomeningocele was repaired. At 7 months of age, he was re-admitted to the hospital for release of the cranial synostosis and partial correction of the malformed skull.

Physical examination at 7 months showed the child to be severely retarded in gross motor and fine motor development. The patient's weight was 4.65 kg, his length 59 cm, and his head circumference 41.5 cm. Despite surgery, the skull was still asymmetric with frontal bossing and with the left parietal bone protuberant. The inner canthal distance was 2.4 cm and the outer canthal distance was 8.3 cm. There was bilateral macrocornea and extensive tearing compatible with the diagnosis of glaucoma. He had a low nasal bridge, a snub nose, and a prominent philtrum. The palate was narrow and somewhat high, but the alveolar ridges were very broad and contributed to this impression. A well-formed right ear was 4.4 cm in height. The left ear was 4.8 cm in height and was compressed on its vertical axis. The neck was short with increased skin folds in the nape. The chest was mildly asymmetric, but without pectus or abnormalities of nipple location. Abdominal examination was within normal limits. The penis was very small, measuring about 1.3 cm in length and 0.5 cm in diameter. There was no hypospadias. The right testis was not palpable. The left testis was in the left inguinal canal. The limbs were normally formed except for the hands and feet. The right hand showed ulnar loops on digits 1, 2, and 3, and arches on digits 4 and 5. The triaxial radius was proximally displaced. The left hand had ulnar loops on all digits. There was hyperextension at the first interphalangeal joint and some flexion at the second interphalangeal joint on both hands. The second toe overrode the first and third toes on the right foot. There were prominent heels, but no rocker bottom feet. The toenails were all mildly hypotrophic, most marked on the left third toe. The immunological studies were normal.

There was no increase in the number of projections in the polymorphonuclear neutrophils. Furthermore, the fetal hemoglobin was mildly increased for age (6 % at 8 months).

Chromosomal Analysis with G-Banding Studies

Chromosome analysis by G-banding (Fig. 2) showed 47 chromosomes in the proband with a translocation between chromosomes 13 and 3 (3q/13q). The extra chromosome present was a der (13). Analysis of the parents' chromosomes revealed a normal karyo-

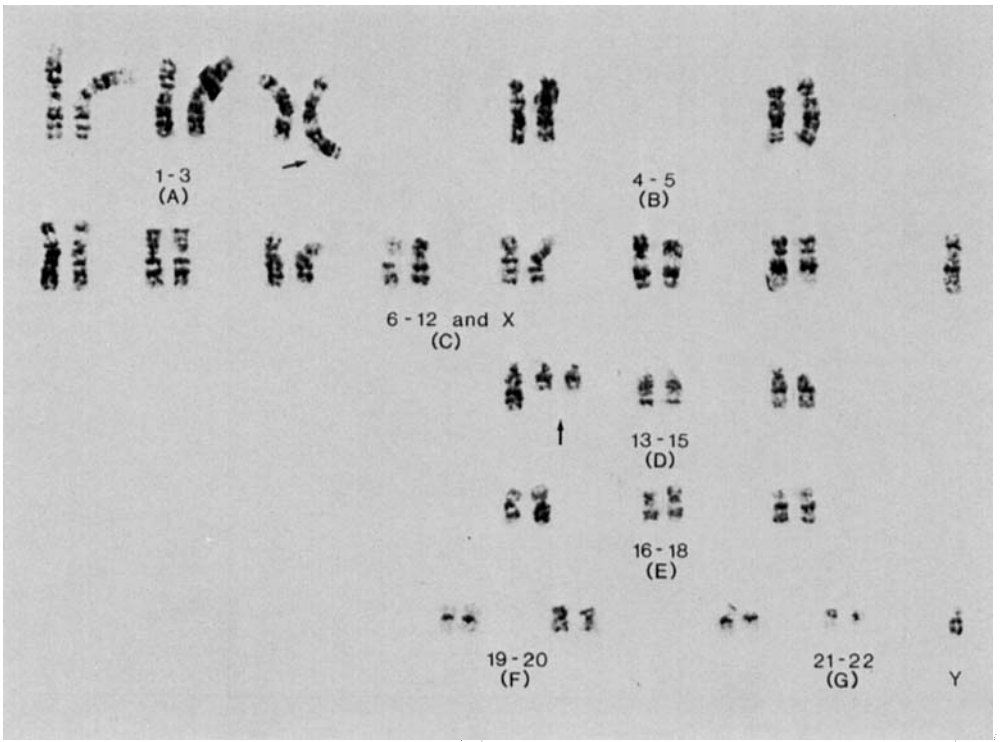

Fig. 2. Proband's karyotype, trypsin banded. Note translocation 13/3 plus der (13).

type for the mother, but showed that the father (Fig. 3) carried the same (3q/13q) translocation as the child. Thus the child was trisomic for the short arm and for the proximal segment of the long arm of chromosome 13, ending at band 13q14 where the original break occurred. The final karyotype was: 47,XY,+der(13),t(3,13)(q24;q14).

Discussion

Since clinical variability sometimes exists even among patients with complete trisomy 13, it is not surprising that patients with partial trisomy 13 show some common clinical features but often show marked differences depending upon the specific regions of the chromosome triplicated (Macintyre et al. 1964, Yunis & Hook 1966, Bloom & Gerald 1968, Escobar & Yunis 1974, Kajii et al. 1974, Schinzel et al. 1974, Schwanitz et al. 1974, Wilroy et al. 1975, Noel et al. 1976, Loevy et al. 1977, Fonatsch et al. 1979). The clinical features which are most commonly attributed to patients trisomic for the short arms and the proximal long arms of chromosome 13 include: sloping forehead, micrognathia, microphthalmia or coloboma, cleft lip and palate, and an increased number of nuclear projections. More specifically, trisomy for band 13q14 is associated with elevated fetal hemoglobin (Lewandowski & Yunis 1977), whereas trisomy for band 13q12 is associated with the persistence of increased nuclear projections of neutrophils (Lewandowski & Yunis 1977), but not all patients display these characteristics (Schinzel et al.

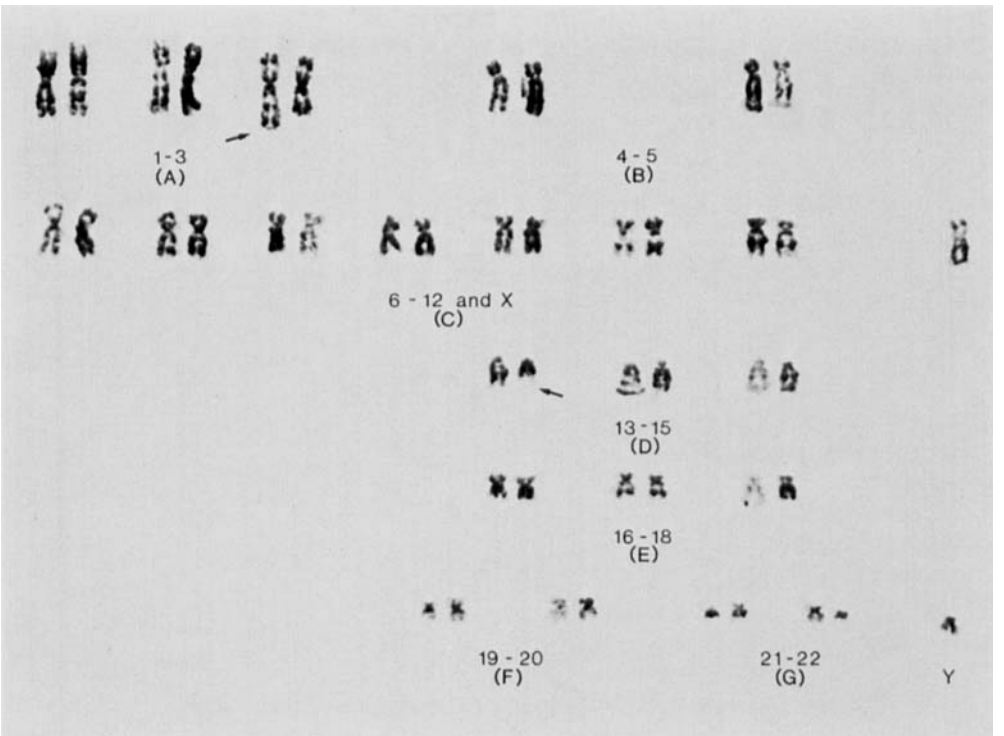

Fig. 3. Father's karyotype, trypsin banded. Note translocation 13/3.

1974). Bossing of the forehead has been associated with trisomy for the distal one third portion (13q21) of the long arm of chromosome 13 (Escobar & Yunis 1974). The bossing effect which we observed in our patient may be a secondary effect due to the bizarre shape of the head (clover-leaf shape or Kleeblattschädel anomaly). Some authors believe that Kleeblattschädel anomaly is a syndrome in itself, whereas others believe that it may be associated with a variety of syndromes. It has, for example, been associated with Carpenter's syndrome (Opitz 1969) and with Pfeiffer's syndrome (Opitz et al. 1972). There is one report of Kleeblattschädel anomaly and partial trisomy 15 resulting from an unbalanced 12/15 translocation (Pederson 1976).

To the best of our knowledge, this is the first report of Kleeblattschädel anomaly and partial trisomy 13. Although trypsin banding does not discriminate between the proximal portion of chromosomes 13 and 15, we feel that we are dealing with a partial trisomy 13, since silver staining for the ribosomal DNA of the extra chromosome shows a satellite configuration identical to that for the two normal #13 chromosomes.

Partial trisomies can arise by *de novo* translocation, pericentric inversion, or as a consequence of parental reciprocal translocation. In the case of our patient, the partial trisomy was traced to a paternal translocation. We have shown cytologically that the distal portion of the q segment of chromosome 13 in the father was translocated to the distal portion of the q segment of chromosome 3. We could not demonstrate

cytologically that any material from chromosome 3 was translocated to chromosome 13. Since the father was phenotypically normal, we presume no loss of genetic material. Either the translocation was non-reciprocal or the segment of chromosome 3 reciprocally translocated to chromosome 13 was too small to be detected by the banding techniques used. Such translocations can give rise to heritable chromosome imbalances. The imbalance in the proband could have arisen during the father's first meiotic division if there were a crossover in the interstitial segment between the centromere and the point of exchange on chromosome 13 followed by a 3:1 segregational event (Fonatsch et al. 1979). Such cases of tertiary trisomy have been reported in infants with Down's syndrome (Chagantr et al. 1975) and in infants with presumed partial trisomy 13 (Macintyre et al. 1964, Hauschtek et al. 1966, Jacobsen et al. 1966, Kaye et al. 1977). Alternatively, non-disjunction at the second meiotic division could form a gamete corresponding to the karyotype of the proband.

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