Discussion

The congenital anomaly described here has not, to our knowledge, been reported before, either sporadically or in kindreds with aniridia. It can be distinguished from primary anophthalmos, a rare autosomal recessive trait, by the complete absence of eyes and of palpebral fissures. In true primary anophthalmos only the ectodermal elements are missing, and the orbit is usually present with eyelids and small palpebral fissures; this condition has not been associated with adrenal and skull defects. Cryptophthalmos, a rare autosomal recessive disorder, is characterised by an absence of palpebral apertures. The eyes in such cases are usually present, although malformed and microphthalmic, and the nose is not usually abnormal, in contrast to our case.

While there is no proof that the defects described in our case were genetically determined, it seems highly likely that they were a consequence of the mating between two parents with aniridia. If this is so, it is possible that this dramatic defect represents the effect of the homozygous condition. Aniridia could therefore strictly be described as 'intermediate' to this severe homozygous phenotype.

It may well be relevant that pregnancies resulting from matings between aniridics have a poor outcome; of the 13 pregnancies known, including three in our patient, only five live children resulted, four with aniridia. The high pre- and perinatal death rate could be the result of fetuses with homozygous aniridia.

It is possible that the adrenal aplasia in this fetus represents the homozygous state of a recessive gene linked to aniridia, which is not apparent in the heterozygote, but this is obviously speculative. The location of the aniridia gene itself remains uncertain. The usually sporadic cases of aniridia with Wilms's tumour in which an 11p interstitial chromosome deletion has recently been found indicate a position on chromosome 11. However, other workers using linkage studies have suggested that the hereditary type of aniridia has its locus on chromosome 1. Perhaps the occurrence of adrenal aplasia in our case will help further in the location of the aniridia gene.

We would like to thank Professor P Polani and Dr A C Berry for their advice and help in preparing this manuscript.

References


Requests for reprints to Dr S V Hodgson, Paediatric Research Unit, The Prince Philip Research Laboratories, Guy's Hospital, London SE1 9RT.

Craniosynostosis and syndactyly: expanding the 11q- chromosomal deletion phenotype*

SUMMARY A patient with a partial deletion (q23→qter) of the long arm of chromosome 11 presented with craniosynostosis and syndactyly. These characteristics, which have not been previously reported with 11q−, expand the phenotype of this syndrome and emphasise the need for chromosome analysis with banding techniques in multiple congenital anomaly syndromes, even if the patient could be classified as having a non-chromosomal syndrome.

We recently evaluated a patient with craniosynostosis of the sagittal suture and syndactyly and found an 11q23→qter deletion. Since neither of these two predominant features has been previously reported in association with this chromosomal anomaly, this case significantly expands the clinical spectrum of this 'syndrome'.

Case report

The patient presented at 26 months of age for

*Supported in part by grants HD-05615 and HD-04612 from the National Institute of Child Health and Human Development

Received for publication 25 February 1980

S V HODGSON* and K E SAUNDERS†
*Paediatric Research Unit,
The Prince Philip Research Laboratories, Guy's Hospital, Guy's Tower, London SE1 9RT;
†Consultant Pathologist, Woolwich Group Hospitals
evaluation of short stature and developmental delay. She was the 3.4 kg, 46 cm long product of an uncomplicated pregnancy. Physical examination suggested sagittal suture cranial synostosis which skull X-rays confirmed. An uncharacterised heart murmur was also noted. Cranietomy was scheduled at 5 months but was delayed for evaluation of a possible tendency towards increased bleeding. The bleeding and clotting studies were all normal except for a slightly prolonged PTT. While surgery was therefore not contraindicated, the postponement resulted in a reassessment of the cranial anomaly which appeared to be non-progressive and surgery was deferred.

When next examined at 26 months she was 76.3 cm tall (>3 SD below the mean), weighed 10.7 kg (3 SD below the mean), had an US/LS of 1.78, and a head circumference of 50 cm (90th centile). She appeared dolicocephalic with coarse facies, hypertelorism, a high arched palate, low set ears, medial epicanthal folds, a broad nasal bridge, and a small upturned nose, but long philtrum. The upper lip was thin and the mandible small but not hypoplastic (fig 1). Soft tissue syndactyly of the 3rd and 4th digits of the hands was noted and confirmed by X-ray, as was syndactyly of the 2nd and 3rd toes bilaterally. The 12th left rib was absent. Cardiac evaluation revealed a grade 2/6 systolic murmur along the left sternal border. There were mild knee contractures and bilateral planovalgus feet. Muscle tone was generally hypotonic and gross motor, fine motor, speech, and adaptive social skills were all delayed. Developmental assessment at the age of 40 months showed significant delay, with gross and fine motor skills at 21 months, language at 24 months, and adaptive social skills at 18 to 24 months.

Dermatoglyphs showed bilateral palmar axial triradii, four ulnar loops and one whorl on the left hand, and three ulnar loops, one radial loop (5th finger), and one arch on the right hand.

Laboratory evaluation revealed a normal T₄ (9.4 μg/dl), normal electrolytes and creatinine, a bone age of 1 year 6 months, and normal urine amino-acid chromatography. Electrocardiogram showed right axis deviation, right atrial enlargement, and right ventricular hypertrophy. Chest X-ray was normal except for the absent 12th rib. A diagnosis of small ventricular septal defect was made. Brain CT scan revealed mild symmetrical ventricular enlargement, and repeat skull series confirmed the uncorrected sagittal synostosis.

The mother was aged 22 years at conception and was gravida 4, para 2, aborta 2 (at 2 months and 6 months without pathological evaluation of either abortus). The father was aged 26 years at conception. Both parents are reported to be of average intelligence. The older sister of the proband is developmentally and phenotypically normal.

**Cytogenetic Evaluation**

Trypsin-Giemsa (TG) chromosome banding from
cells of both blood and skin fibroblasts revealed a non-mosaic 11 distal deletion of the long arm of chromosome 11 distal to band q23. Reverse (R) banding showed absence of the distal dark band, compatible with a terminal deletion of the long arm of chromosome 11 distal to q23 (fig 2). Thus, the patient's karyotype is 46,XX,del(11)(q23→qter). TG banding of both parents was normal.

Examination of the patient's blood for gene markers showed no abnormal inheritance patterns. Specifically she was not missing any allele that she should have inherited from either parent. She was 'homozygous' for the following gene markers: Rh, Jk, P, Ak, 6PGD, ADA, PGM2, EsD, GOT, Gc, E-1, E-2. She was heterozygous for the following markers which excludes their location on the deleted chromosomal segment: PGM1, ACP-1, GPT, GALT, GLO-1, Hp, AMY-2, ABO, MNSs, Fy.

Haemoglobin electrophoresis on cellulose acetate showed a normal pattern. No Hb F was seen and Hb A2 was normal in amount.

Discussion

Since 1973 more than a dozen patients have been reported with deletions of the long arm of chromosome 11q.1–3 Common clinical features include growth retardation and craniofacial abnormalities characterised by trigonocephaly and coarse features. Major congenital abnormalities are uncommon and primarily limited to septal cardiac defects. The remainder of the features are sufficiently non-specific to make clinical diagnosis difficult. The current patient, however, presented with sagittal cranial synostosis and syndactyly neither of which have been previously described in this syndrome. However, craniosynostosis and syndactyly do occur in a variety of other multiple congenital anomaly syndromes. Most characteristic is that of Apert's syndrome (acrocephalosyndactyly) in which the coronal suture is primarily involved, although atypical cases have been described. Since that is a nosological diagnosis, without an identifiable chromosomal defect, but portending an autosomal dominant genetic prognosis, phenotypic variability may be deceptive. As illustrated in the table, our patient shares features with both the 11q− syndrome and Apert's syndrome, as well as differing from both. This suggests that either our patient will remain atypical or that the full spectrum of the 11q− syndrome will not be appreciated until more patients are described and more patients with sporadically occurring atypical craniosynostosis syndromes (especially with syndactyly) are studied with chromosomal analysis. The possibility that some patients have been erroneously categorised as atypical Apert's syndrome is suggested by the occurrence of two cases of pyloric stenosis in fourteen 11q− patients, and the reported increase of this abnormality in Apert's syndrome.4 Similarly, the incidence of mental retardation is said to vary in Apert's syndrome, while it appears to be a consistent finding in the patients with 11q− syndrome. Finally, a case of acrocephalosyndactyly associated with a chromosomal translocation from chromosome 2 to an unspecified C group chromosome (Cq+) was reported by Dodson et al.5 Studied before banding techniques, this case suggested a broader spectrum for Apert's syndrome, with as yet unassociated possible chromosomal defects. Retrospectively, the Cq+ finding could have represented chromosome 11 involvement.

The involvement of the specific region (11q23) for the chromosome break in almost all of the cases of 11q− deletion suggests the presence of some unrecognised characteristic of this part of the chromosome. One observation of an intercallary deletion noted that it occurred in a different region of the chromosome6 and in one case the break is described at the q21 band.7 The involvement of the 11q23 region is interesting when one considers that most of the chromosome changes appear to be simple deletions and are not involved in a recognisable reciprocal translocation with some other chromosome. A second unusual feature is that the deletion does seem to be a terminal deletion. This raises the possibility that there may be some stabilising component of the chromosome in the q23 region.

**Table**

The clinical features of 11q− compared to our patient and Apert's syndrome

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>11q−</th>
<th>Present patient</th>
<th>Apert's syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth retardation</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Syndactyly</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Cranial synostosis</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cardiac defects</td>
<td>+−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Trigonocephaly</td>
<td>+−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Narrow palate</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypertelorism</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pyloric stenosis</td>
<td>2/14</td>
<td>−</td>
<td>Increased incidence</td>
</tr>
</tbody>
</table>

BARBARA M LIPPE, †ROBERT S SPARKES, †‡
BENJAMIN FASS, †§ AND LEE NEIDENGARD §
†Department of Pediatrics, Division of Endocrinology and Metabolism, and
‡Departments of Medicine, Pediatrics, and Psychiatry, Division of Medical Genetics, UCLA Hospital and Clinics, UCLA School of Medicine; and §Tri-Counties Regional Center, San Luis Obispo, California, USA
Case reports

References


Requests for reprints to Dr Barbara Lippe, Department of Pediatrics, UCLA Hospital and Clinics, UCLA School of Medicine, Los Angeles, California 90024, USA.

Interstitial deletion in the long arms of chromosome 1:
46,XY,del(1)(pter→q22::q25→qter)

SUMMARY A child was brought to us with multiple anomalies. On examination we found an interstitial deletion in the long arms of chromosome 1. We studied genetic and chromosome markers, comparing our clinical and cytogenetic findings with other reported cases of chromosome 1 interstitial deletion.

Few cases of chromosome 1 interstitial deletion, with banding, have been published. As far as we know, only four clinical descriptions of patients with this type of deletion have been reported: Turleau et al. 1 46,XX,del(1)(q24q32); Koivisto et al. 2 46,XY,del(1) (q25q32); Garver et al. 3 in two sibs with del(1) (q25q32); and Schwanitz et al. 4 46,XY,del(1) (q22q25) associated with a pericentric inversion (1) (q25p13). All these cases had similar congenital malformations.

Case report

The proband was born on 3.1.77 to non-consanguineous parents. Family history was unremarkable.

Received for publication 10 February 1980

The father was 25 and the mother 21. During pregnancy the mother, who worked with solvents, suffered from vulvovaginitis and metrorrhagia in the first three months and developed oedema which was treated with diuretics. Pregnancy was at term and delivery normal.

At birth the child weighed 1720 g (<3rd centile), was 40 cm tall (<3rd centile), and had a head circumference of 29.5 cm (<3rd centile). When we saw him 11 months later he weighed 4050 g (<3rd centile), was 54 cm tall (<3rd centile), and had a head circumference of 32.5 cm (<10th centile). Physical examination revealed microbrachycephaly with closed fontanelles and fused sutures, frontal bossing, sparse eyebrows, bilateral exophthalmus, epicanthus and hypertelorism, low set ears which were slightly pointed and without lobules, bilateral cleft lip, and cleft palate (fig 1). Other abnormal features included a slightly keel-shaped thorax, bilateral inguinal hernia, hips with bilateral coxa vara, bilateral cryptorchidism with hypoplastic scrotum, short broad hands and feet, clinodactyly of the 5th finger of both hands, and a transverse palmar crease in the right hand. X-ray examination showed the bone age to be retarded and he had only 11 pairs of ribs. Neurological examination was abnormal for his size, although not for his age. The ponderostatural curve rose slowly throughout this period. The VDRL, toxoplasmosis, cytomegalovirus, rubella, CSF, blood and urine tests were all normal.

CHROMOSOME STUDIES

Chromosome analysis was carried out on peripheral blood lymphocytes by G banding, Q banding, and C banding. The karyotype showed an interstitial deletion in the long arms of chromosome 1, because of loss of material between the q22q25 bands: 46,XY,del(1)(pter→q22::q25→qter) (figs 2 3). The parents’ karyotypes were normal. In an attempt to discover the source of the deleted chromosome we studied the C banding pattern of

FIG 1 Facies of the proband.
Craniosynostosis and syndactyly: expanding the 11q-- chromosomal deletion phenotype.
B M Lippe, R S Sparkes, B Fass and L Neidengard

*J Med Genet* 1980 17: 480-483
doi: 10.1136/jmg.17.6.480