Absence/hypoplasia of tibia, polydactyly, retrocerebellar arachnoid cyst, and other anomalies: an autosomal recessive disorder

Lewis B Holmes, Raymond W Redline, Douglas L Brown, Amy J Williams, Tucker Collins

Abstract
Absence or hypoplasia of the tibia has been reported to occur as an isolated hereditary malformation as well as a feature of several autosomal recessive and autosomal dominant syndromes. We report three sibs with absence or hypoplasia of the tibia in association with other malformations whose parents are first cousins once removed. These infants appear to have a "new" autosomal recessive syndrome.


Case reports
The mother was interviewed before and after the birth of her second and third affected children. In none of her pregnancies was there an exposure to a known human teratogen. The family history showed that the parents are first cousins once removed. The mother had no skeletal malformations and reported none in her husband.

The first affected infant, a female, was born at term in the Dominican Republic (table 2). The mother was told by the physician who delivered this infant that she had a large head, unilateral cleft lip deformity, absence of the diaphragm, and short legs with the feet turned outwards and extra toes on the outer aspect of each foot. No records were available to confirm these findings.

The second affected infant, a male, was diagnosed by prenatal ultrasonography at 20 weeks of gestation as having a small (1 cm) cystic mass in the posterior fossa, a unilateral choroid plexus cyst, bowing of the radius and ulna and polydactyly of both arms, absence of the tibia, a club foot deformity, and polydactyly of both feet. The pregnancy was terminated electively after a prostaglandin infusion at 21 weeks of gestation. This fetus weighed 360 g (normal mean (1 SD) 353 g (12.5) 19 had a head circumference of 19 cm, crown-rump length of 20 cm (normal mean (SD) 18.9 cm (4.8)), and crown to heel length of 24.5 cm (normal mean (SD) 26.2 cm (3.6)). The head appeared enlarged and had a hole (1.5 x 1.0 cm) in the calvarium in the left occipital area. In association with a visible bulge in the occipital region (fig 1), there was a multiloculated (1.5 x 1.0 cm) retrocerebellar subarachnoid cyst in the posterior fossa and a normal cerebellar vermis, which excluded the diagnosis of a Dandy-Walker cyst. There was no cleft lip or palate deformity. The facial features included a prominent bridge of the nose, maxillary hypoplasia, and small chin. The diaphragm was intact. There was a long mesentery with a partial malrotation of the large bowel. There was a single extra digit on the ulnar aspect of each hand (fig 1), but no syndactyly. The distance between the knees and ankles appeared shortened. An extra well formed toe was present on the inner aspect of the left foot; there was no syndactyly. The right foot showed an enlarged fifth toe with duplication of the fifth toenail and syndactyly between the fourth and fifth toes.

Postmortem radiographs showed absence of the tibia and a bowed fibula (fig 2). There was no synostosis of the tarsals, the ankle bones were ossified, but the possibility of synostosis could not be ruled out. There was no apparent shortening of the radius. The extra digit was associated with an extra metacarpal in the

Table 1 Phenotypes that include absent tibia

Autosomal recessive
(1) Isolated absence of the tibia
(2) Tibia hemimelia, bifid femur, and split hand/foot
(3) Tibia hemimelia and deafness
(4) Tibia hemimelia and cleft lip/palate

Autosomal dominant
(1) Isolated absence of the tibia
(2) Aplasia of tibia and preaxial polydactyly or absent thumbs
(3) Tibia hemimelia and split hand/foot
(4) Tibia hemimelia and duplication of ulna and fibula
(5) Tibia hemimelia, shortened limbs, and trigonomacrocephaly
(6) Absence of tibia and radius
(7) Sandrow's syndrome of duplication of hands and feet defect, and tibia hypoplasia
(8) Hypoplastic tibiae with postaxial polydactyly

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Table 2 Phenotypes

<table>
<thead>
<tr>
<th>Features</th>
<th>Case 1 (female)</th>
<th>Case 2 (male)</th>
<th>Case 3 (male)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrocerebellar (arachnoid cyst)</td>
<td>&quot;Fluid on brain&quot;</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>(by history)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventriculomegaly</td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cleft lip</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diaphragmatic agenesis</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Malrotation of colon</td>
<td>?</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Radius shortened</td>
<td>?</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Tibia hypoplasia/absence</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Polydactyly</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Feet</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Hands (postaxial)</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>(Post)</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syndactyly of toes 4-5</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Hands and with an extra metatarsal in the feet. Chromosome studies on amniocytes with Giemsa, Dappi, and Methyl A3 stained metaphases showed a normal 46,XY karyotype.

The third pregnancy was monitored by prenatal ultrasonography, which suggested by 12 weeks of gestation that the fetus had a club foot deformity. Prenatal ultrasonography at 19 weeks of gestation identified dilated lateral cerebral ventricles, a retrocerebellar cyst (fig 3), shortening of the tibiae, and polydactyly of the feet. After an elective termination by a destructive procedure, the neuropathology and status of the diaphragm, heart, intestine, liver, spleen, and gonads could not be assessed. There was no cleft palate or polydactyly of either hand. There was preaxial polydactyly of both feet (fig 4), medial rotation of the feet, and shortened tibiae. Radiographs showed shortened and broad tibiae and fibulae and widening of the metaphyses of both femora. Chromosome studies with Giemsa and CA3DA banding of seven metaphases showed a normal 46,XY karyotype; 24 metaphases were counted.

Subsequently, this couple has had two normal pregnancies. These were followed by prenatal sonography with no abnormalities identified and normal infants were born at term.

HOX genes of several different classes have been implicated in limb development. As part of a larger survey of infants with multiple malformations, we performed Southern blot analysis using probes for several HOX genes, looking for structural arrangements. DNA was obtained from infants 2 and 3, the mother, and the father. A total of 10 μg was digested with restriction enzymes, screened by Southern blot analysis and probed with cDNA clones for the HOXD10, C9, and A9 genes. An anomalous band of 45 kb was identified in HindIII digested DNA from infant 2 when probed with the HOXD10 cDNA. HOXC9 and HOXA9 restriction patterns were identical to all other fetuses tested in the survey (data not shown). No anomalous HOXD10 band was found in DNA from infant 3, the mother, or the father. Additionally, this band was not seen in samples from 25 other infants with multiple malformations or in normal adults.

Discussion

In a review of the phenotypes of malformation syndromes associated with absence or hypoplasia of the tibia (table 1), we could identify...
none just like the three sibs we report. Since their parents are unaffected and are related, it is most likely that this disorder is the result of a rare autosomal recessive gene. We did identify two phenotypes which showed some similarity. First, Burn et al\(^8\) reported two sisters who were considered to have orofaciodigital syndrome with tibial dysplasia and had been born to parents who were first cousins. Their facial features included a broad and flattened nasal bridge, cleft palate in one, micrognathia, and hamartomas of the tongue. Their skeletal abnormalities included pre- and postaxial polydactyly, proximal shortening of the tibia with a generalised mesomelia, and shortened and poorly ossified bones in the middle phalanges. Both girls were delayed developmentally, had a bilateral conductive hearing loss, and had oculomotor apraxia. A CT scan of the head showed mild cerebral atrophy in one sister, but not in the other. Burn et al\(^8\) noted that two other sets of similarly affected sibs have been reported with mesomelic shortening of all limbs and flared metaphyses. Our patients differ in having retrocerebellar arachnoid cysts, having no hamartomas of the tongue in the one infant examined carefully (case 2), and no general mesomelia. It is particularly important to note that these children had proximal shortening of the tibia, whereas the shortening was distal in our patients. Secondly, Al-Awadi et al\(^{11}\) and Naguib and Al-Awadi\(^{12}\) reported a brother and sister with hypoplasia of the tibia, syndactyly of toes 2–3, and postaxial polydactyly of both hands. Their parents were related; the mother had syndactyly, the father had polydactyly, and a sister had polydactyly, raising
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We have confirmed in prenatal screening that the malformations of the lower legs in fetuses 2 and 3 could be detected as early as 12 menstrual weeks. This was suspected because of the presence of the appearance of a “club foot” deformity, as was the case in the 16’5 week fetus with absence of the tibia reported by Ramirez et al.

In summary, we have described a new constellation of anomalies characterised by tibial anomalies, polydactyly, and a large retrocerebellar arachnoid cyst which appears to have an autosomal recessive inheritance pattern.

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