

Craniomelic Syndrome: A Newly Recognized Lethal Condition With Craniosynostosis, Distinct Facial Anomalies, Short Limbs, and Intrauterine Growth Retardation

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We report on two sisters with an unusual form of craniosynostosis, protruding nasal spine, micrognathia, short limbs, lung hypoplasia, absent or hypoplastic gallbladder, short intestine with ileal distention, hypoplastic uterus, and intrauterine growth retardation. This combination of defects appears to be a newly recognized and probably autosomal recessive disorder.

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INTRODUCTION

Syndromes with craniosynostosis have been reviewed extensively elsewhere [Cohen, 1986, 1988] and, to date, it is estimated that there are about 90 syndromes with craniosynostosis as one manifestation [Cohen, 1993]. Here, we report on a newly recognized syndrome of craniosynostosis, distinct facial malformations, short limbs, intrauterine growth retardation, and other anomalies. The condition is clearly different from previously reported craniosynostosis syndromes.

CLINICAL REPORTS

The first girl was born at 40 weeks of gestation to healthy, non-consanguineous, 28-year-old parents, with no teratogenic exposures and no family history of birth defects. The pregnancy had been remarkable for small fundal height for dates. Fetal ultrasonography showed a growth restricted fetus with short but straight limbs, an abnormal skull, a small thorax, "poor

ossification," ventriculomegaly, and hydronephrosis. These findings were confirmed by serial exams. Her birth weight was 1.46 kg and Apgar scores were 2 and 2 at 1 and 5 minutes; she died 30 minutes after delivery. Her lymphocyte metaphase karyotype was 46,XX, normal.

The mother's second pregnancy was examined by ultrasonography at 14 weeks, at which time the fetal size was deemed appropriate for dates. At 17.5 weeks, all fetal measurements were consistent with an age of 15 weeks. At 22 weeks, all measurements except the cerebellar diameter were small for dates (biparietal diameter 4 cm, femur length 2.1 cm, head circumference 16.2 cm, abdominal circumference 10.3 cm, fibula 1.74 cm, humerus 2.10 cm, and radius 1.68 cm). The ratio of the head to abdominal circumference was 5 standard deviations below normal, reflecting the unusually small abdomen. The head shape was normal in the axial plane, and the outer and inner orbital diameters were proportional to head size. There was no hydrocephaly. The lips were intact, but the chin appeared to be small. The chest was bell shaped but its circumference, although small, was proportional to the rest of the body. The gallbladder could not be seen. The bowel pattern was normal for gestational age. The limbs were slightly shorter than expected for the degree of growth restriction. Bone density and shape were normal. The distal arms were shorter than expected for humeral length, but the legs were proportionate to the femora. The feet appeared to be normally related to the legs. The toes could not be visualized, but the fingers appeared to be normal. The pregnancy was terminated electively at 24.1 weeks. Birth weight was 190 g.

Both infants had relative macrocephaly and turri-cephaly (Figs. 1, 2). Both had short palpebral fissures, but while the eyes of the older infant were small and "dysplastic" the eyes of the younger one were apparently unremarkable. The nose of each was pinched at the tip with anteverted nares, and each had a distinct and marked protrusion of the nasal spine midway along the bridge of the nose (Figs. 3, 4). Both had marked micrognathia and microstomia, and the

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Fig. 1. AP Case 1. Note the disproportion between head and body, the short limbs, and the facial abnormality.



Fig. 2. AP Case 2. Note the disproportion between head and body, the short limbs, and the facial appearance.

younger one had a U-shaped cleft palate. Their ears were low-set and posteriorly angulated, and those of the older infant were short.

In the older infant, the posterior contour of the skull was marked by a low occipital protrusion that was incompletely invested with bone but completely invested with a dense fibrous tissue (like that associated with fontanels); this protrusion contained herniated cerebellum. The superior margin of this protrusion was demarcated by a thick ridge of bone, and this was the site of the tentorial attachment. Rostral to this the occipital bone swept posteriorly, at a 55° angle, forming a second bulge. The lambdoid sutures were patent but with very ragged margins of both the occipital and parietal bones. The apex of the occipital bone was marked by a short midline notch (extension of the sagittal suture). The squamosal sutures were patent to the greater wing of the sphenoid, but again the margins were ragged ("coast of Norway") and lacunar. The parietals were of very irregular thickness (dendritic ridging and lacunae). The sagittal suture was wide (5 cm) and virtually indistinct from the posterior and anterior fontanels. At the posterior margins of the parietals were islands (5×2 cm) of bone bilaterally.

The coronal sutures were not evident; internally there was a somewhat thickened ridge where the coronal suture would ordinarily be, but externally there was no clue to the presence of a suture. The frontal bones were virtually nonexistent above the supra-orbital rims. Instead there was a huge metopic "fontanel"

continuous with the anterior fontanel. The orbital roofs were distinctly lacunar. The skull base, from the cribriform plate to the foramen magnum, was in a single plane positioned at about 30° to the line of the occipital bone, averaging out the two occipital bulges to a single line. The posterior wall of the sella turcica was canted forward and the middle cranial fossae were rather deep. There was occipito-atlantic instability with about



Fig. 3. Face profile Case 1. Note the short nose and protruding nasal spine.



Fig. 4. Face-skull Case 2. Interosseous soft tissue has been removed to demonstrate the deficient frontal bones and large fontanelles.



Fig. 5. Hand-nails Case 1. Note the short, tapered fingers with talon-like nails.

50% occlusion of the foramen magnum on neck flexion. This infant had marked hydrocephaly and aqueductal atresia/stenosis.

The skull of the younger infant was similar in most respects to that of her sister, but without the irregular sutural margins or lacunae in the plates. Also, there was no occipital bulge; rather the occipital bone was flat. The configuration of the frontal bones and absence of the coronal sutures were identical in the two cases. The apices of the frontal bones were 14 mm rostral to the palpebral fissures, or just above the supraorbital rims. The fontanelles from metopic to posterior formed one continuous opening (Fig. 4). The metopic "fontanel" was 26.5 mm wide, the anterior fontanel was 19.5 mm wide, the sagittal suture was 18 mm at its narrowest, and 24 mm at its widest (midposterior) point. The squamosal suture was open posteriorly, but the proximal lambdoid sutures appeared to be fused. Occipito-atlantic instability with 75% occlusion of the foramen magnum was demonstrated on neck flexion. Neither hydrocephaly nor structural anomalies of the brain were detected.

The limbs of both infants were symmetrically short, the older one having circumferential creases of both the arms and legs. Their hands were short with tapered digits; the older infant had talon-like nails (of the toes, also) and bilateral absence of the middle phalanx of the index finger (Fig. 5). Both infants had equinovarus feet; the younger one had bilateral syndactyly of toes 2 and 3.

Internally, both had small, hypoplastic lungs. On microscopic examination, the airways were large and dilated to the periphery of the lungs. Cartilage, which appeared to be normal in the trachea and hilum of the

lung, was absent from the distal airways. The hearts showed ventricular myocardial hyperplasia, and the right coronary artery ostium was eccentric in the older infant. Each had a hypoplastic/absent gallbladder and short intestines (midgut and colon). Both had marked meconium distention of the mid-ileum (Fig. 6), but the gut in this region and distally had normal ganglion cells.

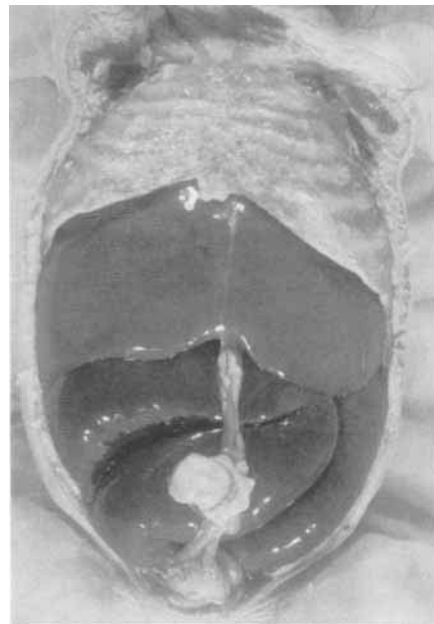


Fig. 6. Thorax-abdomen Case 1. Note the marked intestinal (ileum) distention.

Both had a hypoplastic uterus and short fallopian tubes; the labia majora of the older infant were hypoplastic. The older one also had marked hydronephrosis but a locus of ureteral obstruction could not be identified.

Roentgenograms of both infants showed short but otherwise normally configured long bones and no other abnormalities beyond those of the skull (Figs. 7, 8). Microscopically the bone and cartilage were unremarkable.

DISCUSSION

These sibs had coronal craniosynostosis with large fontanels, a distinct protrusion of the nasal spine, symmetrically short limbs with normal bone morphology, and intrauterine growth retardation. We propose the name *craniomelic syndrome* to identify this newly recognized condition. Two affected sibs, with normal chromosomes in one, from unaffected parents suggests autosomal recessive inheritance.

Despite the large number of craniosynostosis syndromes, the combination with short limbs and lethality limits the differential diagnosis. Both thanatophoric dysplasia (TD), type 2 [Langer et al., 1987], and Ives-Houston syndrome [Ives and Houston, 1980] are lethal conditions with craniosynostosis (cloverleaf skull in the former) and short limbs. However, both have more dramatically short limbs with distinctive radiographic appearance than in craniomelic syndrome. In TD, type 2, the limb bones are short and thick; other radi-

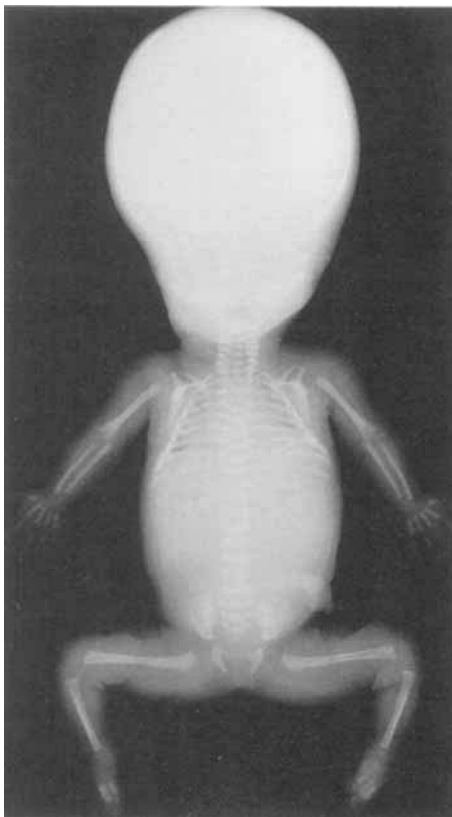


Fig. 7. AP X-ray Case 1. Other than in the cranium there are no skeletal anomalies.



Fig. 8. AP X-ray Case 2. Other than in the cranium there are no skeletal anomalies.

ographic findings include narrow thorax, short flared ribs, platyspondyly, narrow sacrosciatic notches, and horizontal acetabular roofs with spurring. In the autosomal recessively inherited Ives-Houston syndrome the elbows are fused, the forearms dramatically short, and the fingers varying from two-to-four in number.

The fetal aminopterin syndrome has several features in common with craniomelia, notably hypoplasia of the frontal bones, wide fontanels, craniosynostosis, micrognathia, cleft palate, low-set ears, and short limbs [Jones, 1988]. However, the facial features in craniomelia are quite different, and the mother of these sibs was not exposed to aminopterin or other folate antagonist. Campomelic syndrome of the craniosynostotic type, Carpenter syndrome [Cohen, 1986], and cranioectodermal dysplasia [Levin et al., 1977] are easily distinguishable from craniomelic syndrome.

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