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ACE Inhibitor Fetopathy and Hypocalvaria: The Kidney–Skull Connection

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ABSTRACT Two cases of angiotensin converting enzyme inhibitor fetopathy with renal tubular dysgenesis and severely underdeveloped calvarial bone are described. Six additional, unexposed cases of hypocalvaria are described, and possible links between calvarial development and fetal hypotension and/or chronic hypoxia are explored.

The purposes of this paper are (1) to report two cases of angiotensin converting enzyme (ACE) inhibitor fetopathy associated with a hypoplastic calvaria, (2) to explore possible pathogenetic ACE inhibiting links in the kidney–skull connection, and (3) to review briefly six other cases of hypoplastic calvaria together with their associated anomalies—most of unknown etiology. Before presenting case reports and discussion, we summarize the physiology, pharmacology, and reported fetal effects of ACE inhibitors.

ACE INHIBITORS

ACE inhibitors were developed from a serendipitous finding—Brazilian snake venom containing kinase-inhibiting factors (Ferreira, '65). Basic scientists demonstrated its physiological relevance by establishing the relationship between vasoactive peptide hormones and their enzymatic degradation (Yang et al., '70).

All ACE inhibitors[1] have a common 2-methyl propanalol-L-proline moiety. Captopril binds the enzyme by means of a sulfhydryl group; lisinopril does not. Proactive drugs were developed to increase the rate of resorption, to prolong the action of the active agent, or both. Enalapril is a proactive drug; it remains inactive until converted to an active compound in the liver. The primary route of elimination of the ACE inhibitors is the kidney (Williams, '88).

ACE inhibitors block the conversion of angiotensin I to angiotensin II, thus increasing renin and, when measured, reducing angiotensin II and aldosterone. The need for a higher replacement level of angiotensin II to restore blood pressure after the administration of ACE inhibitors suggests that factors other than the fall in angiotensin II may be responsible for reduction in blood pressure (Swartz et al., '79).

The relationship of ACE inhibitors to bradykinin degradation and to prostaglandin production is unresolved. The effects on these two hormones may occur at the tissue level without significant change in blood levels (Williams, '88).

ACE inhibitors have several advantages in treating hypertension. Most antihypertensive agents (e.g., diuretics and β-adrenergic receptor blockers) tend to elevate peripheral resistance and have an effect on the metabolism of glucose, lipids, and electrolytes. In contrast, ACE inhibitors decrease vascular resistance with no known adverse metabolic consequences (Williams, '88; Gavras, '88). In the absence of heart failure, little change in heart rate, cardiac output, or pulmonary wedge pressure is experienced in normal or hypertensive subjects taking

[1]Commonly used ACE inhibitors include captopril, enalapril, and lisinopril. However, other drugs are known such as ramipril, cilazapril, pentopril, and alacepril.

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ACE inhibitors (Vidt et al., '82; Todd and Heel, '86; Gomez et al., '87). It is now known that ACE inhibitors are an effective form of treatment for *all* stages of hypertension and some authors have suggested that ACE inhibitors are the preferred agents for the treatment of hypertension (Sassano et al., '87). Thus, we can expect greater use of ACE inhibitors in the future.

When ACE inhibitors have been administered during pregnancy, a number of cases have been reported with fetal wastage (Kreft-Jais et al., '88) and adverse late fetal and neonatal outcomes such as fetal anoxia, intrauterine growth retardation, oligohydramnios, postnatal anuria, Potter sequence, and respiratory distress (Guignard et al., '81; Rothberg and Lorenz, '84; Knott et al., '89; Schubiger et al., '88; Rosa et al., '89; Scott and Purohit, '89). Renal tubular dysgenesis associated with enalapril exposure was reported by Cunniff et al. ('90) and they noted the similarity to a genetic recessive form of tubular dysgenesis (Allanson et al., '83; Voland et al., '85; Bernstein, '88; Swinford et al., '89).

Less commonly reported ACE inhibitor exposure effects have included a hypoplastic calvaria (Duminy and Burger, '81; Mehta and Moda, '89; Rothberg and Lorenz, '84.) This defect is of particular concern because the fetal brain, inadequately protected by skull bone, could be severely traumatized during passage through the birth canal.

CASE REPORTS

Case #1

The mother, a 26-year-old G_2P_0, had systemic lupus erythematosus with nephrogenic hypertension of 8 years duration managed successfully with prednisone, atenolol, furosemide, and captopril. From 20 weeks gestation, serial ultrasound examinations showed unrelieved oligohydramnios, nonvisualization of the fetal bladder, and mild growth retardation. At 33 weeks a 1.44-kg girl was delivered. Apgar scores were one and five at 1 and 5 min, respectively. Despite maximal ventilatory support there was persistent acidosis and hypoxia. No urine was produced in the 14 hr before death. Autopsy showed pulmonary hypoplasia and deformations resulting from oligohydramnios. There was calcified thrombosis of the inferior vena cava with bilateral extension into the renal veins. Infradiaphragmatic venous return to the heart was via an enlarged azygous vein. The kidneys were large and showed renal tubular dysgenesis on microscopic examination (Fig. 1). The ureters and bladder were small but patent.

The calvarial bones were of normal configuration but very small, leaving the top third of the head unprotected by bone (Fig. 2). The wide "sutures" and "fontanels" consisted of relatively avascular, white fibrous tissue. The cranial base was unremarkable on gross inspection. A 2-cm coronal strip of calvarial bone beginning at the medial edge of the parietal bone was removed, decalcified, and stained with hematoxylin and eosin. The histology is illustrated in Figure 5A and compared to normal calvarial bone (Fig. 5B). The bone is remarkably thin without adequate trabeculation or marrow development in contrast to control calvarial bone.

Case #2

The mother, an 18-year-old primigravida, had essential hypertension of 10 years duration, successfully managed with lisinopril. The pregnancy was reportedly unremarkable with no suspicion of problems until the onset of labor at 32–33 weeks of gestation. After an unsuccessful trial of tocolysis, a 1.48-kg male infant was delivered by cesarean section, with Apgar scores of four and seven at 1 and 5 min, respectively. Persisting respiratory distress required the use of mechanical ventilation and the evacuation of bilateral pneumothoraces. However, his respiratory status improved and the respirator was discontinued on day 2 of life.

From the time of birth to his transfer to the University of Michigan Medical Center at 8 days of age, there was no urine output. The kidneys were of normal size by ultrasonography, but no perfusion was demonstrated on renal scan. Fluid and furosemide challenges did not result in urine output. After 2 weeks on peritoneal dialysis, he began to pass small amounts of dilute urine. A renal biopsy was obtained at 1 month of age (Fig. 3). His urine volume increased over the next several weeks, but at age 15 months he continues to be dependent on peritoneal dialysis and is awaiting renal transplantation.

In the neonatal period, the fontanels were described as large and the sutures were said to be wide. On examination at 1 month of age, the skull plates were small but of ap-

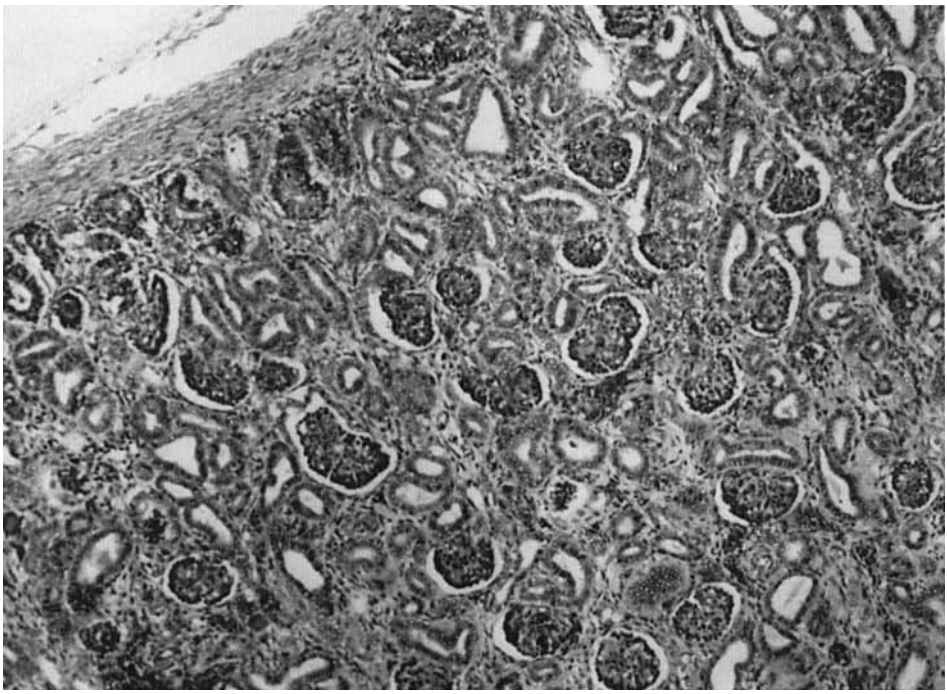

Fig. 1. Section of kidney (Case 1) showing dilation of glomerular spaces, convoluted tubules, and collecting ducts. There is poor to no differentiation between proximal and distal convoluted tubules and intertubular mesenchyme appears to be increased. (Trichrome stain. Original magnification ×100.)

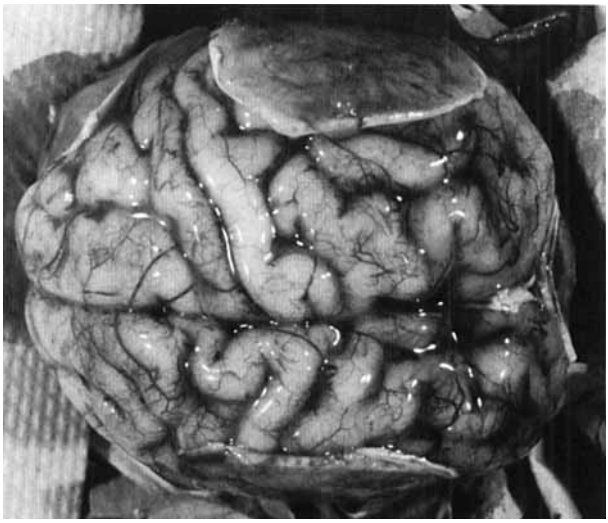

Fig. 2. Skull and brain viewed from above (Case 1). The tissue comprising the fontanels and sutural regions has been removed, leaving only the calvarial bone, to demonstrate the diminutive size of the bones in hypocalvaria.

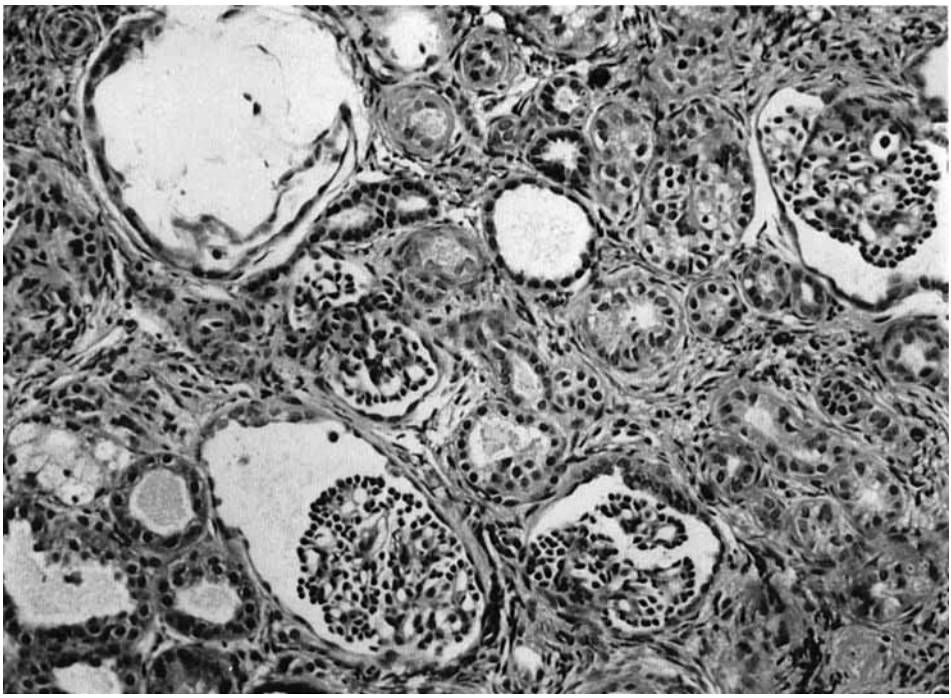

Fig. 3. Renal biopsy at 1 month of age (Case 2) showing dilated glomerular spaces. Also seen are a dilated collecting duct, some dilated tubules, and poor differentiation between proximal and distal convoluted tubules. In other areas of the biopsy specimen, the prior existence of glomeruli and tubules was indicated only by collapsed rings of basement membrane. (Trichrome stain. Original magnification ×200.)

propriate configuration. The midpoint width of the various sutures were: sagittal 3 cm, coronals 3 cm, lambdoidals 2 cm, metopic 2 cm, squamosal < 2 mm. The anterior fontanel measured 6 cm (long) by 4 cm (wide) and the posterior fontanel was 4 by 4 cm. During the ensuing months, considerable expansion of the calvarial bones was evident, and by 3 months of age the metopic, coronal, and lambdoidal sutures were less than 0.5 cm wide, the sagittal suture had narrowed to 1.5 cm, and there was a corresponding reduction in the size of the fontanels.

Case #3

The mother was a 26-year-old primigravida with Melnick–Needles syndrome. Third trimester ultrasonographic examination showed oligohydramnios, intrauterine growth retardation, and multiple anomalies. Labor was stimulated by prostaglandins for a worsening biophysical profile, and a 36-week, 1403-gm male stillborn with multiple anomalies and ambiguious genitalia was delivered from the breech position. The placenta was dysmature with chorangiosis, amnion nodosum, stem villous edema, and a cord length of 25 cm. Autopsy findings, summarized briefly in Table 1, were diagnostic of male Melnick–Needles syndrome. Hypocalvaria was an associated finding, the top one-third of the brain being unprotected by bone (Fig. 4). A 2-cm coronal strip of calvarial bone beginning at the most medial edge of the parietal bone was removed, decalcified, and stained with hematoxylin and eosin. The histology is shown in Figure 5C and compared to normal calvarial bone (Fig. 5B). The bone is thinner than normal calvarial bone and is highly irregular, exhibiting an abnormal network pattern, many reversal lines, and inadequate marrow formation.

TABLE 1. Known cases with hypocalvaria and acalvaria

Striking features	Etiology	Reference
Hypocalvaria, oligohydramnios, postnatal anuria, renal tubular dysgenesis, contractures of elbows and wrists, talipes calcaneovalgus, rockerbottom feet	ACE inhibitory effects (captopril)	Barr and Cohen, Case 1
Hypocalvaria (resolving), postnatal anuria, renal tubular dysgenesis, respiratory distress (resolved), survival at 15 months with severe renal dysfunction	ACE inhibitory effects (lisinopril)	Barr and Cohen, Case 2
Hypocalvaria, left leg ended at midthigh	ACE inhibitory effects (captopril)	Duminy and Berger ('81)
Hypocalvaria, oligohydramnios, Potter sequence, contractures of elbows, knees, and ankles	ACE inhibitory effects (enalapril)	Mehta and Moda ('89)
Hypocalvaria, oligohydramnios, postnatal anuria, intrauterine growth restriction, contractures of ankles, hips, and elbows	ACE inhibitory effects (captopril)	Rothberg and Lorenz ('84)
Hypocalvaria, renal cystic dysplasia, arhinencephaly, small dysplastic eyeglobes, ocular hypertelorism, cleft palate, micrognathia, ear anomalies, defects of long bones, vertebrae, and ribs; omphalocele, abnormal genitalia (46,XY)	Melnick–Needles syndrome	Barr and Cohen, Case 3
Hypocalvaria, massive hydrops, nuchal cystic hygroma, ocular hypertelorism, short nose, micrognathia, brachydactyly, brachymetacarpalism, brachymetatarsalism, postaxial polydactyly (left foot), coarctation of the aorta, persistent left superior vena cava, Meckel diverticulum of the ileum, 46,XY	Unknown	Barr and Cohen, Case 4
Hypocalvaria, oligohydramnios, intrauterine growth restriction, pulmonary hypoplasia, short nose, low-set, posteriorly rotated ears, short sternum	Unknown	Barr and Cohen, Case 5
Hypocalvaria, macrocephaly, hypotrophic legs, small lungs, small thymus	Unknown	Barr and Cohen, Case 6
Hypocalvaria, oligohydramnios, ocular hypertelorism, bilateral cleft lip and palate, microtia, transverse terminal deficiency of fingers and toes, preaxial polydactyly (left hand), cleft sternum, omphalocele, scoliosis, unilateral testicular agenesis, coarctation of the aorta, hydrocephaly	Unknown; maternal cleidocranial dysplasia	Barr and Cohen, Case 7
Hypocalvaria, oligohydramnios, upslanted palpebral fissures, short nose, rounded upper lip, low-set ears, short neck, contractures of elbows, thumbs, and knees, brachydactyly	Unknown; maternal immunotherapy	Barr and Cohen, Case 8
Acalvaria, alobar holoprosencephaly, ocular hypertelorism, oblique facial clefting, cleft lip and palate, low-set, malformed ears	Unknown	Sperber et al. ('86)
Acalvaria, absent orbital floors, cleft lip, metatarsus varus	Unknown	Mannes et al. ('82)
Acalvaria	Unknown	Vergani et al. ('87)

Case #4

A 39-year-old $G_3P_0Ab_2$ woman carried a fetus with marked hydrops shown on ultrasonography at 9 weeks. Chorionic villus sampling at 10 weeks showed a 46,XY karyotype. Elective termination was carried out at 15 weeks by prostaglandin induction. The 137-gm fetus was characterized by marked generalized hydrops, bilateral cystic hygroma, and multiple anomalies summarized

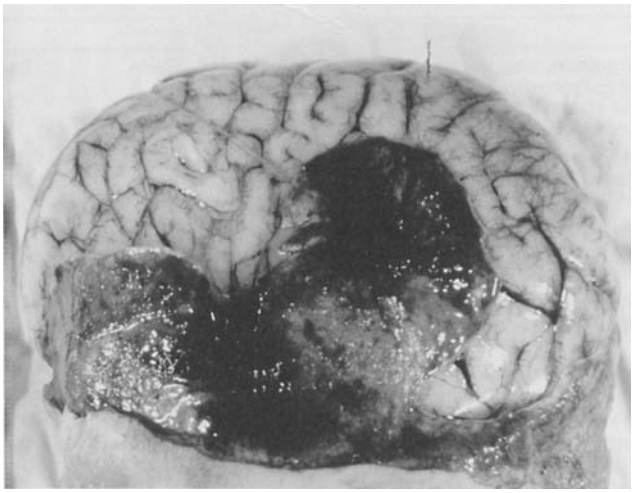

Fig. 4. Skull and brain viewed from the left (Case 3, Melnick–Needles syndrome). As in Figure 2, the tissue comprising the fontanels and intersutural regions has been removed to demonstrate the diminutize size of the calvarial bones and the unprotected state of the brain.

in Table 1. The top one-third of the brain was uncovered by bone. All sutures, including the squamosal, were split; the midsaggital width was 15.0 mm.

Case #5

A 30-year-old $G_3P_1Ab_2$ woman showing an increase in maternal serum α-fetoprotein was referred for ultrasonography. Severe oligohydramnios, fetal bradycardia, and no fetal motion were evident. Elective termination by prostaglandin induction produced an 80-gm fetus whose features are listed in Table 1. The skull plates were small, leaving the top half of the brain uncovered by bone. The distance between the frontal apices was 2.5 cm; distance between anterior parietal apices, 2.5 cm; distance between posterior parietal apices, 2.0 cm; frontal bone height, 2.0 cm; parietal height, 2.5 cm; and occipital bone height, 1.5 cm. Karyotype was 46,XX.

Case #6

A 27-year-old G_2P_1 woman with a history of no fetal motion for 2 weeks and fetal death confirmed by ultrasonography requested induction of delivery at 27 weeks. The 133-gm female fetus (20 week size) was macerated with considerable distortion of all body parts. Macrocephaly with hypoplastic calvarial plates was evident. Other findings are listed in Table 1.

Case #7

A 33-year-old G_1P_1 woman with cleidocranial dysplasia was referred for fetal ultrasonography because of an elevated maternal serum α-fetoprotein. The fetus was hydropic and had an omphalocele and other less well-defined anomalies. The patient elected to have the pregnancy terminated by prostaglandin induction and a 56.4-gm male fetus was delivered at 17 weeks gestation. Hypoplastic calvarial bones were evident in addition to other anomalies listed in Table I. Attempts to grow fetal cells for karyotyping were unsuccessful.

Case #8

A 31-year-old $G_{11}P_0Ab_{10}$ woman was found at 19.6 weeks gestation to have an elevated maternal serum α-fetoprotein, oligohydramnios, and severe fetal growth delay. Ovulation had been induced with clomiphene, and immunotherapy with her husband's leukocytes had been administered. The patient elected to terminate the pregnancy by prostaglandin induction, and a 68.8-gm female fetus was delivered. Hypocalvaria and other anomalies, listed in Table I, were found. The products of five of her prior miscarriages had been karyotyped: four were normal and one was triploid. No karyotype could be obtained from this fetus.

DISCUSSION

Nomenclature: hypocalvaria

Acrania usually refers to absence of the calvaria with the cranial base present. It is commonly distinguished from anencephaly because it is not a neural tube defect, although the brain may be abnormal in some cases (Mannes et al., '82; Vergani et al., '87). However, the term acrania is inaccurate because it implies involvement of both the calvaria—which is composed of membrane bones—and the cranial base—which is preformed in cartilage.

We propose the following terms which we think more accurately describe our observations. We introduce the term *hypocalvaria* to mean hypoplasia of the membrane bones of the skull. The finding of hypoplastic calvariae of different types in ACE inhibitor and Melnick–Needles fetopathies indicates that hypocalvaria is both etiologically and pathogenetically heterogeneous. Our proposed term is also flexible enough to describe the defect independently of whether the brain is normal or abnormal or whether the cartilaginous cranial base is normal or abnormal. *Acalvaria,*[2] referring to aplasia of the membrane bones of the skull, apparently occurs much less commonly than hypocalvaria. Although we have not observed a case, we are aware of three instances in the literature (Sperber et al., '86; Mannes et al., '82; Vergani et al., '87) and these findings are summarized in Table 1.

Although references in the literature to the condition we are calling hypocalvaria are few, we suspect the condition may not be all that uncommon. It seems probable that many cases would be classified as huge fontanels with widely split sutures but in instances in which appropriate degrees of macrocephaly are not present. Our standard is that the calvarial bones are absolutely small for age; lacking age-specific morphometrics, this is a somewhat subjective assessment.

The calvaria may also be defective with *craniotabes.* Prolonged vertex positioning results in compression and resorption of the top of the calvaria. Craniotabes is easily distinguishable from hypocalvaria. Craniotabetic defects may be quite large, ovoid in shape, and asymmetrically placed. The edges feel smooth to clinical palpation; the central area feels soft because of absent bone. Craniotabes need not necessarily result from prolonged vertex positioning; it may occur with any form of intrauterine compression and is an occasional feature of the oligohydramnios (Potter) sequence.

Hypocalvaria is also easily distinguished from cranial defects that may occur with *aminopterin or methotrexate embryopathy, Saethre–Chotzen syndrome, hydrolethalus syndrome,* or *cranium bifidum with large parietal foramina* (see Gorlin et al., '90; Little et al., '90).

In *hypophosphatasia,* the calvarial bones are normal in size and shape, but are composed of osteoid with minimal-to-absent calcification in the lethal form of the disorder. In the infantile form, the cranial sutures appear widened radiographically. In *achondrogenesis,* the skull is poorly mineralized in Types I (Houston–Harris) and II (Fraccaro) and occipital defects occur in Types II (Fraccaro), III (Langer–Saldino, severe), and IV (Langer–Saldino, mild) (see Gorlin et al., '90).

Pathogenetic aspects of hypocalvaria and the kidney–skull connection

The cause of the hypoplastic calvaria found with ACE inhibitor exposure is unknown. Endochondral bone and membrane bone grow and develop in entirely different ways. Long bones require low oxygen tension because nutrition takes place by diffusion through the cartilaginous epiphyses. Membrane bones, on the other hand, have the high degree of vascularity necessary for their own growth, and high oxygen tension is required. The presumed hypotension produced by ACE inhibitor exposure may result in hypoxic effects and thus a hypoplastic calvaria.

Secondary cartilage has been found attached to the edges of normal calvarial bones on occasion (Pritchard et al., '56). In avian experiments, it can be induced by hypoxia and by mechanical factors (Hall, '67a,b). However, no secondary cartilage was found on histologic examination of the calvaria in Cases 1 and 3, the only ones to be examined microscopically.

With presumptive hypotension and hypoxia from ACE inhibition, ischemia was responsible for intracranial hemorrhage in one case (Mehta and Modi, '89) and enceph-

[2]The term was introduced by Sperber et al. ('86). They preferred "acalvaria" to "acrania," indicating also that the latter term incorrectly implies absence of the entire cranium.

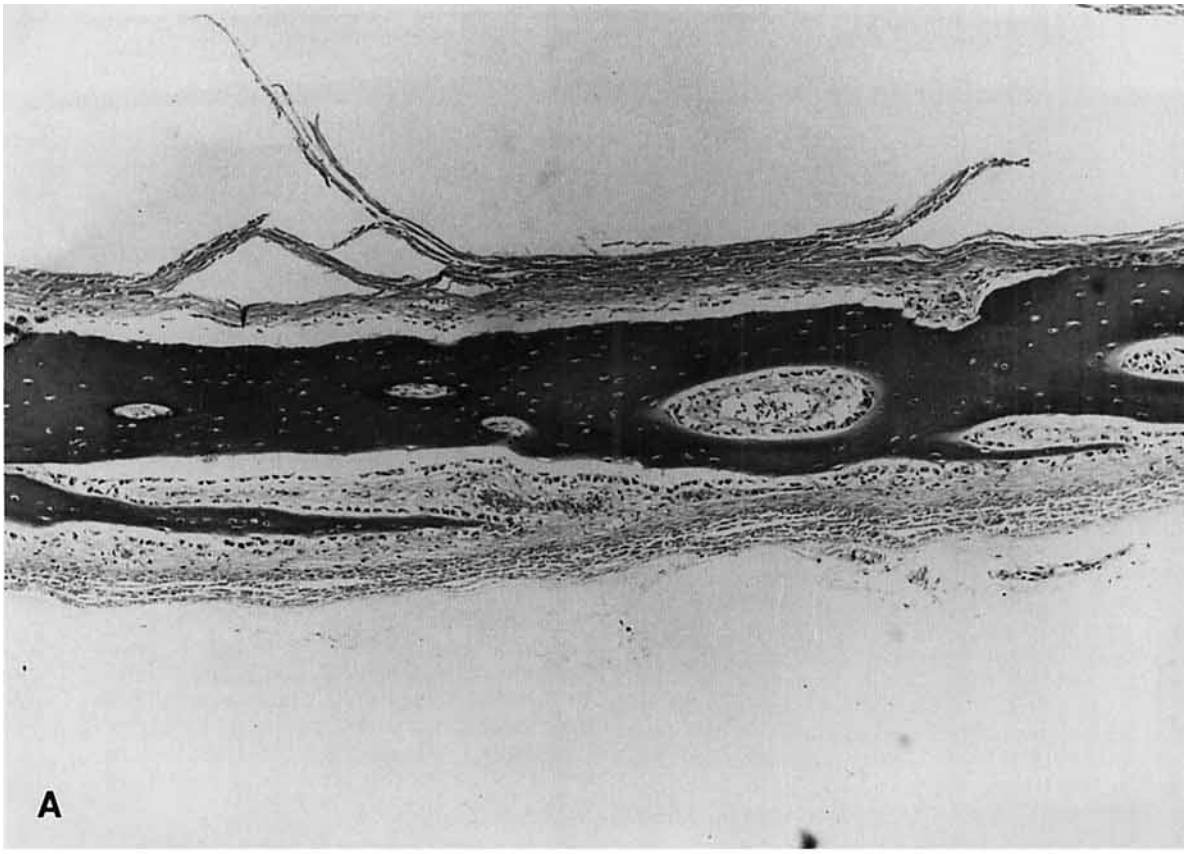

Fig. 5A and B.

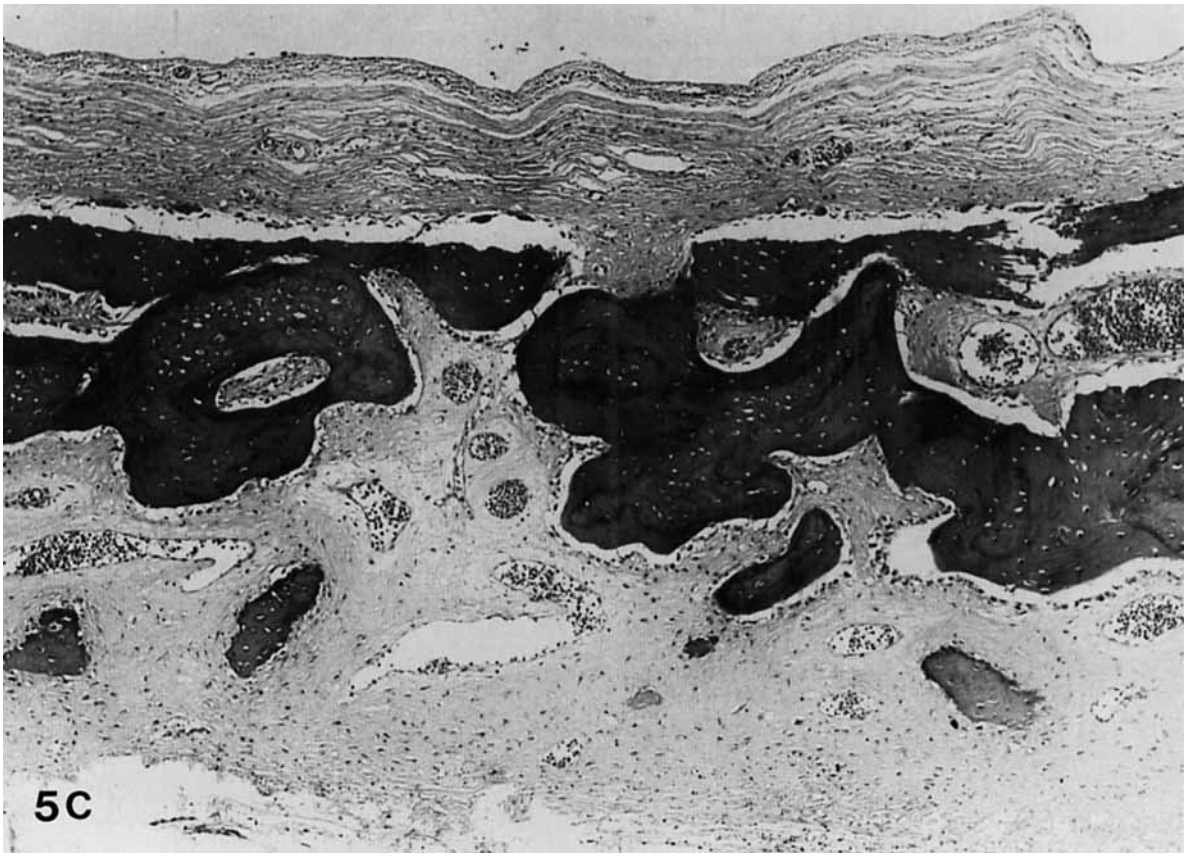

Fig. 5. Skull histology of hypocalvaria. Each section was prepared from a strip of bone beginning at the medial edge of the parietal bone. **(A)** Case 1 (ACE inhibitor exposure, 33 weeks gestation): the bone is thin without adequate trabeculation or marrow development. **(B)** Normal fetus (33 week gestation) for comparison. **(C)** Case 3 (Melnick–Needles syndrome, 36 weeks gestation): the bone is thin and highly irregular, exhibiting an abnormal network pattern, many reversal lines, and inadequate marrow formation. (H&E stain. Original magnification ×100.)

aloclastic prosencephaly in another (Seilanian, '90). Both of these instances were also associated with hypocalvaria.

One known effect of ACE inhibition is on the renal microvasculature at the level of the efferent arterioles. A kidney–skull connection may exist if (1) generalized hypotension produces simultaneous but independent hypoxic effects in the kidney and the calvarial bones or (2) the vessels of the glomeruli and the calvaria react similarly to ACE inhibition.

ACE is widely distributed in the body; it has been found in soluble form in body fluids and in membrane-bound form in arterial endothelial cells within and outside the pulmonary circulation, in epithelial cells with brush borders (placenta, kidney, intestine, and choroid plexus), in neuroepithelial cells, and in the male genital tract (testis, prostate, and epididymis) (Erdös and Skidgel, '87). To our knowledge, osteoblasts have not been studied. If present, it is conceivable that ACE inhibitors may act on one or more osteoblast-derived growth factors (IGF-I, IGF-II, TGF-β1, PDGF, and bFGF)[3] thereby diminishing their autocrine/paracrine actions.

[3]IGF-I, insulin-like growth factor-I; IGF-II, insulin-like growth factor-II; TGF-β1, transforming growth factor-β1; PDGF, platelet-derived growth factor; bFGF, basic fibroblast growth factor (Mohan and Baylink, '90).

The features of ACE inhibitor fetopathy, including anuria-oligohydramnios, renal tubular dysgenesis, and hypocalvaria, suggest that the underlying pathogenetic mechanism is fetal hypotension. For each of our eight cases of hypocalvaria a case can be made for the existence of in utero hypotension/hypoxia, based on the morphologic findings and/or evidence of fetal growth restriction. In the ACE inhibitor-exposed cases, the renal lesion is similar to, if not identical with, that seen in both the genetic recessive form of tubular dysgenesis and ischemic renal injury. To determine how specific this renal lesion is, work is currently under way to examine the kidneys of other fetuses with presumed hypotension and/or chronic hypoxia. Additionally, if chronic fetal hypoxia is present, blood flow to the brain, heart, and kidneys might be preferentially spared at the expense of circulation to acral regions such as the limbs. If that is correct, such hypoxic fetuses should manifest differential growth restriction of the limbs. Our preliminary data suggest that relative shortness of the limbs, particularly the arms, is found under these circumstances. This line of investigation is also being pursued.

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