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Cranial MR Imaging in Rhizomelic Chondrodysplasia Punctata

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The rhizomelic form of chondrodysplasia punctata (RCDP) is a rare autosomal recessive disorder characterized by severe rhizomelic short-limb dwarfism, abnormal facies, psychomotor retardation, congenital cataracts, and joint contractures [1–4]. The condition is usually fatal within the first year of life, although a few patients have survived beyond infancy [1, 2]. We recently performed cranial MR imaging in an infant with RCDP; the findings from that study are reported here.

Case Report

A 2280-g boy was delivered uneventfully at 36-weeks gestation to a 28-year-old gravida 1/para 0 white woman. There was no history of consanguinity, maternal ingestion of warfarin during pregnancy, or dwarfism in the family. The father had bilateral hearing loss since birth, presumably due to maternal measles infection during pregnancy. Delivery was by cesarean section owing to breech presentation, and Apgar scores were 9 at both 1 and 5 min. The infant was noted to have short limbs, multiple flexion contractures, and an unusual facial appearance (prominent forehead, broad nasal bridge, deep-set eyes, prominent epicanthal folds, and slight micrognathia).

Shortly after birth the neonate developed respiratory distress and acidosis and was admitted to the intensive care nursery, where he was found to be mildly hypoglycemic and severely hypocalcemic. Physical examination was remarkable for length, 40.5 cm (<10th percentile); head circumference, 31.3 cm (25th percentile); and decreased red reflexes bilaterally (subsequently proved to be bilateral cataracts).

Radiologic examination demonstrated rhizomelic shortening of the upper and lower extremities, metaphyseal cupping, irregular calcific stippling of multiple ossification centers in the axial and appendicular skeleton ("stippled epiphyses"), laryngeal calcification, and coronal clefts of the vertebral bodies (Fig. 1A). A clinical diagnosis of RCDP was suggested and later confirmed biochemically (decreased plasmalogen levels). The neonate was discharged within 1 week.

The patient was seen at age 2½ months with vomiting, mild dehydration, and apneic episodes (found to be secondary to mild gastroesophageal reflux). During this hospitalization, bilateral conductive hearing loss was also discovered. A cranial MR examination was performed on a 1.5-T scanner (Picker International, Highland Heights, OH) because of failure to thrive. Sagittal T1-weighted and axial T1- and T2-weighted images were obtained. These demonstrated bilateral areas of abnormal signal intensity (increased on T2- and decreased on T1-weighted images) in the periventricular and subcortical white matter, especially in the occipital regions, and mild sulcal prominence (Figs. 1B and 1C). Six months later the patient had a follow-up cranial MR study because of developmental delay. This again demonstrated abnormal white matter signal within the occipital regions with progression of generalized cerebral atrophy (Figs. 1D and 1E).

The patient was still living at 11 months of age.

Discussion

RCDP, the autosomal recessive form of chondrodysplasia punctata, is one of at least five subtypes of this disorder. The other forms [1–5] are the autosomal dominant form (Conradi-Hünermann disease); a lethal X-linked dominant form; an X-linked recessive form; and a mild, sporadic form described by Sheffield et al. [5]. These different variants of chondrodysplasia punctata share a variety of clinical features including congenital cataracts, characteristic facies, joint contractures, and ichthyosiform skin lesions. The rhizomelic form, RCDP, well described by Spranger et al. [1] in 1971, differs from the more common Conradi-Hünermann type by (1) a more severe rhizomelic shortening of the extremities, (2) a much higher prevalence of cataracts and psychomotor retardation, and (3) a much more severe clinical course (being lethal in infancy in the majority of cases).

Because of clinical similarities between RCDP and Zellweger cerebrohepatorenal syndrome, Kretzner et al. [6] suggested the presence of a related underlying biochemical abnormality. Since it was known that the basic biochemical defect in Zellweger syndrome was generalized peroxisomal dysfunction, Heymans et al. [7–9] studied peroxisomal functions in patients with RCDP. They discovered several biochemical abnormalities in these patients, including (1) profound impairment in plasmalogen synthesis, (2) defective phytanic acid oxidation, and (3) failure to process the thiolase enzyme [7–10]. Consequently, RCDP was added to the grow-

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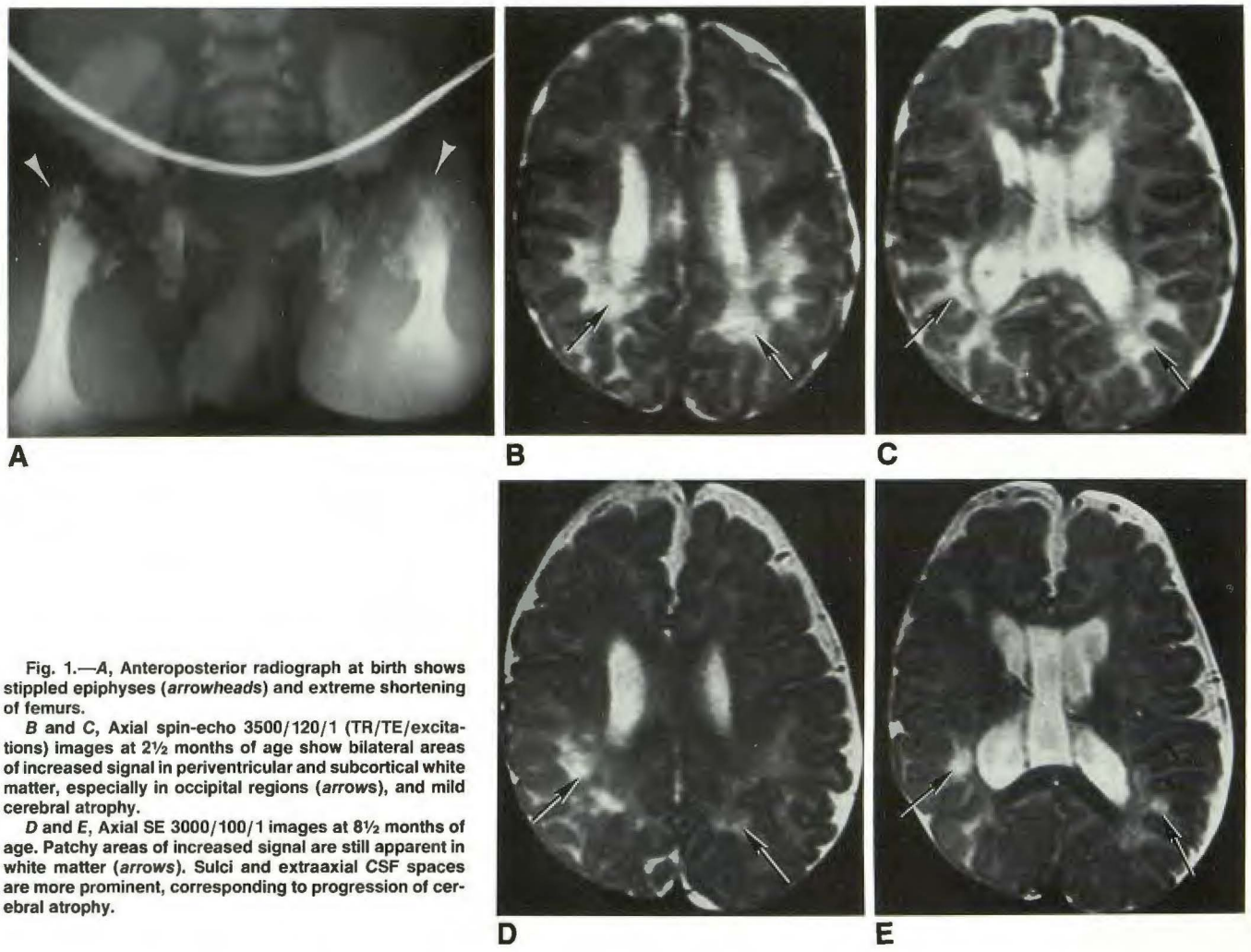

Fig. 1.—*A*, Anteroposterior radiograph at birth shows stippled epiphyses (*arrowheads*) and extreme shortening of femurs.

B and *C*, Axial spin-echo 3500/120/1 (TR/TE/excitations) images at 2½ months of age show bilateral areas of increased signal in periventricular and subcortical white matter, especially in occipital regions (*arrows*), and mild cerebral atrophy.

D and *E*, Axial SE 3000/100/1 images at 8½ months of age. Patchy areas of increased signal are still apparent in white matter (*arrows*). Sulci and extraaxial CSF spaces are more prominent, corresponding to progression of cerebral atrophy.

ing list of diseases characterized by peroxisomal dysfunction [7–9, 11, 12].

At least 12 different peroxisomal disorders are known at this time; 10 of these demonstrate neurologic involvement [13]. The conditions that constitute this disease category show autosomal recessive or sex-linked recessive inheritance and phenotypic heterogeneity. Peroxisomal disorders have been extensively reviewed in the nonradiologic literature in recent years [13–19], and can be divided into three major groups. The first group includes disorders in which there is failure of formation or maintenance of the peroxisome with subsequent defective function of multiple peroxisomal enzymes. Among this group is the prototypical peroxisomal abnormality, Zellweger syndrome, characterized by complete absence of peroxisomes. The other conditions in this group are neonatal adrenoleukodystrophy, infantile Refsum disease, and hyperpipecolic acidemia. RCDP and combined peroxisomal–β-oxidation enzyme protein deficiency make up the second group of disorders. In these diseases, structurally abnormal peroxisomes are usually present, although several peroxisomal functions are impaired. The final group consists of a variety of disorders with a single enzyme defect but normal numbers of peroxisomes and includes X-linked adrenoleukodystrophy among others.

Peroxisomes are present in all cells except mature erythrocytes and are quite numerous in nervous tissue [13]. They are especially abundant within oligodendrocytes, where they can be demonstrated in processes near developing myelin sheaths, particularly during the peak of myelin formation [13, 20]. These findings suggest that peroxisomes play a major role in myelinogenesis [13]. They are involved in a wide variety of catabolic and anabolic reactions, several of which are potentially important in neurologic disorders; for example, plasmalogen biosynthesis, very long chain fatty acid (VLCFA) oixidation, and hydrogen peroxide decomposition [10, 13–19].

Neuropathologic findings have been described in peroxisomal disorders [13–19, 21–24]. These include disordered neuronal migration and white matter de- or dysmyelination (i.e., sudanophilic leukodystrophy). Neuropathologic changes have been less well documented in patients with RCDP [2, 13].

No satisfying pathogenetic hypothesis has been proposed for the migration anomalies seen in these peroxisomal disor-

ders, although circulating toxic lipid metabolites may play a role [23]. White matter abnormalities, on the other hand, well demonstrated in this case, may be related to deficient biosynthesis of a major myelin component (e.g., the plasmalogens), to myelin instability due to the accumulation of VLCFAs in myelin gangliosides, or to an immune reaction elicited by these VLCFA-containing gangliosides [13, 20–25]. While VLCFA metabolism is not affected in RCDP, plasmalogen biosynthesis is profoundly decreased, suggesting a prominent role for this phospholipid in the pathogenesis of the severe neurologic deficit invariably present in the disorder. Recent reports indicate that plasmalogens, besides being major components of myelin, may also protect animal cell membranes by scavenging reactive oxygen species [26].

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