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Clinical Letter

Chondrodysplasia Punctata: A Clue to the Zellweger Spectrum Disorders

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Patient description

This one-day-old, former 36-week preterm male infant presented with hypotonia and multifocal seizures. Prenatal and family histories were not available. Prominent dysmorphic features included a high forehead, a widely spread sagittal suture, and a palpable liver. Stimulation elicited a slight grimace and only minor movements of the extremities. Muscle tone was low, and tendon reflexes were weak and symmetric. Focal myoclonic activity of the extremities correlated well with the spike trains on the electroencephalogram and ceased following phenobarbital administration. Metabolic laboratory assessment revealed mildly abnormal liver function and proteinuria. A plain X-ray of the hand showed chondrodysplasia punctata (CDP; Fig). The severe clinical presentation, along with the abnormal hand radiograph, strongly suggested a diagnosis of cerebrohepatorenal disease of Zellweger that was confirmed by an elevated ratio of C26:C22 fatty acids in plasma and by molecular genetic testing demonstrating a *PEX1* gene mutation.

Discussion

This report describes the unique association of Zellweger syndrome and CDP. The hallmark of CDP is stippling of epiphyses at birth.[1] The characteristic calcification in epiphyseal cartilage disappears with age as the epiphyses become irregular and accompany rhizomelia (long bone shortening). CDP may be found in the peroxisomal biogenesis disorders in the Zellweger spectrum (PBD-ZSD) that develop due to autosomal recessive mutations of one of 13 different PEX genes that are involved in the creation and proper function of peroxisomes.[2] The PBD-ZSD include diseases wherein peroxisomes are effectively absent, including Zellweger syndrome, neonatal adrenoleukodystrophy, infantile Refsum disease, and hyperpipecolic acidemia, and diseases such as rhizomelic CDP wherein peroxisomes are present, but their function is impaired. Symptoms related to abnormal brain, liver, kidney, eye, and bone function vary greatly from one individual to another.

The severe prototypic peroxisomal biogenesis disease was named for Hans Zellweger.[3] Zellweger syndrome, also referred to as the cerebrohepatorenal syndrome of Zellweger, is characterized clinically by severe neurological dysfunction, craniofacial abnormalities, liver dysfunction, and cerebral dysgenesis, wherein a failure in neuronal migration promotes medial pachygyria and lateral polymicrogyria.[2] Although CDP is associated with PBD-ZSD, the presence of radiologically evident CDP in infants with Zellweger

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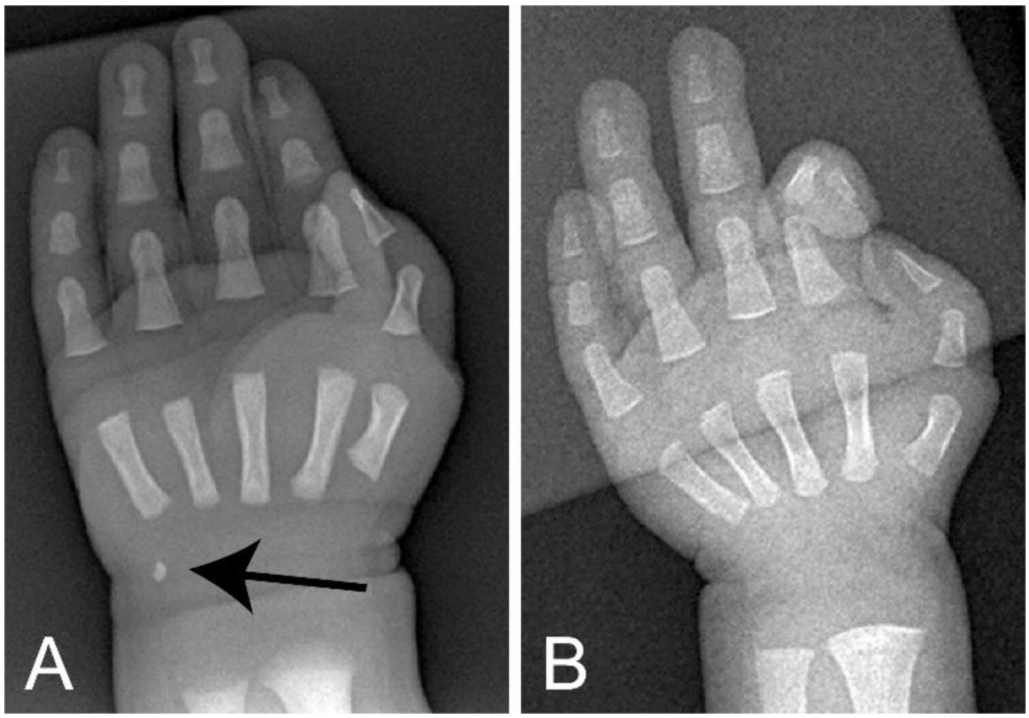

FIGURE. Chondrodysplasia punctata. (A) The radiograph of the infant's hand demonstrates stippling (a spot) near the proximal end of the fifth metacarpal (arrow). (B) The radiograph of an unaffected, same-aged child is shown as a reference.

disease is unclear. Most of the severely affected infants with the classic Zellweger phenotype die within the first year of life.[4] The milder neonatal forms of adrenoleukodystrophy and infantile Refsum disease are characterized by a prominent leukodystrophy, and symptoms may not develop until late infancy. Rhizomelic CDP has a distinct phenotype characterized by rhizomelia, seizures, recurrent respiratory tract infections, and congenital cataracts.[4,5] CDP can also be seen in babies born to mothers with autoimmune disease and in warfarin embryotoxicity.[1] Therefore the diagnosis of Zellweger spectrum disorders involves the detection of increased levels and impaired degradation of very-long-chain fatty acids[6] and confirmation by genetic testing.[2]

Although the patient's clinical presentation suggested Zellweger disease, the broad differential diagnosis of floppy infant syndrome was substantially narrowed upon review of the hand radiograph. Radiographs of the chest or other body regions are often performed during hospitalization and should be carefully screened for abnormal bone formation. Recognition of the bony abnormality on routine radiographs (that are not always reviewed by subspecialists) may significantly narrow the differential diagnosis of floppy infant syndrome, minimize laboratory evaluations, and provide an early diagnosis wherein life-prolonging interventions may require ethical considerations.

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