A 2-MONTH-OLD INFANT was referred for evaluation of poor weight gain, a weak suck, and hypotonia. The infant was the product of a full-term pregnancy during which the mother received no prenatal care, and was delivered by cesarean section because of a breech presentation. The birth weight was 3300 g. The parents were second cousins and had had a previous stillborn infant with facial dysmorphogenesis.

On physical examination the infant was alert but extremely hypotonic. Dysmorphic features included a high forehead, flat, broad nasal bridge, micrognathia, and a high arched palate (Figure 1). The sucking response was poor. The fontanels were large and the liver was palpable 3 cm below the right costal margin (Figure 2). The left testis was cryptorchid.

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Denouement and Discussion

Zellweger (Cerebro-Hepato-Renal) Syndrome

Figure 1. The forehead is high and the facies flat.

Figure 2. The anterior fontanel, outlined, is huge. The liver, also outlined, extends below the right costal margin.

The first siblings with Zellweger syndrome were reported independently by Bowen et al in 1964 and Smith et al in 1965. Although the phenotypic features were well described, it was not until 1973 that Goldfischer et al determined that peroxisomal defects were present in the disorder.

Zellweger syndrome is the prototype of peroxisomal disorders. Peroxisomes are single membrane-bound cytoplasmic organelles that contain at least 40 enzymes involved in a host of essential metabolic functions, including the catabolism of very-long-chain fatty acids; the biosynthesis of plasmalogens involved in myogenesis; the metabolism of alkyl glycerophospholipids and bile acids; the catabolism of pimelic acid, dicarboxylic acids, and phytic acid; and the oxidation of polyamines. Peroxisomal disorders are usually classified into 2 groups: those with defective peroxisomal structure resulting in impairment or loss of multiple peroxisomal functions and those with defects in a single enzyme or pathway.

The peroxisomal disorders associated with defective structure of the organelle include Zellweger syndrome, neonatal adrenoleukodystrophy, rhizomelic chondrodysplasia puncta, and infantile Refsum syndrome. Single peroxisomal enzyme deficiencies include X-linked adrenoleukodystrophy, classic Refsum disease, and pseudo-Zellweger syndrome (3-ketoacyl-coenzyme A thiolase deficiency), among others.

CLINICAL MANIFESTATIONS

Infants with Zellweger syndrome have a striking constellation of clinical features. The typical facial features include a high forehead, shallow supraorbital ridges, upslanting palpebral fissures, flat and broad nasal bridge, and micrognathia. The facies and occiput are flat. The anterior fontanel is large. Eye abnormalities include Brushfield spots, epicanthal folds, glaucoma, cataracts, and optic nerve dysplasia. The neck has redundant folds of skin. Hepatomegaly is usually present. Severe hypotonia and a weak suck are characteristic. Neonatal seizures are common. Most infants are born by breech presentation.

POSTNATAL COURSE

Infants with Zellweger syndrome have severe feeding difficulties and a marked failure to gain weight. Prolonged jaundice and diarrhea are common. Liver function abnormalities may lead to liver failure or cirrhosis. Hepatic and renal cystic dysplasia and proteinuria are often present. Severe psychomotor retardation and seizures are the result of abnormal fetal brain development. Most affected infants die in the first year of life, frequently in the first few months after birth.

ETIOLOGY AND DIAGNOSIS

Zellweger syndrome is inherited in an autosomal recessive fashion. At least 2 different genetic loci, one at chromosome 7q11.23 and a second at 1p22-p21, have been identified in infants with this disorder.

The diagnosis of Zellweger syndrome is usually suggested by the classic clinical picture. The clinical diagnosis can be supported by demonstration of elevated plasma and tissue levels of very-long-chain fatty acids, phytanic acid, pimelic acid, and bile salt precursors. Decreased plasmalogens synthesis is also noted. Prenatal diagnosis is possible using immunoblotting of peroxisomal β-oxidation enzymes in cultured amniocytes.

COMMENT

Although the peroxisomal disorders may have a wide range of phenotypic expression, investigation for a peroxisomal disorder may be warranted in patients who have a combination of 3 of the following clinical characteristics: psychomotor retardation, hypotonia, impaired hearing, low or broad nasal bridge, hepatomegaly, and abnormal electroretinogram in addition to 1 or more of the following features: large fontanels, shallow orbital ridges, epicanthal folds, antverted nostrils, and retinitis pigmentosa.

Zellweger syndrome must be distinguished from Down syndrome, with which it is sometimes confused because of the hypotonia and facial features.

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REFERENCES