Peroxisomal Bifunctional Enzyme Complex Deficiency With Associated Retinal Findings

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ABSTRACT
Peroxisomal bifunctional enzyme complex deficiency is a recently recognized abnormality of fatty acid metabolism. We herein present the association of a flecked retina with peroxisomal bifunctional enzyme deficiency, a clinical association not previously reported. We suggest the finding of a flecked retina in an infant presenting with hypotonia, seizures, and failure to thrive is highly suggestive of this diagnosis.

INTRODUCTION
Disorders of peroxisomal biogenesis are an unusual yet well recognized group of metabolic abnormalities. Included in this group of diseases is Zellweger cerebrohepatorenal syndrome,1 neonatal adrenoleukodystrophy (NALD),2 and infantile phytic acid storage disease (Refsum's disease). The biochemical abnormalities that characterize this group of diseases include impaired beta-oxygenation of long-chain fatty acids (VLCFA), impaired oxygenation of phytic acid and piperocic acid, decreased plasmalogen synthesis, and abnormal bile-acid metabolism. Patients with peroxisome biogenesis defects present clinically with severe psychomotor retardation, hypotonia, failure to thrive, and abnormalities of visceral organs (liver and adrenal glands) and the skeletal system.3 The diagnosis of NALD is generally made on clinical grounds and confirmed by demonstrating low levels of peroxisomes in body tissues and by finding high levels of VLCFA.3,4

Recently, several cases have been described in which tissue peroxisomes were present in normal numbers in patients previously diagnosed as having NALD.5,6 Using immunoblot studies of peroxisomal beta-oxygenation enzymes, a deficiency of one of the three enzymes, bifunctional enzyme (enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydroxinsase) was identified, whereas the other two enzymes were present at normal levels.5 We herein report two cases of patients with peroxisomal bifunctional enzyme deficiency who, during infancy, were found to have a flecked retina, a clinical association that heretofore has not been reported.

CASE REPORTS
Case 1. An infant girl was born at 36 weeks of gestation, birth weight 2340 g, to a 23-year-old primigravida with a history of ethanol abuse, drug abuse, and syphilis. The infant displayed severe hypotonia, seizures, and feeding difficulty. Work up revealed high levels of serum long-chain fatty acids and low levels of plasma carnitine. Complementation studies of cultured skin fibroblasts were performed at the Peroxisomal Diseases Laboratory, Kennedy Institute for Handicapped Children, Baltimore, Md, revealing a deficiency in the peroxisomal bifunctional enzyme complex (personal communication, Moser HW, Watkins PA, Moser AB). At age 2 months, the infant showed mild arteriolar attenuation and multiple small, round, deep retinal lesions in the midperiphery, typical of a flecked retina (Fig 1). A fluorescein angiogram showed normal arteriolar filling and a mottled appearance of fluorescence in the posterior pole. Ocular examination at 10 months of age showed progression of the retinopathy to that of a tapetoretinal degeneration (Fig 2), and flat scotopic and photopic electroretinogram (ERG) patterns were recorded. The child died at 12 months of age; no postmortem examination was performed.

Case 2. A term infant girl who was a second cousin to the patient in case 1, birth weight 2880 g, displayed severe hypotonia at birth and in early infancy began exhibiting seizure activity. Ocular examination performed 2 days later revealed a visually insignificant anterior polar cataract in the right eye and normal fundi bilaterally. Elevated serum long-chain fatty acid levels and the patient's clinical picture suggested an initial diagnosis of NALD. However, upon review, in light of the complementation study results in patient 1, her second cousin, the diagnosis was changed to peroxisomal bifunctional enzyme complex deficiency. Unfortunately, cultured skin fibroblasts were not available for complementation analysis and electroretin-
CoA hydratase/3-hydroxyacyl-CoA dehydroxidase), and peroxisomal beta-ketothiolase. Loss of any of these enzymes results in the accumulation of VLCFA (20 to 30 carbon atoms) in various human tissues, most importantly in the brain and adrenal glands.5

This group of peroxisomal disorders includes Zellweger cerebrohepato-renal syndrome, NALD, and infantile Refsum’s disease, the rhizomelic form of chondrodysplasia punctata.3 Recently, several cases that were originally diagnosed as either Zellweger syndrome or NALD have been shown to have normal and intact peroxisomes and an isolated deficiency of the bifunctional enzyme.5 Because of their classic clinical presentation and marked elevation of the VLCFA, the cases herein reported were likewise initially diagnosed as NALD. However, subsequent complementation studies performed on patient 1 indicated a marked deficiency in the peroxisomal bifunctional enzyme complex, resulting in a change in diagnosis.

Previously reported ocular findings in NALD include pigmentary retinopathy, arteriolar narrowing, optic atrophy, and an extinguished electroretinogram.3 Reports of the ocular findings in peroxisomal bifunctional enzyme deficiency are lacking. The two cases reported herein define a characteristic clinical marker for the peroxisomal bifunctional enzyme deficiency. In both children, a flecked retina was noted to develop in the first few months of life. We suspect that this represents a deposition of material, possibly VLCFA in the retinal pigment epithelium or deep retinal layers. With the deterioration of the clinical condition and progression of disease, the characteristic retinal spots begin to fade, with atrophy of the overlying retinal layers and damage to the retinal pigment epithelium. We suspect that a picture of complete tapetoretinal degeneration represents the end-stage fundus appearance of this disease.

Because the ophthalmoscopic picture of a flecked retina is so striking, and to our knowledge not present in association with other systemic conditions in infancy, we suggest that
these fundus findings in the neonatal period may represent a marker for peroxisomal bifunctional enzyme deficiency and serve as a means to clinically differentiate this condition from NALD. We hope that pediatricians and neonatologists will be aware of this association and will request funduscopic examinations on patients who present with severe hypotonia, seizures, and failure to thrive in the neonatal period. The finding of a flecked retina with this systemic background is highly suggestive of the diagnosis of peroxisomal bifunctional enzyme deficiency.

REFERENCES