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## Commentary

# Infantile Refsum Disease

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Disorders attributable to peroxisomal dysfunction are well recognized on the basis of their clinical and biochemical characteristics. These observations have resulted in a preliminary classification that recognizes two major groups of disorders, both of which are genetically determined. Group 1 consists of the generalized peroxisomal disorders that frequently cause signs and symptoms in the newborn period, are inherited in an autosomal recessive manner, and result from a failure of the peroxisomes to form or maintain themselves so that functional defects are present in more than one enzyme of this organelle. It is to this category that infantile Refsum disease (IRD) belongs [1, 2]. Other members of this group include Zellweger syndrome, neonatal adrenoleukodystrophy (NALD), and hyperpipecolic acidemia. Group 2 consists of a growing number of disorders in which the peroxisomes are normal in appearance, and only one enzyme defect occurs. This class includes X-linked adrenoleukodystrophy, hyperoxaluria type 1, acatalasia, acyl-CoA oxidase deficiency, bifunctional enzyme deficiency, and pseudo-Zellweger syndrome–thiolase deficiency. A third group, in which peroxisomes are present, but multiple enzyme defects occur, is exemplified by rhizomelic chondrodysplasia punctata (RCDP), but the position of this disorder in the classification is uncertain. Several recent reviews [3–5] provide further details of the distinguishing biochemical features of peroxisomal disorders.

Attention to the peroxisome as a cause of disease in humans stems from the observation that these organelles are completely absent in Zellweger syndrome; this was attributed to defective formation of the membrane [6]. More recent studies [3, 7] have shown that the primary defect involves the protein import mechanisms. The peroxisomal enzymes do not reach their target and are rapidly degraded in the cytosol [3, 7]. The resulting biochemical and pathologic abnormalities are used to distinguish the various groups. In Zellweger syndrome, all three enzymes involved in the $\beta$-oxidation of very long chain fatty acids (VLCFA) are absent [8]. In some forms of infantile-onset peroxisomal disorders (group 2), only a single enzyme may be defective, but the disorders are difficult to distinguish from group 1 disorders on a clinical basis alone. Morphologic abnormalities such as the presence, the absence, or a reduction in the number of peroxisomes provide important further information. The commonality of morphologic and biochemical defects in the four group 1 disorders led to the belief that they may represent a single disease entity, with the clinical variability reflecting the degree of severity of the biochemical defect. Recent complementation analysis, however, has shown that the situation is more complex.

Complementation analysis is a procedure in which cultured skin fibroblast cells from patients with different peroxisomal disorders are fused and compared with (1) cells that are cocultivated but not fused and (2) self-fusion controls. Complementation is said to have occurred when the fused cells acquire the capacity to synthesize plasmalogens or to form peroxisomes, as shown by the production of particle-bound catalase. If the fused cells are unable to synthesize plasmalogens or to form particle-bound catalase, they are assigned to the same category. Brul et al. [9] have shown six complementation groups, with RCDP forming a separate group 1. Zellweger syndrome, IRD, and hyperpipecolic acidemia made up group 2. Patients with the classic form of Zellweger

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syndrome who died at 3 and 5 months made up groups 3 and 5. Group 4 included patients with NALD.

Roescher et al. [10] in our laboratory studied cells from 19 patients with different disorders of peroxisome biogenesis; they also found six groups. The first group consisted of 13 patients with Zellweger syndrome, NALD, hyperpipecolic acidemia, and the IRD phenotype. Group 2 consisted of two patients, one with Zellweger syndrome and one with NALD. Three other groups consisted of one patient each with the classic Zellweger phenotype. The sixth group consisted of one patient with the NALD phenotype. McGuinness et al. [11] found similar results by complementation analysis in which the capacity of VLCFAs to undergo $\beta$-oxidation was used as a measure of complementation.

The combined results suggest the existence of *at least six different entities that are genetically heterogeneous*. No correlation has been found between the genotype and phenotype, suggesting that six or more different mechanisms exist for the clinical manifestations. As the primary defect has not yet been determined, patients continue to be described by using the previous nomenclature, as Dubois et al. [12] have done in this issue of the Journal.

Boltshauser et al. [13] and Scotto et al. [14] independently described IRD on the basis of the presence of elevated levels of phytanic acid in plasma. This led to the erroneous belief that IRD was an infantile variant of the well-known adult type of Refsum disease. It is now clear that phytanic acid is variably elevated in all of the disorders of peroxisomal biogenesis as well as in RCDP, which has a distinctly different clinical picture. Patients with IRD differ from those with classic Refsum disease. The former have an infantile onset of the disorder, minor dysmorphism, mental retardation, hepatomegaly, sensorineural hearing loss, retinal pigmentary degeneration, and hypocholesterolemia, as noted in the patients of Dubois et al. [12]. The chondrodysplasia and renal cysts common to Zellweger syndrome are absent. The multiple biochemical abnormalities in this group of disorders—namely, increased levels of VLCFAs and bile acid intermediates, and reduced plasmalogen synthesis—are not seen in Refsum disease of later onset. Deficient $\alpha$-oxidation of phytanic acid, however, is common to both conditions [15]. Notably, the elevation of plasma levels of phytanic acid in disorders of peroxisomal biogenesis is not as high as in Refsum disease. Although an age-related increase in phytanic acid is a feature of disorders of peroxisomal biogenesis, age alone does not appear to account for the lower elevation seen in the second decade of life in children with IRD [3, 5, 16]. Interestingly, the only source of phytanic acid in humans is the diet. It has been shown that phytanic acid, which is a highly branched fatty acid, is degraded via the $\alpha$-oxidative pathway to pristanic acid, which is then further degraded by ordinary $\beta$-oxidation. $\alpha$-Oxidation of phytanic acid has been shown to be a mitochondrial rather than a peroxisomal process in rat, monkey, and human liver [17, 18]. Therefore, the reason for its elevation in the peroxisomal disorders is presently unclear. An increase in pristanic acid, as well as phytanic acid, in the serum of patients with generalized peroxisomal disorders has been shown, which is not present in classic Refsum disease [19, 20]. It has been suggested that peroxisomal oxidation of pristanic acid may be defective in these disorders and that the accumulated pristanic acid may be a potent inhibitor of phytanic acid oxidase [18]. Alternatively, in the peroxisomal disorders, secondary changes may occur in mitochondrial membranes, as seen in Zellweger syndrome, that account for the defective oxidation of phytanic acid [6].

Pathologic studies on biopsy specimens of liver from patients considered to have IRD show an absence of peroxisomes or abnormally small peroxisomes with minimal catalase activity [21]. Skin fibroblasts from six patients with this diagnosis were examined by electron microscopy and cytochemical procedures to determine peroxisomal catalase activity. Four of the cell lines had peroxisomes with strong catalase activity similar to that of control subjects, whereas the liver biopsy specimens from two of the four patients showed no typical peroxisomes but marginally reactive bodies [22]. This observation points out the variability in tissues with respect to cytochemically recognizable peroxisomes in IRD and could explain the clinical heterogeneity in the siblings described by Dubois et al. Only one case report [23] of a postmortem examination of a patient with IRD has been published. It describes a micronodular cirrhosis; hypoplastic adrenal glands; and lipid-laden macrophages in liver, lymph nodes, and cerebral white matter. A mild and diffuse reduction of axons and myelin was noted in the corpus callosum, periventricular white matter, corticospinal tracts, and the optic nerves. The brain showed severe hypoplasia of the cerebellar granule layer and ectopic Purkinje cells in the molecular layer. These changes have been described as "granule cell aplasia" in metabolic diseases such as $GM_2$ gangliosidosis or in diseases without a known cause [23]. Such changes may be present in a more severe form in the female sibling presented by Dubois et al., with associated changes in the white matter accounting for the symmetrical signal abnormalities on MR in the region of the dentate nuclei.

Disorders of peroxisomal dysfunction manifested in infancy that are characterized by dysmorphism, hepatomegaly, hypotonia, retinitis pigmentosa, and, in some cases, seizures should be distinguished by these characteristics from other disorders with infantile onset. This clinical picture warrants a biochemical assay for peroxisomal function [24]. As exciting insights into the biological basis of the peroxisomal disorders become available, the genetic and phenotypic heterogeneity of these disorders will be clarified.

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