Peroxisome Disorders and Cutaneous Manifestations

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Beside complex structures such as endoplasmic reticulum or mitochondria that electron microscopy reveals in human cells, there are organelles bounded by a single membrane; some of these vesicles contain hydrogen-peroxide-generating enzymes and were therefore called 'peroxisomes' to reflect their role in peroxide metabolism. It was later found that enzymes catalyzing the β -oxidation of fatty acids were located not only in mitochondria but also in peroxisomes; in fact the most important metabolic role of the peroxisome seems to be shortening of very-long-chain fatty acids (> 22 carbon atoms) and oxidizing di- and trihydroxy-coprostanic acids and pristanic acid, a metabolite of phytanic acid [1]. Thus peroxisomes contain enzymatic activities for β -oxidation of fatty acids that are distinct from the mitochondrial pathway.

Peroxisomes are present in almost all mammalian cells (except erythrocytes) including keratinocytes [2].

Several inborn defects of peroxisomal function have been identified: Zellweger syndrome [3], adrenoleukodystrophy (ALD) [4], rhizomelic chondrodysplasia punctata [5], CHILD syndrome [6], hyperpiperolic acidemia and infantile Refsum's disease [7]. Of these, Refsum's disease [8], as well as rhizomelic chondrodysplasia punctata [5] and CHILD syndrome [6] are associated with skin alterations, an ichthyotic-like condition [9].

In this issue of Dermatology, Papini et al. [8] report the dermatological findings in a patient with X-linked ALD and the metabolic disturbances detectable in the skin surface lipids.

X-linked ALD is a rare peroxisomal disorder, affecting 1/20,000 males. The disease is characterized by an accumulation of very-long-chain fatty acids because of impaired shortening in peroxisomes. Diagnosis of X-linked ALD is based on the demonstration of high serum levels of very-long-chain fatty acids. Clinical manifestations are central nervous system demyelination and adrenal insufficiency. However, striking variation of the clinical phenotype exists. The gene locus for ALD has been mapped to the terminal segment of the long arm of the X chromosome (Xq28) [10]. The gene responsible for the production of the ALD protein has been found recently by Mosser et al. [4]. It encodes a protein with homology to a 70-kD peroxisomal membrane protein which is involved in peroxisome biogenesis. The sequence of ALD protein and 70-kD peroxisomal membrane protein is very similar but not identical. Both proteins belong to the ATP-binding transporter protein superfamily. Gartner et al. [11] localized the human peroxisomal membrane protein 70-kD gene, which has a documented role in Zellweger syndrome, to chromosome 1. Aubourg et al. [12] reported reversal of neurologic and neuroradiologic features in a boy with ALD by bone marrow transplantation from his fraternal twin brother. Rizzo et al. [13] concluded from their study that dietary erucic acid therapy is effective in ALD.

The skin proved to be of importance in ALD when Moser et al. [14] showed that elevated C26 fatty acid was present in cultured skin fibroblasts. The cutaneous alterations so far reported in ALD include alopecia, ichthyosis-form scaling and hyperseborrhea, the relationship of which, if any, with the basic biochemical defect remains unknown. The observations by Papini et al. [8] that skin surface lipids are abnormal in that they contain a marked increase in a very-long-chain fatty acid may be of interest in this respect.

Patchy nonscarring alopecia has previously been observed in several patients with X-linked ALD. Females heterozygous for ALD may have loss of body hairs and sparse scalp hair [15]. However, more in-depth investigations on hair have not yet been performed in those patients; histology from a bald area of the patient reported by Papini et al. [8] showed hypotrophy of the hair follicles and hyper-plasia of sebaceous glands. Light microscopy of the hair shafts revealed incomplete twisting. Scanning electron microscopy documented hair shaft abnormalities such as cuticular alterations, trichorrhexis-nodosa-type fractures, hair casts and longitudinal grooves. The scanning electron-

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microscopic findings confirmed the preliminary data reported by Calvieri et al. [16], who were able to correlate the severity of hair shaft anomalies to the severity of the other clinical symptoms.

Ichthyosis-like scaling was found in the patient of Papini et al. [8], which has not been reported in other cases with X-linked ALD. Interestingly, in Refsum's disease, characterized by a deficiency in the α -hydroxylation of fatty acids with accumulation of phytanic acid, ichthyosis is an important dermatological finding. Minor elevations of phytanic acid have been found not only in Refsum's disease but also in other peroxisomal disorders such as Zellweger syndrome and ALD. Deficiency of peroxisomes in hepatocytes and cultured skin fibroblasts is demonstrable in the infantile form of Refsum's disease. Refsum's disease can be diagnosed by lipid analysis of the blood and the skin.

Hyperseborrhea and sebaceous gland hypertrophy are other features of the case of ALD presented by Papini et al. [8]; whether these might be related to the abnormal lipid metabolism in the skin, to the neurologic disturbances or to some alteration in adrenal hormones remains unknown.

ALD is a rare inborn error of lipid metabolism that should call the attention of dermatologists to peroxisomal function.

Exposure to certain hypolipidemic drugs (clofibrate), plasticizers and herbicides leads to peroxisome proliferation. It has been found that these chemicals trigger receptors (so-called peroxisome-proliferator-associated receptors, PPAR) that are members of the nuclear hormone receptor superfamily, to which retinoic acid receptors and retinoid X receptors belong [17]. A target gene for PPAR has been recently identified, that is the acylcoenzyme A oxidase gene, which encodes the key enzyme of the peroxisomal fatty acid β -oxidation system [15].

Furthermore, a convergence of PPAR and retinoid-dependent signaling pathways is suggested by the facilitating binding of PPAR to cognate response elements by retinoid X receptor α [18], the ligand of which is 9-cis-retinoic acid.

The cutaneous phenotype of inborn errors of peroxisomal function may bring important informations as to the biological relevance of such in vitro findings. Alopecia, seborrhea and ichthyosiform scaling reported by Papini et al. [8] may be a gleam in this darkness.

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