For Happier Patients, Accurately Identify Adult Refsum's Disease

This rare disease can be successfully managed with early, accurate identification and diet modifications.

By Christopher J. Dussel, BS and Robert T. Brodell, MD

Adult Refsum's Disease is a rare autosomal recessive degenerative disorder, frequently affecting Scandinavian and other Northern European populations. Physicians know it by several names (Table). Manifestations result from the inability to break down dietary phytanic acid and its accumulation in serum and tissues.[1] It is characterized by variable age of onset (commonly age 20-30), slow progression, and several hallmark symptoms. Its rarity and the variable nature of symptoms contribute to frequently delayed diagnosis.

Biochemical Pathology

Phytanic acid is a 20-carbon, branched chain fatty acid derived from several dietary sources including dairy products, meats, ruminant fats, and chlorophyll-containing vegetables. An enzyme deficiency prevents its alpha oxidation, resulting in pathogenic build-up. The exact mechanism of damage induced by increased levels of phytanic acid in Adult Refsum's Disease is still debated.[1]

Diagnosis

Consider Adult Refsum's Disease in the differential diagnosis of any patient who presents with a delayed onset of ichthyosis in association with neurologic impairment.[1] Detection of elevated levels of plasma phytanic acid confirms diagnosis. In children, measure phytanic acid oxidase levels in cultured fibroblasts.[1] Do not confuse Adult Refsum's with "Infantile Refsum's Disease," which is due to defective peroxisomal biogenesis.[2] Early diagnosis is key, because patients who begin appropriate therapy before significant neurological damage occurs can live normal lives. The mnemonic HAPPIER (Table) is useful in recalling the hallmark symptoms of Adult Refsum's disease.

Some degree of progressive hearing loss has been reported in up to 80 percent of cases. It usually begins asymmetrically in the second decade of the disease course and severity increases by the fourth decade.[3] Refsum's is also characterized by early onset cerebellar ataxia and increased protein in the cerebrospinal fluid, without pleocytosis.[2] A fourth hallmark is sensorimotor polyneuropathy. The lack of action potentials can eventually lead to weakness or paralysis, which can be reversed by treatment.[4] Ichthyosis is a characteristic but not an early indicator. It occurs after most other symptoms have already been manifested. Small white scales and dryness are present on the lower trunk and limbs, resembling Ichthyosis Vulgaris. Histological examination (H&E) reveals variably sized vacuoles in the epidermal, basal, and suprabasal cells corresponding to lipid accumulation seen with lipid stains of frozen sections. Electrocardiographic abnormalities are common and reflect arrhythmias. Retinitis Pigmentosa often presents early in the disease course as declining near vision and night-blindness.

Other less common features of Adult Refsum's include anosmia, miosis, renal tubular abnormalities, cardiomyopathy, and skeletal deformities (shortened phalanges, epiphyseal dysplasia, etc.).[1]

Adult Refsum's Disease

Synonyms:
- Phytanic Acid Storage Disease
- Hypertrophic Neuropathy of Refsum
- Heredopathia Atactica Polyneuritiformis
- Disorder of Cornification 11 (DOC 11)

Hearing Loss
Ataxia
Protein in CSF
Polyneuropathy
Ichthyosis
EKG abnormalities
Retinitis Pigmentosa

Treatment Options

Long-term treatment of Refsum's Disease is often successful because it is one of the few inherited disorders with an exogenous cause.[5] Reduction of dietary intake of phytanic acid is the most common treatment and has been shown to improve or halt many symptoms.[5] Newer treatment regimens, such as therapeutic plasma exchange, have successfully lowered plasma phytanic acid levels during acute attacks.[6] An in vitro gene therapy approach has recently proven useful in restoring enzyme activity but will require greater study.[5]

Moisturizing creams containing lactic acid 12% or urea 40% can be used daily for associated dryness and scaliness.

1. DiGiovanna J. "Ichthyosiform Dermatoses". Fitzpatrick's Dermatology in General Medicine, Volume 1. 1999 (581-601). McGraw-Hill Companies, Inc.

2. Di Donato S,et al. "The complex clinical & genetic classification of inherited ataxias II. Autosomal recessive ataxias." Neurological Sciences. 22(3) 2001:219-228.

3. Aslan I, Oysn C, et al. "The site of the hearing loss in Refsum's disease." Internl J Ped Otorhinolaryngology. 61(2), November, 2001. pp. 129-134.

4. Griggs R, Lou J, Snyder R. "Refsum's disease: long term treatment preserves sensory nerve action potentials and muscle function." Electorencephaly and Clinical Neurophysiology. 98(3), March, 1996. pp. 25-26.

5. Feher MD et al. "Refsum's disease: a peroxisomal disorder affecting phytanic acid alpha-oxidation. Journal of Neurochemistry. 80(5),2002:727-735.

6. Weinstein R. "Phytanic acid storage disease (Refsum's disease): Clinical characteristics, pathophysiology and the role of therapeutic apheresis in its management. J Clin Apheresis. 14(4),1999:181-184.