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MAJOR REVIEW

# Adult Refsum Disease: A Form of Tapetoretinal Dystrophy Accessible to Therapy

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**Abstract.** Adult Refsum disease is characterized by an elevated plasma phytanic acid level and high concentrations of phytanic acid in a variety of tissues. Besides tapetoretinal degeneration, additional symptoms are anosmia, skeletal malformations, chronic polyneuropathy, cerebellar ataxia, sensorineural hearing loss, ichthyosis, and cardiac abnormalities. A diet low in phytanic acid ameliorates polyneuropathy and ataxia and slows or even stops the other manifestations. In order to be able to apply dietary therapy, as many patients as possible (even better if all of them are) have to be identified at an early stage. The ophthalmologist plays a crucial role in achieving this goal because of the early manifestation of the tapetoretinal degeneration. (**Surv Ophthalmol 55**:531–538, 2010. © 2010 Elsevier Inc. All rights reserved.)

**Key words.** adult Refsum disease • anosmia • ataxia • blood plasma filtration • ichthyosis • phytanic acid • polyneuropathy • sensorineural hearing loss • tapetoretinal degeneration

## I. Introduction

Adult Refsum disease (ARD, OMIM # 266500), often referred to as Refsum disease, has long been conceived as a complex disorder with involvement of multiple systems, including the retina. The modern view is that adult Refsum disease is first and foremost a retinopathy in which additional symptoms may develop if not treated appropriately. The full clinical picture includes retinitis pigmentosa (RP), hand–feet deformities, anosmia, sensorineural hearing loss, a chronic sensorimotor polyneuropathy, ataxia, ichthysosis and, in severe cases, cardiomyopathy[34] (Table 1).

The disorder was first described in 1946 by Norwegian neurologist Sigvald Refsum (1907–1991).[28] British neurologist Brian Gibberd (1931–2006) further characterized the manifestations of the disease and established the routine treatment with a diet low in phytanic acid. This was possible after Klenk and Kahlke in 1963 discovered elevated





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TABLE 1

*Ophthalmic and Non-ocular Symptoms in Adult Refsum Disease*

| Ophthalmologic Symptoms | Other Symptoms |
|---|---|
| Retinitis pigmentosa | Peripheral polyneuropathy |
| Miosis | Ataxia |
| Attenutated pupillary light response | Anosmia |
| Attenuated effect of mydriatica | Shortened metacarpals und metatarsals |
| Iris atrophy | Sensorineural hearing loss |
| Cataract | Ichthyosis |
| | Cardiac arrythmias |

levels of phytanic acid[3,7,11,15] (tetramethylhexadecanoic acid) in blood and other tissues of patients with adult Refsum disease.[16] An isolated elevation of phytanic acid is the pathognomonic biochemical abnormality. An increase of plasma phytanic acid levels, along with other biochemical abnormalities, may be seen in disorders that completely lack peroxisomes or exhibit severe loss of their function. These cause a more serious clinical picture than adult Refsum disease (Table 2).[36]

## II. Clinical Features

Adult Refsum disease is rare; its exact prevalence is not known. It usually becomes manifest before the age of 20. However, the disease has been diagnosed up to age 50. The diagnosis can be supported by the presence of shortened metacarpal and 4th metatarsal bones early in life,[27] found in about 30% of patients (Fig. 1). Most of the patients also suffer from anosmia athough many do not realize it, and this manifestation needs to be elicited with detailed questioning and examination.[10] Untreated adult Refsum disease carries a poor prognosis.[28] Blindness and the complete loss of hearing prior to age 40 cause severe impairment to the patient's quality of life, and cardiac arrhythmias can be fatal. An early sign of the disease is retinal degeneration, found in all patients at the time of diagnosis. This cannot be distinguished from the isolated form of retinitis pigmentosa (Figs. 2–4). Patients complain of night blindness during childhood or adolescence. Later on, visual field constriction and attenuation of visual acuity emerge. Fundoscopy reveals attenuated retinal vessels and pigment epithelium degeneration; however, adult Refsum disease often lacks the typical spicular intraretinal pigmentation characteristic of RP.[21] Claridge et al found that there is an average gap of 11 years between the first visit of a Refsum patient to an ophthalmologist and the diagnosis of "adult Refsum disease" (range 1–28 years).[5]

TABLE 2

*Additional Disorders Associated with an Elevated Blood Plasma Level of Phytanic Acid*

1. Zellweger spectrum disorders, including
   - Zellweger syndrome
   - Neonatal adrenoleukodystrophy
   - Infantile Refsum disease
2. Autosomal recessive rhizomelic chondrodysplasia punctata type 1 (PEX7 deficiency)

These diseases constitute disorders in which the biogenesis of peroxisomal enzymes is deficient (1) or essential peroxisomal enzymes are lacking (2). The term "infantile Refsum Disease" is an unfortunate one, since the cause of the disease (defect in peroxisome biogenesis) is entirely different from the adult form of Refsum disease and, like other diseases mentioned here, follows a much more serious course.

## III. Biochemistry

In the majority of cases the isolated increase in the plasma level of exclusively phytanic acid is caused by the deficient activity of phytanoyl-CoA-hydroxylase (*PHYH*), a peroxisomal protein that catalyzes the first step in the α-oxidation of phytanic acid (Fig. 5).[3,12,13] In a few cases levels of phytanic acid are only slightly raised, but in all patients levels of pristanic acid are grossly reduced so a phytanic:pristanic acid ratio may be a more sensitive diagnostic indicator. Phytanic acid is transported in blood plasma, bound to very low density lipoprotein and low density lipoprotein (LDL).[33] Plasma lipid level changes account for some of the daily variation in phytanic acid levels.

In most patients adult Refsum disease is caused by mutations in the gene coding for phytanoyl-CoA hydroxylase, called *PAHX* (or *PHYH*). Direct metabolization of this branched long chain fatty acid via β-oxidation is impossible because of the methyl group at the third carbon atom. In 1997, the gene for phytanoyl-CoA-hydroxylase was localized on chromosome 10,[9,25] but because not all patients demonstrate this gene defect, the disorder has to be considered a genetically heterogeneous disease. In 2003, mutations in a second gene, *PEX7* on chromosome 6, was identified as an alternative cause of adult Refsum disease.[11,30] *PEX7* encodes the Peroxin-7 receptor protein in the peroxisomal-targeting system-2 (PTS-2) pathway. This protein promotes the uptake of several proteins into peroxisomes, thus playing an essential role in the transport of phytanoyl-CoA hydroxylase. The consequence is once again a disruption of the α-oxidation