MAJOR REVIEW

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

Klaus Rüether, MD, 1 Eleanor Baldwin, BSc, RD, 2 Minne Casteels, MD, PhD, 3 Michael D. Feher, MD, FRCP, 2 Morten Horn, MD, 4 Susan Kuranoff, MA, 5 Bart P. Leroy, MD, PhD, 6 Ronald J. Wanders, PhD, 7 and Anthony S. Wierzbicki, DM, Dphil, FRCPath 2

1 Charité-Eye Hospital, Campus Virchow-Klinikum, Berlin, Germany; 2 Refsums Clinic Chelsea and Westminster Hospital Foundation Trust, London, UK; 3 Department of Molecular Cell Biology, Katholieke Universiteit Leuven, Belgium; 4 Department of Neurology, Ulleval University Hospital, Oslo, Norway; 5 Refsum Disease Support Network, Basel, Switzerland; 6 Department of Ophthalmology and Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium; and 7 Genetic Metabolic Diseases Laboratory, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

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 • phytic 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, ichthyosis 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 phytic acid. This was possible after Klenk and Kahlke in 1963 discovered elevated
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 phytic 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 although 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.\(^{29}\) 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).\(^{5}\)

### 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 \(\alpha\)-oxidation of phytanic acid (Fig. 5).\(^{3,12,13}\) In a few cases levels of phytic acid are only slightly raised, but in all patients levels of pristanic acid are grossly reduced so a phytic acid: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 metabolism of this branched long chain fatty acid via \(\beta\)-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,\(^{8,25}\) 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 \(\alpha\)-oxidation

### TABLE 1

<table>
<thead>
<tr>
<th>Ophthalmologic Symptoms</th>
<th>Other Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinitis pigmentosa</td>
<td>PerIPHERAL POLYNEUROPATHY</td>
</tr>
<tr>
<td>Miosis</td>
<td>Ataxia</td>
</tr>
<tr>
<td>Attenuated pupillary</td>
<td>Anosmia</td>
</tr>
<tr>
<td>light response</td>
<td>Shortened metacarpals</td>
</tr>
<tr>
<td>of mydriatica</td>
<td>und metatarsals</td>
</tr>
<tr>
<td>Iris atrophy</td>
<td>Sensorineural hearing loss</td>
</tr>
<tr>
<td>Cataract</td>
<td>Ichthyosis</td>
</tr>
<tr>
<td></td>
<td>Cardiac arrhythmias</td>
</tr>
</tbody>
</table>

### TABLE 2

<table>
<thead>
<tr>
<th>Additional Disorders Associated with an Elevated Blood Plasma Level of Phytanic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Zellweger spectrum disorders, including</td>
</tr>
<tr>
<td>- Zellweger syndrome</td>
</tr>
<tr>
<td>- Neonatal adrenoleukodystrophy</td>
</tr>
<tr>
<td>- Infantile Refsum disease</td>
</tr>
<tr>
<td>2. Autosomal recessive rhizomelic chondrodysplasia punctata type 1 ((PEX7) deficiency)</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>
of phytanic acid. *PEX7* was already known previously because it is also responsible for another, more severe peroxisomal disease, the autosomal recessive rhizomelic chondrodysplasia punctata type 1.

An alternative variable capacity metabolic pathway exists for phytanic acid through ω-oxidation to produce urinary 3-methyl-adapic acid as a final excretion product.33

### IV. Pathogenesis

Phytanic acid cannot be synthesized in the human body; it is solely derived from exogenous dietary sources as a byproduct of the degradation of chlorophyll. While chlorophyll in vegetables is a potential source of phytanic acid, it cannot be digested by humans.6 In contrast, ruminant animals, with the help of their gastric flora, are able to absorb...
the chlorophyll-bound phytol and metabolize it to phytanic acid. The main sources of phytanic acid are milk products and meat of ruminant animals, such as beef, lamb, and veal, as well as predatory fish (e.g., cod, tuna). The daily intake with a normal diet is 50–100 mg.

The accumulation of phytanic acid in fat-containing tissues, including nerves, brain, and adipose tissue, is considered to be the main culprit of the symptom complex of adult Refsum disease. Although it is supposed that symptoms arise from the accumulation of phytanic acid in nerve tissues, the total percentage of body phytanic acid in nerves is low. In contrast, although representing only 1–5% of total fatty acids, body fat is the most important storage compartment of phytanic acid because of the large amount of body fat.

To date, the pathogenesis of adult Refsum disease has not yet been elucidated in its entirety. High levels of phytanic acid could probably cause changes of the cell membrane with subsequent functional disturbances. Another hypothesis is that an increased phytanic acid level could be detrimental to the prenylation of proteins, because there are isoprenoids with a structure similar to phytanic acid. There are indications that the accumulation of phytanic acid during gene expression can contribute to the development of adult Refsum disease by influencing nuclear receptors. Finally, it has been shown that phytanic acid causes damage to

![Goldmann Visual Fields](image)

**Fig. 3.** Visual field (Goldmann perimeter III4) of a 16-year-old patient with Refsum disease (same patient as in Fig. 2). Visual acuity is 1.0, bilateral.

![Electroretinogram (ERG)](image)

**Fig. 4.** Electroretinogram (ERG) of a 16-year-old patient with Refsum disease (same patient as in Fig. 2). The left side shows the scotopic ERG with increasing stimulus intensity. On the right side the oscillatory potentials and the photopic recordings are displayed. In all recordings no responses are detectable.
OMEGA-OXIDATION OF PHYTANIC ACID AS AN ALTERNATIVE THERAPY FOR REFSUM DISEASE

Deficient in Refsum disease

3-Methyl adipic acid

Fig. 5. A: α-oxidation pathway of 3-methyl-branched fatty acids. B: ω-oxidation as alternative metabolic pathway for phytanic acid.
mitochondria, either by oxidative stress comparable to rotenone and/or through its protonophoric action at the mitochondrial membrane. The functions of phytanol-CoA-hydroxylase other than the \( \alpha \)-oxidation of phytanic acid, such as its participation in protein–protein interactions, may play a role in the pathogenesis of adult Refsum disease.

V. Therapeutic Aspects

Adult Refsum disease is among those rare forms of retinal dystrophies for which a treatment is available. The aim of a therapeutic intervention in adult Refsum disease is to lower the body’s content of phytanic acid. The primary question relates to how this goal can be achieved, and for ophthalmologists in particular, what can be gained by doing so.

A. DIET

A special diet for Refsum patients was first reported in 1966, but has subsequently been substantially amended to reduce the number of highly restricted foods. A number of publications detail the specifics, and the latest version of the diet is available from www.refsumdisease.org. The diet centers on the avoidance of milk products, meat, and fats of ruminant animals, as well as fish. Fat-free dairy products and soy products, such as soy cheeses and fish substitutes, can reduce the perception of dietary restriction. Pork and poultry are acceptable, as are all vegetables. Because food products vary in their content of phytanic acid, both seasonally and regionally, consultation with a professional dietician is mandatory. Repeated skilled dietetic support seems important to help with dietary compliance. The aim of these diets is to limit the intake of phytanic acid to less than 10 mg a day, the amount that can be degraded via \( \alpha \)-oxidation. In a healthy person, the half-time for eliminating the entire body store of phytanic acid is 1 to 2 years. In patients with adult Refsum disease, this period is extended considerably, even though a rudimentary path of metabolism occurs by way of \( \alpha \)-oxidation. The dietary effects are undisputed. Nearly all Refsum patients registered in Norway prior to the introduction of a disease-specific diet progressed to near blindness. Half died before reaching age 30. By lowering the blood plasma level of phytic acid, the peripheral neuropathy can be halted and often reversed. Unsteadiness in gait and muscle strength loss can lead to a considerable increase of blood levels of phytic acid. Thus, it is very important not to reduce caloric intake, especially when beginning a Refsum diet. This also means that other causes of a reduced caloric intake, such as surgery, infections, or other concomitant diseases, may have been counterproductive to efforts aimed at lowering the blood level of phytic acid and may in some cases aggravate clinical signs. Refsum patients and their treating physicians should be aware of this, and treatment should always be accompanied by a diet that avoids a negative caloric balance.

B. BLOOD PLASMA FILTRATION PROCEDURES

Very high blood plasma levels of phytic acid—exceeding 100 mg/dL (3,200 \( \mu \)mol/L)—may be toxic, resulting in life threatening conditions. In this situation, it is advisable to apply blood plasma filtration procedures such as plasmapheresis; although, nowadays, more selective procedures are implemented (e.g., LDL-apheresis). Particularly at the beginning of a diet, apheresis can be helpful in reducing blood plasma levels. Nevertheless, an appropriate diet is the major priority, and apheresis alone cannot be considered an alternative to dietary management. If diet results in acceptable blood plasma levels (<10 mg/dL [320 \( \mu \)mol/L]), there is no evidence that additional plasmapheresis has any further positive effect on the course of the disease. Because of the small number of patients, it is difficult to carry out a systematic study to fulfill the required evidence-based criteria, and it is particularly important to document the course of disease in those patients treated with plasmapheresis or similar procedures.

C. COURSE OF DISEASE DURING DIET

The dietary effects are undisputed. Nearly all Refsum patients registered in Norway prior to the introduction of a disease-specific diet progressed to near blindness. Half died before reaching age 30. By lowering the blood plasma level of phytic acid, the peripheral neuropathy can be halted and often reversed. Unsteadiness in gait and muscle strength may improve, and sensory deficits may decrease. But although manifestations of adult Refsum disease such as retinal dystrophy, hearing loss, and anosmia appear not to be reversible, their progress can be slowed. Starting the diet early increases the probability of maintaining vision until late in life and is a prerequisite for a normal lifespan. Making a diagnosis as early as possible is essential and is an important role for the ophthalmologist.
ADULT REFSUM DISEASE

D. FUTURE THERAPEUTIC OPTIONS

Alternative therapies are being pursued. As has happened in other enzyme-deficiency disorders, enzyme therapy, based on supplementation of the missing enzyme phytanoyl-CoA-hydroxylase, may become a reality. Also, induction of the remaining residual activity of the phytanoyl-CoA hydroxylase by adding an alternative substrate (co-substrate rescue therapy) may be achievable. Another approach could be the utilization of an alternative metabolic pathway for phytic acid, by means of \( \omega \)-oxidation, which can be achieved through hydroxylation of phytic acid.\(^{17}\) The latter is even more promising, as established drugs may increase phtyic acid hydroxylation via the cytochrome P450 4A1 system.\(^{32}\) Any new form of therapy will have to equal or improve upon the effects of diet and the encumbrances diet puts upon the patient. In the near future the existing mouse model for adult Refsum disease will likely play a major role in the development of new therapeutic strategies.\(^{8}\)

VI. Conclusion

When first diagnosing a tapetoretinal dystrophy, the ophthalmologist should consider adult Refsum disease as part of the differential diagnosis and specifically ask for associated manifestations such as skeletal deformities (examining hands and feet can be useful), an impaired sense of smell, neurological changes, loss of hearing, skin changes, and, in severe polysymptomatic cases, cardiac rhythm disorders. Known RP-patients should be asked whether such symptoms have emerged. In cases of RP, where no X-linked or dominant inheritance pattern is evident and where the above-mentioned symptoms cannot be ruled out entirely, the blood level of phytic acid should be determined—and preferably also a phytic:pristanic acid ratio. Gas chromatography/mass spectrometry is a standard test available in many laboratories specializing in the diagnosis of inborn errors of metabolism. Reference labs performing this test can be found through the Directory of Rare Analyses (American Association of Clinical Chemistry; www.aacc.org), the Association of Clinical Biochemistry (UK; www.acb.org.uk), or through the Society for Study of Inborn Errors of Metabolism (www.ssiem.org). Although the efficacy of dietary management varies among individual patients, a diet low in phytic acid is the therapy of choice for adult Refsum disease. Individualized treatment and close follow-up by a dietician is crucial to success. Supportive apheresis may be used when necessary for symptomatic management in acute flare-ups. Medical care of Refsum patients requires interdisciplinary cooperation, whereby ophthalmologists need to collaborate closely with neurologists, pediatricians, internists, metabolic specialists, and dieticians. Patients should be informed of patient organisations. Information about groups in different countries can be obtained from Retina International (www.retina-international.org).

VII. Method of Literature Search

This paper is based on the conclusions of the 1st International Refsum Disease Symposium held at the Charité - Hospital, Humboldt University, Berlin, Germany April 1–2, 2005. At that symposium a group of clinicians and basic science researchers interested in adult Refsum disease, as well as patients and relatives, shared available knowledge. Our own experiences, as well as published case reports about missed diagnoses, prompted us to summarize the essential information on adult Refsum disease in an ophthalmologic journal. The aim is to bring adult Refsum disease to mind and minimize the rate of false or missed diagnoses. The available knowledge about the clinical features, biochemistry, pathogenesis, and therapeutic aspects has been reviewed in the literature using PubMed. As all authors are working on this subject, our own experiences have also been incorporated.

References


The authors reported no proprietary or commercial interest in any production mentioned or concept discussed in this article. The authors wish to thank Frank Brunsmann, Rainald von Gizycki, Alfred Hildebrandt (leaders of the project ‘‘Rare retinal degenerations’’, supported by the German Ministry of Health [BMG]) for organizing the 1st International Refsum Disease symposium held at the Charité - Hospital, Humboldt University, Berlin, Germany April 1–2, 2005, and for reviewing the manuscript.

Reprint address: Prof. Dr. Med. Klaus Rüther, Charité Augenklinik Campus Virchow-Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany. e-mail: klaus.ruether@charite.de.

Outline

I. Introduction
II. Clinical features
III. Biochemistry
IV. Pathogenesis
V. Therapeutic aspects
A. Diet
B. Blood plasma filtration procedures

C. Course of disease during diet
D. Future therapeutic options

VI. Conclusion
VII. Method of literature search